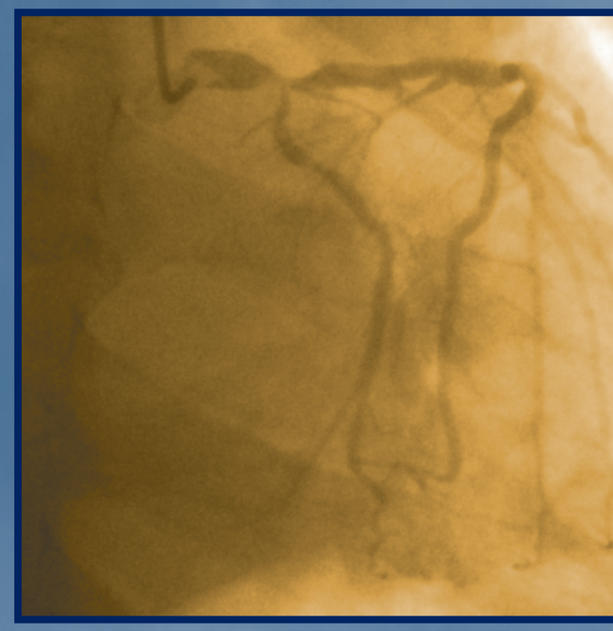
Risk Stratification In Patients Undergoing Percutaneous Coronary Revascularization

Risk Stratification In Patients Undergoing Percutaneous Coronary Revascularization



SCOT GARG

SCOT GARG

Risk Stratification In Patients Undergoing Percutaneous Coronary Revascularization

Scot Garg

Financial support for the publication of this thesis was generously provided by:

Elixir Medical
Biosensors
InfraRedx
Abbott Vascular
Boston Scientific
Cardialysis

ISBN 978-94-6169-049-4

Risk Stratification in Patients Undergoing Percutaneous Coronary Revascularization

Risicostratificatie bij patiënten die een percutane coronaire revascularisatie ondergaan

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. H.G. Schmidt

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

donderdag 21 april 2011 om 9:30 uur

door

Scot Anil Garg

born in Greenock, Scotland

PROMOTIECOMMISSIE

Promotor:	Prof.dr. P.W.J.C. Serruys
Overige leden:	Prof.dr. P.J. de Feyter
	Prof.dr. W.J. van der Giessen
	Prof.dr. F. Zijlstra

In loving memory of my father and sister, and dedicated to my family

Table of Contents

General Introduction and Outline of Thesis

INTRODUCTION

The decision making process for patients with obstructive coronary artery disease requiring revascularization is evolving. Historically, patients with the most complex coronary artery disease were preferentially treated by surgical revascularization; however technological advances in percutaneous therapy have ensured that some of these patients can now receive equally effective treatment with percutaneous coronary intervention (PCI). Intertwined with these developments are a lower threshold to investigate patients with symptoms suggestive of coronary artery disease, an increasingly elderly population in need of revascularization, the changing dynamics of the doctor-patient relationship, and a greater emphasis on guideline driven patient care. Consequently decisions regarding revascularization are now more complex than ever before.

Myocardial revascularization is only considered appropriate, *"when the expected benefits, in terms of survival or health outcomes (symptoms, functional status, and/or quality of life) exceed the expected negative consequences of the procedure."*[1] Therefore the question is no longer simply whether coronary lesions can be dealt with technically, it must now be combined with an equally important consideration as to whether this is the most appropriate treatment for the patient in question. Coupled with is the greater involvement of patients in clinical decision making, reiterating the importance of transparency. It is clearly apparent therefore that methods to effectively risk stratify patients undergoing revascularization are important to ensure patients receive appropriate individualised treatment.

The importance of these concepts is further emphasised by their central presence in three recent consensus documents developed to guide myocardial revascularization on both sides of the Atlantic. These comprise of: (i) the 2009 appropriateness guidelines for coronary revascularization from the joint American Colleges;[1] (ii) the 2009 focused update on coronary revascularization by the American College of Cardiology and the American Heart Association;[2] and (iii) the 2010 guidelines for myocardial revascularization by the joint task force of the European Society of Cardiology and the European Society of Cardiothoracic Surgeons.[3-4]

On the background of this expanding decision making process and the increasing use of PCI to treat complex disease, the primary goals of this thesis were to:

(i) Analyse current and newly developed tools available to stratify risk in patients undergoing PCI;
(ii) Assess the impact of clinical factors, coronary anatomy, and coronary stents on clinical outcomes;
(iii) Investigate the benefits and risks of current coronary stents and explore the potential future developments of these devices;
(iv) Assess the long-term outcomes in patients with complex disease treated with PCI using drug-eluting stents.

Part 1 of this thesis starts by taking a step back from assessing risk in patients undergoing revascularization, and discusses which patients should actually be revascularized. After establishing that there is a need for revascularization, aspects of the device most responsible for revolutionizing interventional cardiology, the coronary stent, are reviewed in Part 2. The field of coronary stents is rapidly

changing, and whilst Chapter 2.1 is devoted to currently established stents, Chapter 2.2 explores the new stent technology on the horizon, whilst one of the major ongoing concerns with these devices, stent thrombosis, is examined in Chapter 2.3.

Part 3 introduces the concepts and tools available to individualise the assessment of patients in need of revascularization. Following on from this, Part 4, which includes Chapters 4.1 to 4.7 examines established and newly proposed risk models to assess patients undergoing PCI. In particular, Chapters 4.1to 4.3 focus on the euroSCORE and the SYNTAX score, whilst Chapters 4.4 and 4.5 report evaluation of the newly developed ACEF and Clinical SYNTAX score when applied to the respective LEADERS and ARTS-II populations. The current status of clinical and angiographic risk assessment in patients with left main lesions is discussed in Chapter 4.6, with a validation of the newly proposed Global Risk Classification in left main patients from the SYNTAX trial reported in Chapter 4.7.

Part 5 (Chapters 5.1-5.3) focuses on assessing the impact of clinical factors on outcomes after PCI. Chapter 5.1 demonstrates the changing risk profile of patients enrolled in coronary stent trials, whilst Chapters 5.2 and 5.3 respectively examine the influence of age, and body mass index on clinical outcomes.

Part 6 includes a series of studies assessing the impact of coronary anatomy, as quantified using the SYNTAX score, on outcomes after PCI. Chapters 6.1 and 6.2 report 1-year outcomes according to the SYNTAX score from the respective all-comers LEADERS, and RESOLUTE patient populations. Similarly, Chapter 6.3 reports outcomes according to the SYNTAX score in a population of patients who all presented with acute myocardial infarction from the STRATEGY and MULTI-STRATEGY studies. Continuing this theme, Chapter 6.4 includes a patient level meta-analysis of 1-year outcomes from over 6500 patients with a SYNTAX score who were enrolled in contemporary coronary stent trials. Following this, Chapters 6.5 and 6.6 report longer term follow-up according to the SYNTAX score, with Chapter 6.5 reporting 2-year outcomes from the LEADERS study, and Chapter 6.6 reporting 5-year outcomes from the SIRTAX study. Part 6 is concluded by Chapter 6.7, which assesses the long-term impact of the completeness of revascularization in patients with complex disease who are treated by PCI or surgery.

Moving forward, Part 7 assesses the influence of stent type on outcomes in those treated by PCI. The section is opened by the 3- and 4-year outcomes of the SPIRIT II study, which assessed the paclitaxel- and everolimus-eluting stents. Following this are the results from studies assessing newer generation stents including the zotarolimus-eluting Resolute stent (Chapter 7.3), the novolimus-eluting ElixirD-ESyne stent (Chapter 7.4) and the biolimus-eluting stent BioMatrix stent (Chapters 7.5 and 7.6).

The final section Part 8, focuses on the long-term outcomes of patients with complex disease who were treated with drug-eluting stents. Chapters 8.1-8.3 all report 5-year outcomes from the ARTS-II registry; in particular whilst Chapter 8.1 reports outcomes from the full registry, Chapter 8.2 and 8.3 respectively report outcomes in more specific sub-groups of patients, namely those with proximal left anterior descending artery disease and diabetes mellitus. Chapter 8.4 assesses the long-term

outcomes in patients from the RESEARCH and T-SEARCH registries who had left main disease, whilst the thesis concludes with Chapter 8.5, which reports the 5-year outcomes of patients with chronic total occlusions from the RESEARCH registry.

REFERENCES

1. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization: a report by the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol.* 2009;53:530-553.
2. Kushner FG, Hand M, Smith SC, Jr., King SB, 3rd, Anderson JL, Antman EM, Bailey SR, Bates ER, Blankenship JC, Casey DE, Jr., Green LA, Hochman JS, Jacobs AK, Krumholz HM, Morrison DA, Ornato JP, Pearle DL, Peterson ED, Sloan MA, Whitlow PL, Williams DO. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2009;54:2205-2241.
3. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D, Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas PE, Widimsky P, Alfieri O, Dunning J, Elia S, Kappetein P, Lockowandt U, Sarris G, Vouhe P, von Segesser L, Agewall S, Aladashvili A, Alexopoulos D, Antunes MJ, Atalar E, Brutel de la Riviere A, Doganov A, Eha J, Fajadet J, Ferreira R, Garot J, Halcox J, Hasin Y, Janssens S, Kervinen K, Laufer G, Legrand V, Nashef SA, Neumann FJ, Niemela K, Nihoyannopoulos P, Noc M, Piek JJ, Pirk J, Rozenman Y, Sabate M, Starc R, Thielmann M, Wheatley DJ, Windecker S, Zembala M. Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2010;31:2501-2555.
4. Guidelines on myocardial revascularization. *Eur J Cardiothorac Surg.* 2010;38 Suppl:S1-S52.

PART I

The Need for Revascularization

Chapter 1

Stable Angina: Medical therapy vs. PCI vs. CABG

Oxford Textbook of Interventional Cardiology
1st Edition, p219-234

Scot Garg, Joanna Wykrzykowska, Patrick W. Serruys

Introduction

Coronary artery disease (CAD) represents a wide spectrum of underlying anatomical disease ranging from near normal, minor single-vessel disease (SVD), to extensive triple-vessel disease. Its presentation is similarly variable, from a single episode of chest pain to acute coronary syndrome (ACS) or even death. The aim of treatment in CAD is to relieve symptoms and improve quality of life, reduce cardiovascular (CV) events, and prolong survival. There have been vast improvements in management over the years, following a greater understanding of the underlying pathophysiology, the identification and appropriate management of risk factors, development of new medication, and advances in revascularization techniques, both percutaneous and surgical. These developments have resulted in a move towards an anatomic treatment for CAD even though it is the minor lesion, so-called vulnerable plaque, which is suggested as the most likely culprit for mortality. Nevertheless, in those patients presenting with ACS or ST-elevation myocardial infarction the long-term benefits of percutaneous coronary intervention (PCI) have been confirmed in multiple randomized trials[1]; however, debate surrounds the ideal management of the majority of patients who have angina, and who have not experienced any previous CV events or had an interventional procedure, so-called stable CAD.

Medical therapy versus mechanical revascularization

Medical therapy which encompasses lifestyle modification, risk factor reduction, and pharmacological therapy (antiplatelet and antianginal) has a strong evidence base and clearly has a central role in the management of every patient with CAD. Intuitively it would seem apparent that PCI would be the ideal treatment for every patient, however the current evidence taken at face value would tend to suggest otherwise. The largest trial to date comparing PCI (and best medical therapy) with best medical therapy (BMT) was the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) whose publication has been well publicised and debated amongst general cardiologists, interventional cardiologists, and the general public. This trial, which recruited only 6.4% of the 35 539 patients who were assessed for entry, reported at median follow-up of 4.6 years no significant difference in the primary event rate (death or non fatal MI) with PCI compared with BMT (19.0% vs. 18.5%; 95% confidence interval [CI], 0.87–1.27; $p = 0.62$)[2]. This added to the evidence from earlier meta-analyses in 2000[3] and 2005[4] both of which concluded that PCI improved symptoms but did not reduce mortality or the incidence of CV events. There is no doubt that PCI helps relieve symptoms[2,3,5] but what is its true effect on mortality and morbidity,

and can these general conclusions be applied to all groups of patients? The importance of this issue cannot be overstated given the vast resources that are spent on managing these patients who comprise 85% of the PCI workload in the United States[2]. Most importantly a recent meta-analysis which included the COURAGE data and comprised 7915 patients found a 20% reduction in all cause death amongst the PCI-treated patients compared with BMT (271 deaths vs. 335 deaths; odds ratio [OR], 0.80; 95% CI, 0.64–0.99; p = 0.263)[6].

It is essential to consider some of the limitations of the previous trials which have been performed comparing the two groups. They have all suffered from the low risk[7] of the population being studied, and have been under-powered to detect a significant mortality difference. In addition, mean follow-up time has been just under 4 years, which may be too short to detect morbidity in the BMT group, whilst those in the PCI group may experience peri-procedural events which will be detected on short-term follow-up. Importantly in the COURAGE trial the rate of spontaneous MI (not peri-procedural) in the BMT group was higher than in the PCI arm (119 vs. 108), but peri-procedural MIs were much higher in the PCI group (35 vs. 9). Peri-procedural MIs are not benign and do affect prognosis[8], some of these may occur through trying to achieve the 'perfect' angiographic appearance, when simpler less complicated procedures may produce the same symptomatic benefit, at a lower risk. The advantages of PCI are further reduced by high cross over rates, ranging from 6–44%, from BMT to PCI although this is a reality of the chronic nature of CAD rather than a 'fault' of the trials. The benefit of PCI has also been hampered by the trials being performed before the drug eluting stent (DES) era. It is well documented that restenosis, which is reduced significantly by DES compared with bare metal stent (BMS) or balloon angioplasty (POBA), is not a benign phenomenon and can present as an acute MI in between 9.5–19.4% of cases[9].

The presence of ischaemia affects clinical outcome but amongst the trials there is considerable variation in the objective evidence of ischaemia required for patient enrolment, with some simply relying on symptoms and angiographic evidence of stenosis. PCI is very effective at relieving the subjective symptoms of ischaemia. Evidence from the nuclear subset of the COURAGE trial which looked at 313 patients who had myocardial perfusion imaging before, and 6–18 months post randomization, would suggest that it is also more effective than BMT at relieving objective ischaemia. In this subset of patients those having PCI and BMT had a greater reduction in significant myocardial ischaemia than BMT controls (p = 0.004), and this translated clinically into a significantly lower rate of death and MI in these patients (13.4% vs. 24.7%, p = 0.037). Also of note were the zero rates of death and MI in those patients having no evidence of residual ischaemia at 6–18 months, compared with a rate of 39.3% in those with grater than 10% residual ischaemia. In summary, PCI with BMT has been shown to be better than BMT at relieving subjective and objective ischaemia, and this has translated into better clinical outcomes. The SWISS II study showed similar benefits in the presence of proven silent ischaemia[10]. Future trials need to ensure that the degree of myocardial ischaemia is accurately assessed to guarantee the validity of the conclusions reached.

In the 'real world' aggressive medical therapy is frequently difficult to implement because real-world patients experience side effects from therapy, and may subsequently be non-compliant with medication, or lifestyle advice. The COURAGE trial has shown what can be achieved in the ideal world with reductions in blood pressure, LDL cholesterol, smoking rates, and improvements in diet, and exercise; however, these require additional resources and the manpower which most healthcare providers are simply unable to deliver.

In summary, medical therapy plays an important part in the management of patients with CAD, and the role of revascularization should be considered to be complementary to BMT which is central to management. PCI should be considered if BMT fails to control symptoms in those patients who are deemed to be at a low risk of CV events, whilst in those who are at higher risk, revascularization with either PCI or coronary artery bypass grafting (CABG) and BMT must be considered early.

Risk stratification

From the previous discussion it is apparent that risk stratification plays a vital role in helping guide the management of patients with CAD. It also has an important role in providing patients, and their relatives, with answers to questions they may have about the likely course of their condition and their prognosis, and can also help inform other health professions planning other treatments and procedures.

Which patients are at high risk of events? The European Society of Cardiology defines those patients with an annual CV risk of >2% as high risk, <1% as low risk, and between 1–2% intermediate risk, and recommends that risk stratification takes into consideration:

1. Clinical evaluation of the patient

A clinical evaluation of the patient is essential in all cases and can provide information with regards prognosis,

and the following factors—although by no means exhaustive—are all associated with an increased risk of adverse prognosis in those with stable CAD:

- History of diabetes mellitus, hypercholesterolaemia, hypertension, and renal impairment.
- Severity of angina presentation.
- Current smoking.
- Examination findings suggestive of peripheral vascular disease, or signs of left ventricular (LV) dysfunction.
- An abnormal ECG (previous MI, left bundle branch block, left anterior hemiblock, LV hypertrophy, atrial fibrillation, and second- or third-degree heart block).

2. Response to stress testing

Stress testing provides additional information regarding the patient's risk, and currently numerous different non-invasive stress tests are available, which are able to provide prognostic information obtained not only from the presence or absence of ischaemia, but also from the degree and severity of ischaemia, the exercise capacity, and the ischaemic threshold.

There are no randomized trials comparing individual stress tests, and issues other than the patient's physical and functional ability to exercise, or the presence of an abnormal ECG such as availability, local expertise, and preference of the referring physician do have an influence on which test is ultimately used. Table 14.1 lists the criteria on non-invasive stress testing which suggest a high risk of CV events and subsequently indicate the need for revascularization. Currently multisliced CT scanning provides an anatomical assessment of CAD, with limited data available on its correlation with inducible ischaemia; however, with further evaluation in progress this may change. Whichever test is used, a normal result doesn't exclude the presence of CAD or the risk of future events.

3. An assessment of left ventricular function

LV function is the most important marker of prognosis in those patients with CAD. Studies have shown that mortality is inversely proportional to LV function, and in those with an LV ejection fraction <35%, the annual risk of mortality is in excess of 3%[11].

Table 14.1 Prognostic variables and criteria indicating a high risk of cardiovascular events amongst various non-invasive stress tests

Modality	Prognostic variables	Criteria for high risk of CV events	Annual mean CV event rate in normal test
Echocardiography	LVEF at rest LVEF on exercise	LVEF <35% at rest LVEF <35% on exercise	
Stress echocardiography	Number of resting WMA Number of inducible WMA with stress	WMA (involving >2 segments) developing at: ◆ A low dose of dobutamine (≤10mg/kg/min) or ◆ At a low heart rate (<120bpm) Stress echocardiographic evidence of extensive ischaemia	<0.5%[11]
Exercise testing	Exercise-induced angina Exercise capacity BP response to exercise Changes in ST segment Exercise-induced ischaemia	High-risk Duke treadmill score (< −10)*	Low Duke score (>4) 0.25% (annual mortality)
Myocardial perfusion imaging	Large stress-induced perfusion defects Defects in multiple coronary arteries Transient post stress LV dilation Lung uptake with Tl-201	Stress-induced: ◆ Larger perfusion defect (particularly if anterior) ◆ Multiple perfusion defects of moderate size ◆ Moderate perfusion defect with LV dilation or increased lung uptake (Tl-201) Large, fixed perfusion defect with LV dilation or increased lung uptake (Tl-201)	0.7%[67]

* The Duke treadmill score equals the exercise time in minutes minus (5× the ST-segment deviation, during or after exercise, in millimetres) minus (4× the angina index, which has a value of '0' if there is no angina, '1' if angina occurs, and '2' if angina is the reason for stopping the test)[68].

BP, blood pressure; LVEF, left ventricular ejection fraction; Tl-201, thallium-201; WMA, wall motion abnormality.

4. An assessment of the coronary anatomy

Coronary anatomy provides valuable information in assessing the patient's risk of CV events, and in particular the extent, severity, and location of the disease are important factors which influence prognosis. A simple risk assessment can be based on the number of coronary arteries involved, which is supported by data from the CASS medical registry which showed that 12-year survival was 91%, 74%, 59%, and 50% in those with normal, single-, double-, or triple-vessel disease respectively[12], furthermore survival rates were poorer in those with a combination of two- or three-vessel disease and a left main stem (LMS) lesion. Early data has shown the poor prognosis in LMS lesions treated medically[13], and the improved survival with revascularization, which at the time of publication was predominantly CABG, in those with triple-vessel disease, two-vessel disease which includes the proximal left anterior descending artery (LAD), or two- or three-vessel disease and a positive exercise test[14].

It has been argued that coronary angiography is inappropriate in those patients who are deemed low risk after non-invasive testing in view of the risk of the procedure, and the small chance that repeat revascularization is required.

Once the patient has been risk stratified, and a decision reached to proceed with mechanical revascularization, the patient must be evaluated with respect to their suitability for PCI or CABG. This decision is often complex and requires a multidisciplinary team approach, with the cardiologist, interventional cardiologist, and cardiac surgeon all participating in the discussion. The last two decades have provided us with a large body of evidence to guide these complex decisions, and in the following section we will review the available data on stenting in multivessel disease (MVD) and CABG, including the most recent evidence from the SYNTAX, FAME, and CARDIA trials.

Mechanical revascularization: PCI versus CABG

After its introduction in the 1960s, CABG become the accepted treatment for MVD[15]; however, advances made in the percutaneous treatment of stable CAD from POBA to stenting with initially BMS[16] and now DES[17–19], have made PCI a progressively more attractive alternative (Fig. 14.1). All randomized clinical trials to date, whether performed in the early days with POBA or more recently with BMS or DES, show no mortality difference between PCI and CABG[20–22]. However the advantage of CABG over PCI in terms of restenosis rate and the need for re-intervention has progressively narrowed, especially in some patient subsets.

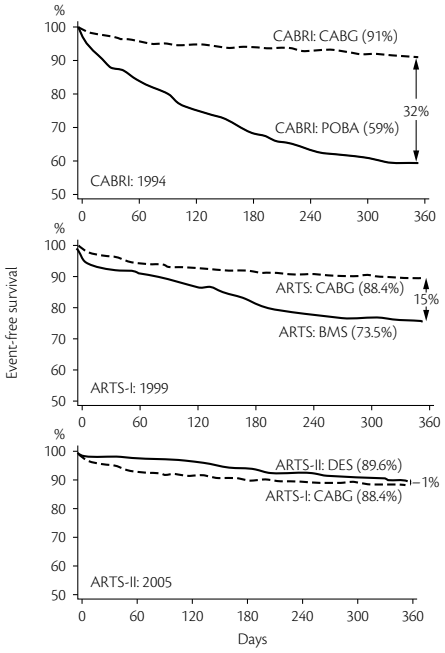


Fig. 14.1 Event-free survival at 1 year follow-up in the CABRI, ARTS-I, and ARTS-II studies showing a reduction in the difference in outcomes between CABG compared with balloon angioplasty, bare-metal stenting, and drug-eluting stents. Reproduced from Serruys, PW, ARTS I – the rapamycin eluting stent; ARTS II – the rosy prophecy. *Eur Heart J* 2002; **23**:757–9 by permission of Oxford University Press.

Pre-DES era: balloon angioplasty and bare metal stenting versus CABG

The six randomized trials comparing POBA to CABG are summarized in Table 14.2, together with the results at the longest published follow-up. In 1995, prior to the publication of the BARI trial, a 3-year meta-analysis was published of the other five trials which found no difference in the rates of death and non-fatal MI (CABG vs. POBA HR 1.03; 95% CI 0.81–1.32; p = 0.81)[20].

In view of the superior results with stenting compared with POBA (Fig. 14.2)[16], five subsequent randomized trials compared BMS to CABG in MVD. These five trials are summarized in Table 14.3 together with results at the longest published follow-up. The ARTS-I study was the largest of these trials and enrolled 1205 patients with

Table 14.2 Results at longest reported follow-up in the six randomized trials of balloon angioplasty versus coronary artery bypass surgery

Study	Year	No. of patients	Longest reported follow-up (years)	Death POBA vs. CABG	MI POBA vs. CABG	Re-intervention POBA vs. CABG
CABRI[69]	1994	1054	1	3.9% vs. 2.7% p = NS	p=NS	33.6% vs. 6.5% p <0.001
ERACI[70]	1993	127	3	4.7% vs. 9.5% p = 0.5	7.8% vs. 7.8% p = 0.8	37% vs. 6.3% p <0.001
RITA[71]	1993	1011	6.5	7.6% vs. 9.0% p = 0.51	10.8% vs. 7.4% p = 0.08	44.3% vs. 10.8%
EAST[72]	1994	392	8	20.7% vs. 17.3% p = 0.40	–	65.3% vs. 26.5% p <0.001
BARI[73]	1991	1829	10	71.0% vs. 73.5% p = 0.18	16.4% vs. 16.6% p = NS	76.8% vs. 20.3% p <0.001
GABI[74]	1994	359	13	25% vs. 21.9% p = 0.64	4.3% vs. 5.6% p = 0.6	82.9% vs. 58.8%

CABG, coronary artery bypass grafting; NS, not significant; POBA, balloon angioplasty; BARI, Bypass Angioplasty Revascularization Investigation; CABRI, Coronary Angioplasty versus Bypass Revascularization Investigation; EAST, Emory Angioplasty versus Surgery Trial; ERACI, Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty versus Coronary Artery Bypass Surgery in Multivessel Disease; GABI, German Angioplasty Bypass Surgery Investigation; RITA, Randomized Intervention Treatment of Angina.

MVD that had an equivalent baseline chance for complete revascularization. There was no difference between the two groups in either the prespecified primary endpoint of major adverse cardiac and cerebrovascular events (MACCE) at 1 year, or mortality at 5 years (8% vs. 7.6%; p = 0.83). However, when compared with CABG the rates of repeat revascularization were higher in the stenting group both at 1-year (16.8% vs. 3.5%) and 5-year (30.3% vs. 8.8%; p <0.001) follow-up[15,23].

A meta-analysis of all five trials showed similar MACCE rates and higher repeat revascularization rates in the PCI group at both 1- and 5-year follow-up[22,24,25]. The only study that has been at variance with these randomized trial results has been the New York Cardiac Registry[26] which looked retrospectively at risk-adjusted outcomes in 60 000 patients undergoing PCI or CABG. Risk adjusted survival was significantly higher in the CABG group (HR 0.64; 95% CI 0.56–0.74) with the difference being most pronounced in patients with three-vessel disease and proximal LAD disease. The criticism of this registry is that risk adjustment is likely to be impossible and that clinical judgement could not be adjusted for in this complex cohort of patients (J. Daemen, N. Kukreja, and P.W.J.C. Serruys, personal correspondence).

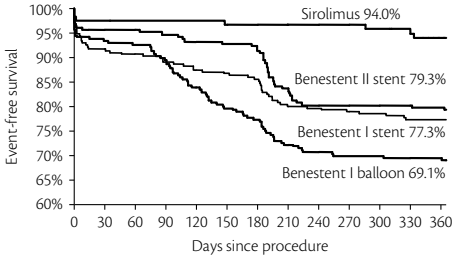


Fig. 14.2 The improved event-free survival in the Benestent I and II trials with the use of a bare-metal stent (Benestent I stent) or a heparin-coated stent (Benestent II) compared to only balloon angioplasty (Benestent balloon). The event-free survival, however, is much greater with a sirolimus-eluting stent.

The DES era—the game is getting closer

Randomized trials comparing DES and BMS have shown a reduction in the restenosis rates with DES. In addition, DES use has expanded to more complex patients and lesions including patients with MVD, which comprise close to 40% of PCI patients. The effectiveness of these devices has been shown in 'real world' registries such as RESEARCH and T-SEARCH[27]. ARTS-II was the first CABG-PCI registry/trial to evaluate the performance of DES specifically in MVD against CABG. It prospectively collected data on 607 patients with MVD treated with DES[28] who were then compared to historical CABG control from ARTS-I. One-year follow-up showed that PCI with DES was non-inferior to CABG with respect to MACCE rates. The rates of repeat revascularization, although lower than in the BMS arm of ARTS-I, were still significantly higher than in the historical CABG controls. These results were maintained at

Table 14.3 Results at longest reported follow-up in five randomized trials of bare metal stenting versus coronary artery bypass surgery

Study	Year	No. of patients	Longest reported follow-up (years)	Death PCI vs. CABG	MI PCI vs. CABG	Re-intervention PCI vs. CABG
AWESOME[75]	2000	142	3	24% vs. 27% p = NS	–	–
ARTS-I[23]	2001	1205	5	8.0% vs. 7.6% p = 0.83	9.5% vs. 6.4%	30.3% vs. 8.3% p <0.001
ERACI-II[76]	2001	450	5	7.1% vs. 11.5% p = 0.18	2.8% vs. 6.2% p = 0.13	28.4% vs. 7.2% p = 0.0002
MASS-II[77]	2003	611	5	15.5% vs. 12.8% p = NS	11.2% vs. 8.3%	32.2% vs. 3.5%
SOS[78]	1999	988	6	10.9% vs. 6.8% p = 0.022	–	–

CABG, coronary artery bypass grafting; NS, not significant; PCI, percutaneous coronary intervention; ARTS-I, Arterial Revascularization Therapy Study; AWESOME, Angina With Extremely Serious Operative Mortality Evaluation; ERACI-II, Argentine Randomized Study: Coronary Angioplasty with Stenting versus Coronary Bypass Surgery in Multivessel Disease; MASS-II, Medicine, Angioplasty or Surgery Study for multivessel coronary artery disease; SOS, Stent or Surgery

3-year follow-up with equivalent survival without MACCE (80.6% vs. 83.8%, p = 0.21) and lower freedom from repeat revascularization with PCI (85.5% vs. 93.4%, p <0.001). In ERACI-III which prospectively added a 205 patient cohort to the ERACI-II population, PCI with DES had a lower MACE rate than an historical CABG group (freedom from MACE was 88% vs. 80.5%; p = 0.038)[29]. One observational study in 1680 patients confirmed these findings with equivalent MACCE rates in a non-diabetic population with two-vessel disease[30]. However, again the New York registry of 17 400 patients appeared to contradict these results showing lower mortality rates for CABG at 18 months post procedure (adjusted survival of 96% vs. 94.6%; p = 0.003). Notably the difference was smaller than with a similar registry for BMS and the same concern regarding inability to adjust for all confounding risk factors remained.

SYNTAX, FAME, and CARDIA—results of the randomized trials: more answers but also more questions

Some of these earlier controversies in data interpretation are finally being partially resolved following the results of three major randomized trials presented in 2008 of DES versus CABG in patients with MVD. In addition, these trials also attempted to define more clearly which specific patient populations benefit from CABG or PCI.

Synergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) is a prospective, multicentre, multinational, randomized trial of all-comers design. It recruited 1800 patients with the goal to assess the best revascularization treatment for patients with de novo triple-vessel or LMS disease by randomizing them to either stenting with a paclitaxel-eluting Taxus® stent (Boston Scientific, Natick, USA) or CABG and also keeping a registry of those patients who were eligible for only PCI or only CABG[31]. The trial design was unique in that it employed the angiographic scoring system of lesion severity called the 'SYNTAX score'[32]. The patients recruited in SYNTAX are a unique study group in the PCI field, given their exceptionally complex anatomy and advanced disease. The average SYNTAX patient received 4.6 stents compared to the average 1.5 stents implanted in everyday practice. In addition, the patient profile included 33% with >100mm stented length, 84% with bi/trifurcations, 22% with chronic total occlusions, and 39% with LMS disease. Some of the sickest patients in the trial were not eligible for surgery and were treated with DES. The main results are summarized in Table 14.4. One of the most interesting results came from the SYNTAX score subgroup analysis which showed that PCI but not surgical outcomes were influenced by the angiographic SYNTAX score (lesion complexity). Analysis showed non-inferior results of PCI to CABG in patients with a SYNTAX score up to 32, whilst CABG was superior in those with a SYNTAX score above 32. Further analysis of the data will be required together with longer-term follow-up. The complexity of the patient population in this study certainly makes the data generalizable; however, one has to keep in mind that the surgery and

Table 14.4 12-month results from the SYNTAX study[31]

Events at 1 year	PCI N = 903 (%)	CABG N = 897 (%)	P-value
MACCE	160 (17.8)	109 (12.1)	0.002
Death/CVA/MI	69 (7.6)	69 (7.7)	0.98
All-cause death	39 (4.3)	31 (3.5)	0.37
MI	43 (4.8)	29 (3.2)	0.11
CVA	5 (0.6)	20 (2.2)	0.003
Repeat revascularization	124 (13.7)	53 (5.9)	<0.001

CVA, stoke; MACCE, major adverse cardiovascular and cerebrovascular events (all-cause death, CVA, MI, and repeat revascularization); MI, myocardial infarction.

complex PCI in this study was performed in highly selected centers of excellence in Europe and the United States who were used to high volumes of complex patients and cases.

The CARDIA (Coronary Artery Revascularisation in Diabetes) study randomized 510 diabetic patients with MVD or complex SVD to treatment with either CABG (n = 254) or PCI (n = 256; 71% DES). The primary outcome—death, MI and stroke—was comparable between CABG and PCI at 1 year (10.2% vs. 11.6%; p = 0.63), whilst repeat revascularization was significantly higher in the PCI group with a rate of 9.9% vs. 2.0% for CABG (p = 0.001). Similar results were seen in the DES subgroup analysis with no difference in the primary endpoint (CABG vs. DES PCI, p = 0.98) and higher repeat revascularization with DES compared to CABG group. Stroke, however, was more prevalent in the CABG group[33]. The results of the Future Revascularization Evaluation in patients with Diabetes Mellitus; Optimal Management of Multivessel Disease (FREEDOM) trial which is enrolling at least 2000 diabetic patients with MVD randomized to CABG versus multivessel stenting with DES are eagerly awaited.

Lastly, the Fractional flow reserve versus Angiography for Multivessel Evaluation (FAME) trial offers another approach to MVD treatment. It incorporates the idea of revascularizing the territory which has evidence of reversible ischaemia and uses the fractional flow reserve (FFR) measurement as a gold standard for the haemodynamic significance of the lesion. The premise of the study is based on the result that deferral of PCI based on the FFR cut-off point of 0.75 has been associated with favorable outcomes in patients with MVD[34] and that only lesions with inducible ischaemia benefit from invasive mechanical revascularization over medical therapy. FAME enrolled 1005 patients with at least two vessels with >50% lesions randomized to either angiographic guided, or FFR-guided stenting using an FFR cut off value of 0.8. The main results are shown in Fig. 14.3 There was a 35% reduction in overall MACE which was achieved without prolonging the procedure, (p = 0.51) and approximately one-third of angiographically significant lesions were found not to be haemodynamically significant by FFR. In addition the FFR-guided stenting strategy lead to a significant reduction in contrast use (272 ± 133mL vs. 302 ± 127; P <0.001) and a significant cost saving ($5332 vs. $6007, p <0.001) compared to the angiographic-guided stenting[35].

Lesion subsets

The previous section has been a general discussion comparing PCI and CABG. In the next section we have concentrated on six commonly encountered lesion subsets.

Single-vessel disease

Patients having revascularization have significantly lower 1-year mortality with SVD when compared with those having MVD; in fact the RITA trial showed this trend was maintained at 4.7 years follow-up (5.8% vs. 3.9%). In addition, those with SVD having revascularization have lower rates of MI and cardiac death compared to MVD, and also have better angina control at 1 and 3 years, compared to those with MVD having the same type of revascularization[21].

At present, approximately 4% of CABG is performed for SVD, however previously the rates were much

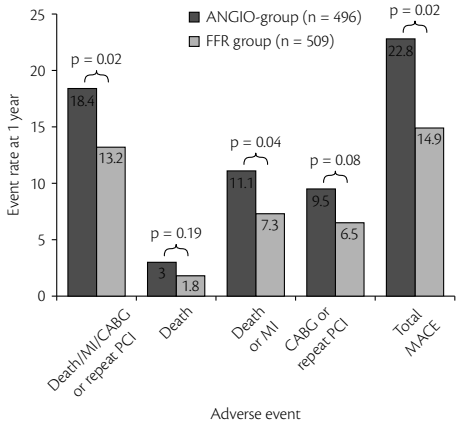


Fig. 14.3 The adverse event rates at one year from the 1005 patients in the FAME study showing improved outcomes with the use of an FFR-guided strategy[35].

higher, for example in the New York surgical registry of over 29 000 patients the rate of single-vessel CABG was 8.7%[36]. These initial high rates of surgical revascularization are the result of the early trials which showed a distinct advantage for CABG compared with medical therapy in patients with specific SVD—namely a significant proximal LAD lesion[37]; in fact in the previously mentioned New York registry 74.3% (n = 1917) of patients having single-vessel CABG, had proximal LAD disease. It is not surprising therefore that most data on the outcomes of revascularization in patients with SVD has concentrated on those with a significant proximal LAD lesion.

Two registries have concurred with the initial trials regarding surgical revascularization in those with significant proximal LAD disease; the New York registry was by far the larger containing 3-year outcome data on 23 808 patients (PCI = 21 231, CABG = 2577) with SVD. At follow-up those patients with SVD not including an LAD lesion had a much better survival with PCI than CABG (95.3% vs. 92.4%, p = 0.003); however, if there was a >70% LAD lesion, CABG conferred a significantly better prognosis. (96.6% vs. 95.2%, p = 0.01). Irrespective of the type of revascularization there was no significant difference between outcomes in those with SVD in the non-proximal LAD. In fact any patient with a proximal LAD lesion, whether with single-, double-, or triple-vessel disease did better with CABG. The Duke registry was much smaller, containing 9263 patients (medical therapy 2449; PCI 2924; CABG 3890), but concluded similar results at mean 5.3-year follow-up. Patients with SVD, including those with SVD and a mid/distal LAD lesion <75% severity, had better survival with PCI compared with CABG, whilst those with SVD due to a proximal LAD lesion >95% tended to do better with CABG.

It is, however, important to accept the limited clinical applicability of this data in the current era. Two main factors which may have influenced outcome were stent usage, which was only 11.8% in the New York registry, and usage of left internal mammary artery (LIMA) grafts. The Duke registry ran from 1984–1990 and the New York registry from 1993–1995, and although there is no comment on LIMA usage, in the 1980s studies reported rates of LIMA use of approximately 15%[37], whilst in the late 1990s rates of over 90% have been reported[38]. The relevance of low or even moderate use of the LIMA graft is the fact that they have significantly higher patency at follow-up, and confer a long term survival benefit when compared with saphenous vein grafts[39,40].

In recent years two meta-analyses have been published examining outcomes in patients with proximal LAD disease randomized to either PCI or surgical revascularization; Kapoor *et al.* concentrating on any surgical technique[41], whilst Aziz *et al.* examined specifically those having the minimally invasive direct coronary artery bypass (MIDCAB)[42]. In both studies patients tended to be young with a total mean age of 58.9 years, and with well-preserved ejection fractions (mean of 61.4%). The PCI technique varied in both, but of note the usage of DES was low, comprising of only 18.8% in Kapoor *et al.*'s study.

Kapoor *et al.* showed no differences in procedural stroke or MI, whilst Aziz *et al.* showed no difference in MI, and stroke at maximum follow-up. In both studies angina relief was significantly greater after CABG than after PCI, and following on from this, repeat revascularization was significantly less after CABG than after PCI; with results maintained to 5 years in Kapoor *et al.*'s study (7.3% vs. 33.5%, p <0.0001). Results from both studies showed that no significant difference in survival amongst patients assigned to either CABG or PCI, this extending out to 5 years in Kapoor *et al.*'s study. The excellent long-term prognosis of both treatments is further enhanced following the publication of Goy *et al.*'s randomized study comparing bare-metal stenting with LIMA grafting for proximal LAD lesions, which showed no mortality difference at 10-year follow-up (PCI 8% vs. CABG 4%; p = 0.4)[43].

So what can be concluded from the evidence presented? Many clinicians would have no hesitation for contemplating PCI for a single-vessel lesion (excluding proximal LAD) and registry data would support that in the current absence of randomized data—which is unlikely to ever be available. With regards proximal LAD lesions, data has shown no significant difference in mortality between PCI and CABG (up to 10 years) and the final decision should therefore be influenced by other factors such as patient preference, operator skill, and lesion characteristics.

Bifurcation lesions

Coronary artery bifurcations are at an increased risk for the development of coronary atherosclerosis because of turbulent flow and low shear stress, and have long posed a problem for interventional cardiologists. Despite advances in PCI they are associated with higher rates of MACE, restenosis, and a lower probability of success when compared to single-vessel intervention. Currently there is no randomized data comparing the treatment of patients with only bifurcation lesions between PCI and CABG; however, 1310 patients (657

CABG, 653 PCI), comprising 72.8% of the total cohort in the SYNTAX study had a bifurcation lesion.

Of the previous published studies most specified the number of vessels diseased, as opposed to the precise lesion type, and therefore did not include a separate subset of patients with bifurcation lesions, or report the percentage of lesions which were bifurcation lesions. The ARTS-II study did have a bifurcation subset which comprised approximately 34% of the total cohort; however the study compared PCI in these patients with PCI in non-bifurcation lesions. The results showed no significant difference in 1-year MACCE between PCI in the bifurcation and non-bifurcation lesions (13.3% vs. 11.0%, p = 0.46)[44]; which is comparable with the MACCE in the surgical arm of ARTS-I (12.2%), which included 188 (31%) patients who had bifurcation lesions[15].

There is a lack of randomized data at present to point to whether PCI or CABG is appropriate for non-LMS bifurcation lesions; however interventionalists are moving away from mandatory complex bifurcation stenting techniques towards the provisional T-stenting techniques[45] in view of recent studies showing similar outcomes between the two techniques, and only a low requirement of side-branch stenting in the single-stent strategy[46]. This is important as some would argue that bifurcation lesions should simply be regarded as high-risk single-vessel lesions, and treated accordingly, whilst being aware of the extent of the myocardium at risk, i.e. how large and important is the side branch? The ARTS-II data show similar MACCE in dealing with bifurcation lesions compared to a surgical cohort, and therefore the decision with regards revascularization technique should be based on the same arguments as previously discussed with SVD, namely patient preference, operator skill, lesion characteristic, and extent of myocardium at risk.

Chronic total occlusions

Chronic total occlusions remain the most challenging aspect of a complete revascularization strategy. They are present in up to 20% of patients but their procedural success rate has been the lowest of all interventional procedures, 60–70% (with conventional techniques), and reaches 98% on the second attempt only in most experienced hands[47]. Use of novel techniques such as retrograde technique[48], dedicated wires (Miracle series and Confienza), smaller balloons with very low crossing profiles (1mm in diameter) and other dedicated devices (Tornus, laser and blunt dissection devices) has improved acute procedural success, however, it has not reduced the likelihood of complications (such as perforation and dissection).

Multidetector CT has been very helpful in predicting interventional success as the assessment of lesion length and degree of calcification is more accurate than with angiography[49]. Even with better acute outcomes, long-term patency of chronic total occlusions remains low and has improved only somewhat with the use of DES[50–52]. In the PRISON II trial restenosis rates in chronic total occlusion lesions were 11% with sirolimus-eluting stents and 41% with BMS (p = 0.001)[50]. The ability to achieve complete revascularization in patients with a combination of MVD and chronic total occlusion whilst challenging is also of the utmost importance as it confers a long-term survival benefit[53–55].

Diabetes

Diabetic patients present a particular challenge for all revascularization strategies given the extent of their coronary disease, its aggressive nature, and other comorbidities. The long-term survival in diabetics after both PCI and CABG is lower than in non-diabetics[56,57]. Until recently, based on BARI trial experience where mortality was 19% with CABG and 35% with PCI in diabetics (HR 1.87; p = 0.00249), CABG has usually been advocated as the preferred revascularization strategy for diabetic patients. However, as BMS and DES were introduced the mortality difference between CABG and PCI has been eliminated, and now only the difference in the need for repeat revascularization has remained. In the ARTS-I trial amongst diabetics there was no mortality difference between PCI with BMS, and CABG (6.3 vs. 3.1%; p = 0.294); however, there was a 20% absolute difference in freedom from repeat revascularization in favour of CABG. The 3-year follow-up of the ARTS-II trial looking at outcomes in diabetic patients showed that this difference in freedom from MACCE and target-vessel revascularization has narrowed significantly since the introduction of DES, such that there was no significant difference between the MACCE in ARTS-II and the CABG arm of ARTS-I (p = 0.09). The incidence of death, CVA, and MI was significantly lower in ARTS-II than in ARTS-I PCI (adjusted OR, 0.67; 95% CI, 0.27–1.65) and was similar to that of ARTS-I CABG[25]. The analysis of this and other similar trials has been limited by the post hoc nature of the substudy.

The first dedicated trial of CABG versus PCI in diabetics using 70% DES was recently published[33]. As previously noted, there was no difference in the primary outcome of MACE at 1 year (Fig. 14.4). Overall repeat revascularization was higher in the stenting group (9.9% vs. 2%) and also in the DES subgroup compared to the CABG group, but the absolute difference has

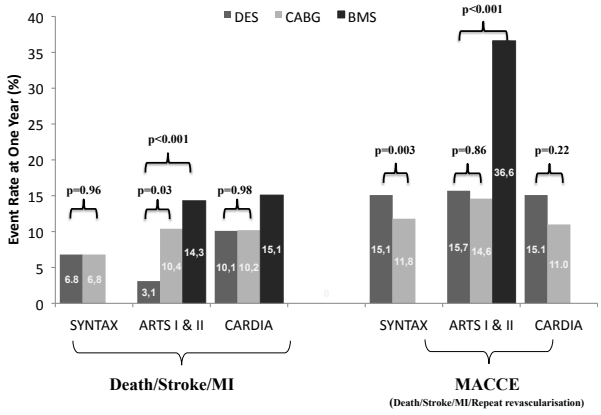


Fig. 14.4 The combined rates of death, stroke, and MI, and MACCE (death, stroke, MI, and repeat revascularization with either PCI or CABG) at 1 year amongst diabetic patients from ARTS-I, ARTS-II, CARDIA, and SYNTAX studies. From the limited data available there is an improvement in events with the use of drug-eluting stents, but repeat revascularization is still a prominent problem; however, matters appears to be improving.

narrowed to only 7% in favour of CABG. With further improvements in DES technology, this difference is likely to become even smaller, and the higher incidence of stroke in diabetic patients undergoing CABG may offset its benefit in terms of lower repeat revascularization rates.

Chronic renal insufficiency

Chronic renal insufficiency often complicates diabetes and is also a risk factor for accelerated CAD. In addition, patients with moderate renal insufficiency are at risk for worsening of disease both after contrast administration during complex PCI and during CABG. To our knowledge the only study to date that looked specifically at long-term outcomes of patients with moderate renal disease is ARTS-I[58]. At 5 years, there was no significant difference between the two groups in terms of mortality (14.5% vs. 12.3%, p = 0.81), or combined endpoint of death, cerebrovascular accident, or MI (30.4% in the stent group vs. 23.3% in the CABG group, p = 0.35). The rate of repeat revascularization was 18.8% in the stent group and 8.2% in the surgery group (p = 0.08). The event-free survival at 5 years was 50.7% in the stent group and 68.5% in the surgery group (p = 0.04). Larger prospective analysis of these patients with and without concomitant diabetes will be helpful in determining the relative risks of the two revascularization approaches.

Low and high body mass index (BMI) or the obesity paradox

Another group of patients that probably merits further investigation is the underweight and overweight group. In ARTS-I trial obese patients treated with bypass surgery had a significant advantage over low BMI patients in terms of freedom from MACE and repeat revascularization[59]. For patients who had been randomized to undergo CABG, there was a significant decrease in repeat revascularization procedures in obese patients (p = 0.03). Major adverse cardiac or cerebrovascular event rates were significantly lower for patients who were obese (11%) or overweight (16%) compared with patients who had a normal BMI (24%; p = 0.008). No such effect of BMI was observed on outcomes of treatment with stents. In the ARTS-II trial, BMI had no effect on outcomes of stenting with sirolimus-eluting stents[60]. These results contrast with findings of the BARI trial where obesity conferred significant increased risk in the surgical group[61,62]. On the other hand another found a U-shaped relationship with a BMI of 30 being optimal[63].

Risk–benefit and cost–benefit analysis of choosing between PCI and CABG

Whilst clinical trial evidence shows that both CABG and PCI increase health-related quality of life (HRQL), in the long term CABG has a greater HRQL, and lower repeat revascularization rate, especially compared to bare-metal stenting[64]. This deferred benefit, however, occurs at the expense of higher morbidity and delayed relief from pain in the time period immediately post procedure. Thus a decision regarding the procedure choice for a particular patient should be carefully weighed. Recently performed analysis based on ARTS study data using risk–benefit acceptability curve (RBAC), showed that the average patient has a risk of 0.7 for an additional revascularization procedure during

the 3-year period after the index PCI procedure, in exchange for being pain free within 1 month of the initial treatment. Specifically, there is a risk of 0.96 clinical events at 3 years, including a risk of 0.57 for repeat PCIs and 0.33 for additional CABG events[65]. Similar analysis further stratified by other patient characteristics such as SYNTAX score will need to be performed in the current DES era. The SYNTAX trial may raise a further issue of the increased risk of stroke in CABG patients in exchange for the higher risk of repeat revascularization events with PCI[31].

Assuming the advantageous risk–benefit ratio, the issue of cost-effectiveness of the PCI versus CABG is an important one from a societal standpoint. In the BARI trial initial PCI costs were lower than CABG costs, however, at 5-year follow-up given the need for repeat procedures in the PCI group the cost difference has narrowed. At 10–12 years there was no economic advantage of one procedure over the other[66]. In the ARTS-I trial at 1 year PCI was less expensive, however, at 3 years whilst a cost saving was still present, it was significantly reduced in the stent arm due to repeat procedures[64]. Similar cost analysis will be needed in the SYNTAX and FREEDOM trials given the high costs of DES, and often wide spread use of glycoprotein IIb/IIIa inhibitors and novel antithrombin agents in the PCI arm.

Summary

A large proportion of patients with CAD have stable symptoms. Patients must undergo risk stratification using available resources and expertise to determine who requires additional revascularization. In those deemed low risk, symptoms can be appropriately controlled with medication with no detriment to long-term prognosis. Those patients who are high risk, or not controlled with medical therapy, should undergo revascularization, although the ideal form of revascularization is yet to be determined.

Whilst over the last decade we have accumulated a lot of evidence regarding outcomes of PCI versus CABG in the treatment of MVD, it is only recently that trials such as SYNTAX are starting to provide us with scores and tools in terms of anatomic and clinical patient characteristics that will allow us to better individualize the treatment choice for each patient. The SYNTAX score is one such tool that may facilitate better decision making in complex cases. This tool, however, still requires both retrospective and prospective validation in larger cohorts of patients.

References

1. Fox KA, Poole-Wilson P, Clayton TC, *et al.* 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial. *Lancet* 2005; **366**(9489):914–20.
2. Boden WE, O'Rourke RA, Teo KK, *et al.* Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007; **356**(15):1503–16.
3. Bucher HC, Hengstler P, Schindler C, *et al.* Percutaneous transluminal coronary angioplasty versus medical treatment for non-acute coronary heart disease: meta-analysis of randomised controlled trials. *BMJ* 2000; **321**(7253):73–7.
4. Katritsis DG, Ioannidis JP. Percutaneous coronary intervention versus conservative therapy in nonacute coronary artery disease: a meta-analysis. *Circulation* 2005; **111**(22):2906–12.
5. Henderson RA, Pocock SJ, Clayton TC, *et al.* Seven-year outcome in the RITA-2 trial: coronary angioplasty versus medical therapy. *J Am Coll Cardiol* 2003; **42**(7):1161–70.
6. Schomig A, Mehilli J, de Waha A, *et al.* A meta-analysis of 17 randomized trials of a percutaneous coronary intervention-based strategy in patients with stable coronary artery disease. *J Am Coll Cardiol* 2008; **52**(11):894–904.
7. Poole-Wilson PA, Voko Z, Kirwan B-A, *et al.* Clinical course of isolated stable angina due to coronary heart disease. *Eur Heart J* 2007; **28**(16):1928–35.
8. Ioannidis JP, Karvouni E, Katritsis DG. Mortality risk conferred by small elevations of creatine kinase-MB isoenzyme after percutaneous coronary intervention. *J Am Coll Cardiol* 2003; **42**(8):1406–11.
9. Lee MS, Pessegueiro A, Zimmer R, *et al.* Clinical presentation of patients with in-stent restenosis in the drug-eluting stent era. *J Invasive Cardiol* 2008; **20**(8):401–3.
10. Erne P, Schoenenberger AW, Burckhardt D, *et al.* Effects of percutaneous coronary interventions in silent ischemia after myocardial infarction: the SWISSI II randomized controlled trial. *JAMA* 2007; **297**(18):1985–91.
11. Fox K, Garcia MA, Ardissino D, *et al.* Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. *Eur Heart J* 2006; **27**(11):1341–81.
12. Emond M, Mock MB, Davis KB, *et al.* Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) Registry. *Circulation* 1994; **90**(6):2645–57.
13. Coles JC, Goldbach MM, Ahmed SN, *et al.* Left main-stem coronary artery disease: surgical versus medical management. *Can J Surg* 1984; **27**(6):571–3.
14. Rahimtoola SH. A perspective on the three large multicenter randomized clinical trials of coronary bypass surgery for chronic stable angina. *Circulation* 1985; **72** (6 Pt 2):V123–35.

15. Serruys PW, Unger F, Sousa JE, *et al.* Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med* 2001; **344**(15):1117–24.
16. Serruys PW, de Jaegere P, Kiemeneij F, *et al.* A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Engl J Med* 1994; **331**(8):489–95.
17. Daemen J, Ong AT, Stefanini GG, *et al.* Three-year clinical follow-up of the unrestricted use of sirolimus-eluting stents as part of the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. *Am J Cardiol* 2006; **98**(7):895–901.
18. Daemen J, Serruys PW. Optimal revascularization strategies for multivessel coronary artery disease. *Current Opin Cardiol* 2006; **21**(6):595–601.
19. Stone GW, Ellis SG, Cannon L, *et al.* Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. *JAMA* 2005; **294**(10): 1215–23.
20. Sim I, Gupta M, McDonald K, *et al.* A meta-analysis of randomized trials comparing coronary artery bypass grafting with percutaneous transluminal coronary angioplasty in multivessel coronary artery disease. *Am J Cardiol* 1995; **76**(14):1025–9.
21. Pocock SJ, Henderson RA, Rickards AF, *et al.* Meta-analysis of randomised trials comparing coronary angioplasty with bypass surgery. *Lancet* 1995; **346**(8984):1184–9.
22. Daemen J, Boersma E, Flather M, *et al.* Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. *Circulation* 2008; **118**(11): 1146–54.
23. Serruys PW, Ong AT, van Herwerden LA, *et al.* Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. *J Am Coll Cardiol* 2005; **46**(4):575–81.
24. Mercado N, Wijns W, Serruys PW, *et al.* One-year outcomes of coronary artery bypass graft surgery versus percutaneous coronary intervention with multiple stenting for multisystem disease: a meta-analysis of individual patient data from randomized clinical trials. *J Thorac Cardiovasc Surg* 2005; **130**(2):512–19.
25. Daemen J, Kuck KH, Macaya C, *et al.* Multivessel coronary revascularization in patients with and without diabetes mellitus 3-year follow-up of the ARTS-II (Arterial Revascularization Therapies Study-Part II) trial. *J Am Coll Cardiol* 2008; **52**(24):1957–67.
26. Hannan EL, Racz MJ, Walford G, *et al.* Long-term outcomes of coronary-artery bypass grafting versus stent implantation. *N Engl J Med* 2005; **352**(21):2174–83.
27. Daemen J, Serruys PW. Lessons from the unrestricted use of drug-eluting stents: Insights from the RESEARCH and T-SEARCH Registry. *Indian Heart J* 2006; **58**(1):10–14.
28. Serruys PW, Ong ATL, Morice MC, *et al.* Arterial Revascularisation Therapies Study Part II- Sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. *EuroIntervention* 2005; **1**(2):147–56.
29. Rodriguez AE, Maree AO, Mieres J, *et al.* Late loss of early benefit from drug-eluting stents when compared with bare-metal stents and coronary artery bypass surgery: 3 years follow-up of the ERACI III registry. *Eur Heart J* 2007; **28**(17):2118–25.
30. Javaid A, Steinberg DH, Buch AN, *et al.* Outcomes of coronary artery bypass grafting versus percutaneous coronary intervention with drug-eluting stents for patients with multivessel coronary artery disease. *Circulation* 2007; **116**(11 Suppl):I200–6.
31. Serruys PW, Morice MC, Kappetein AP, *et al.* Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009; **360**(10):961–72.
32. Sianos G, Morel MA, Kappetein AP, *et al.* The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention* 2005; **1**:219–27.
33. Kapur A, Hall R, Malik I, *et al.* Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. *JACC* 2010; **55**(5):432–40.
34. Berger A, Botman KJ, MacCarthy PA, *et al.* Long-term clinical outcome after fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. *J Am Coll Cardiol* 2005; **46**(3):438–42.
35. Tonino PA, De Bruyne B, Pijls NH, *et al.* Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009; **360**(3): 213–24.
36. Hannan EL, Racz MJ, McCallister BD, *et al.* A comparison of three-year survival after coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol* 1999; **33**(1):63–72.
37. Chaitman BR, Ryan TJ, Kronmal RA, *et al.* Coronary Artery Surgery Study (CASS): comparability of 10 year survival in randomized and randomizable patients. *J Am Coll Cardiol* 1990; **16**(5):1071–8.
38. Karthik S, Fabri BM. Left internal mammary artery usage in coronary artery bypass grafting: a measure of quality control. *Ann R Coll Surg Engl* 2006; **88**(4):367–9.
39. Cameron A, Davis KB, Green G, *et al.* Coronary bypass surgery with internal-thoracic-artery grafts – effects on survival over a 15-year period. *N Engl J Med* 1996; **334**(4):216–19.
40. Loop FD, Lytle BW, Cosgrove DM, *et al.* Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events. *N Engl J Med* 1986; **314**(1):1–6.
41. Kapoor JR, Gienger AL, Ardehali R, *et al.* Isolated disease of the proximal left anterior descending artery: comparing

the effectiveness of percutaneous coronary interventions and coronary artery bypass surgery. *J Am Coll Cardiol Intv* 2008; **1**(5):483–91.

42. Aziz O, Rao C, Panesar SS, *et al.* Meta-analysis of minimally invasive internal thoracic artery bypass versus percutaneous revascularisation for isolated lesions of the left anterior descending artery. *BMJ* 2007; **334**(7594):617.
43. Goy JJ, Kaufmann U, Hurni M, *et al.* 10-year follow-up of a prospective randomized trial comparing bare-metal stenting with internal mammary artery grafting for proximal, isolated de novo left anterior coronary artery stenosis: the SIMA (Stenting versus Internal Mammary Artery grafting) Trial. *J Am Coll Cardiol* 2008; **52**(10):815.
44. Tsuchida K, Colombo A, Lefevre T, *et al.* The clinical outcome of percutaneous treatment of bifurcation lesions in multivessel coronary artery disease with the sirolimus-eluting stent: insights from the Arterial Revascularization Therapies Study part II (ARTS II). *Eur Heart J* 2007; **28**(4):433–42.
45. Morice M-C. Bifurcation lesions: a never-ending challenge. *Eur Heart J* 2008; **29**(23):2831–2.
46. Steigen TK, Maeng M, Wiseth R, *et al.* Randomized Study on Simple Versus Complex Stenting of Coronary Artery Bifurcation Lesions: The Nordic Bifurcation Study. *Circulation* 2006; **114**(18):1955–61.
47. Hoye A, Onderwater E, Cummins P, *et al.* Improved recanalization of chronic total coronary occlusions using an optical coherence reflectometry-guided guidewire. *Catheter Cardiovasc Interv* 2004; **63**(2):158–63.
48. Kukreja N, Serruys PW, Sianos G. Retrograde recanalization of chronically occluded coronary arteries: illustration and description of the technique. *Catheter Cardiovasc Interv* 2007; **69**(6):833–41.
49. Mollet NR, Hoye A, Lemos PA, *et al.* Value of preprocedure multislice computed tomographic coronary angiography to predict the outcome of percutaneous recanalization of chronic total occlusions. *Am J Cardiol* 2005; **95**(2):240–3.
50. Suttorp MJ, Laarman GJ, Rahel BM, *et al.* Primary Stenting of Totally Occluded Native Coronary Arteries II (PRISON II): a randomized comparison of bare metal stent implantation with sirolimus-eluting stent implantation for the treatment of total coronary occlusions. *Circulation* 2006; **114**(9):921–8.
51. Ge L, Iakovou I, Cosgrave J, *et al.* Immediate and mid-term outcomes of sirolimus-eluting stent implantation for chronic total occlusions. *Eur Heart J* 2005; **26**(11):1056–62.
52. Lotan C, Almagor Y, Kuiper K, *et al.* Sirolimus-eluting stent in chronic total occlusion: the SICTO study. *J Interv Cardiol* 2006; **19**(4):307–12.
53. Valenti R, Migliorini A, Signorini U, *et al.* Impact of complete revascularization with percutaneous coronary intervention on survival in patients with at least one chronic total occlusion. *Eur Heart J* 2008; **29**(19):2336–42.
54. Suero JA, Marso SP, Jones PG, *et al.* Procedural outcomes and long-term survival among patients undergoing percutaneous coronary intervention of a chronic total occlusion in native coronary arteries: a 20-year experience. *J Am Coll Cardiol* 2001; **38**(2):409–14.
55. Aziz S, Stables RH, Grayson AD, *et al.* Percutaneous coronary intervention for chronic total occlusions: improved survival for patients with successful revascularization compared to a failed procedure. *Catheter Cardiovasc Interv* 2007; **70**(1):15–20.
56. Niles NW, McGrath PD, Malenka D, *et al.* Survival of patients with diabetes and multivessel coronary artery disease after surgical or percutaneous coronary revascularization: results of a large regional prospective study. Northern New England Cardiovascular Disease Study Group. *J Am Coll Cardiol* 2001; **37**(4):1008–15.
57. Detre KM, Guo P, Holubkov R, *et al.* Coronary revascularization in diabetic patients: a comparison of the randomized and observational components of the Aypass Angioplasty Revascularization Investigation (BARI). *Circulation* 1999; **99**(5):633–40.
58. Aoki J, Ong AT, Hoye A, *et al.* Five year clinical effect of coronary stenting and coronary artery bypass grafting in renal insufficient patients with multivessel coronary artery disease: insights from ARTS trial. *Eur Heart J* 2005; **26**(15):1488–93.
59. Gruberg L, Mercado N, Milo S, *et al.* Impact of body mass index on the outcome of patients with multivessel disease randomized to either coronary artery bypass grafting or stenting in the ARTS trial: The obesity paradox II? *Am J Cardiol* 2005; **95**(4):439–44.
60. Khattab AA, Daemen J, Richardt G, *et al.* Impact of body mass index on the one-year clinical outcome of patients undergoing multivessel revascularization with sirolimus-eluting stents (from the Arterial Revascularization Therapies Study Part II). *Am J Cardiol* 2008; **101**(11):1550–9.
61. Gurm HS, Brennan DM, Booth J, *et al.* Impact of body mass index on outcome after percutaneous coronary intervention (the obesity paradox). *Am J Cardiol* 2002; **90**(1):42–5.
62. Gurm HS, Whitlow PL, Kip KE. The impact of body mass index on short- and long-term outcomes inpatients undergoing coronary revascularization. Insights from the bypass angioplasty revascularization investigation (BARI). *J Am Coll Cardiol* 2002; **39**(5):834–40.
63. Wagner BD, Grunwald GK, Rumsfeld JS, *et al.* Relationship of body mass index with outcomes after coronary artery bypass graft surgery. *Ann Thorac Surg* 2007; **84**(1):10–16.
64. Legrand VM, Serruys PW, Unger F, *et al.* Three-year outcome after coronary stenting versus bypass surgery for the treatment of multivessel disease. *Circulation* 2004; **109**(9):1114–20.
65. Federspiel JJ, Stearns Sm Van Domburg R, *et al.* Risk-benefit trade offs in revascularisation choices. *Medical Decision Making*. In press.
66. Weintraub WS, Becker ER, Mauldin PD, *et al.* Costs of revascularization over eight years in the randomized and

eligible patients in the Emory Angioplasty versus Surgery Trial (EAST). *Am J Cardiol* 2000; **86**(7):747–52.
67. Underwood SR, Anagnostopoulos C, Cerqueira M, *et al.* Myocardial perfusion scintigraphy: the evidence. *Eur J Nucl Med Mol Imaging* 2004; **31**(2):261–91.
68. Mark DB, Hlatky MA, Harrell FE, Jr., *et al.* Exercise treadmill score for predicting prognosis in coronary artery disease. *Ann Intern Med* 1987; **106**(6):793–800.
69. First-year results of CABRI (Coronary Angioplasty versus Bypass Revascularisation Investigation). CABRI Trial Participants. *Lancet* 1995; **346**(8984):1179–84.
70. Rodriguez A, Mele E, Peyregne E, *et al.* Three-year follow-up of the Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty Versus Coronary Artery Bypass Surgery in Multivessel Disease (ERACI). *J Am Coll Cardiol* 1996; **27**(5): 1178–84.
71. Henderson RA, Pocock SJ, Sharp SJ, *et al.* Long-term results of RITA-1 trial: clinical and cost comparisons of coronary angioplasty and coronary-artery bypass grafting. *Lancet* 1998; 352(9138):1419–25.
72. King SB, III, Kosinski AS, Guyton RA, *et al.* Eight-year mortality in the Emory Angioplasty versus Surgery Trial (EAST). *J Am Coll Cardiol* 2000; 35(5):1116–21.
73. The final 10-year follow-up results from the BARI randomized trial. *J Am Coll Cardiol* 2007; **49**(15): 1600–6.
74. Kaehler J, Koester R, Billmann W, *et al.* 13-year follow-up of the German angioplasty bypass surgery investigation. *Eur Heart J* 2005; **26**(20):2148–53.
75. Morrison DA, Sethi G, Sacks J, *et al.* Percutaneous coronary intervention versus repeat bypass surgery for patients with medically refractory myocardial ischemia: AWESOME randomized trial and registry experience with post-CABG patients. *J Am Coll Cardiol* 2002; **40**(11):1951–4.
76. Rodriguez AE, Baldi J, Pereira CF, *et al.* Five-Year Follow-Up of the Argentine Randomized Trial of Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients With Multiple Vessel Disease (ERACI II). *J Am Coll Cardiol* 2005; **46**(4):582–8.
77. Hueb W, Lopes NH, Gersh BJ, *et al.* Five-year follow-up of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. *Circulation* 2007; **115**(9):1082–9.
78. Booth J, Clayton T, Pepper J, *et al.* Randomized, controlled trial of coronary artery bypass surgery versus percutaneous coronary intervention in patients with multivessel coronary artery disease: six-year follow-up from the Stent or Surgery Trial (SoS). *Circulation* 2008; **118**(4):381–8.

Part II

Coronary Stents

Chapter 2.1

Coronary Stents –Current Status

J Am Coll Cardiol 2010; 56(10): S1-S42

Scot Garg, Patrick W. Serruys

STATE-OF-THE-ART PAPERS

Coronary Stents

Current Status

Scot Garg, MB, ChB, Patrick W. Serruys, MD, PhD

Rotterdam, the Netherlands

Coronary artery stents revolutionized the practice of interventional cardiology after they were first introduced in the mid-1980s. Since then, there have been significant developments in their design, the most notable of which has been the introduction of drug-eluting stents. This paper reviews the benefits, risks, and current status of Food and Drug Administration-approved drug-eluting stents. (J Am Coll Cardiol 2010;56:S1–42) © 2010 by the American College of Cardiology Foundation

In 1964, Charles Theodore Dotter and Melvin P. Judkins described the first angioplasty (1). Thirteen years later, Andreas Grüntzig performed the first balloon coronary angioplasty (2), a revolutionary treatment that lead to the birth of a new specialty, interventional cardiology. Since that first procedure, there have been extensive developments and advances that have culminated in percutaneous coronary intervention (PCI) being 1 of the most frequently performed invasive medical procedures in clinical practice today.

Coronary stents, which were first developed in the mid-1980s (3), have ultimately replaced "plain old balloon angioplasty" (POBA) as the preferred method of performing PCI, after the observed improvements in angiographic and clinical outcomes seen with their use (4,5). The majority of PCI procedures now involve a coronary stent, and therefore, interventional cardiologists are faced with a wide choice of coronary stents to implant. This choice ranges from conventional bare-metal stents (BMS) and drug-eluting stents (DES) that are widely used in contemporary practice to newer stents such as DES with biodegradable polymers, DES that are polymer-free, DES with novel coatings, dedicated bifurcation stents, self-expanding stents, and biodegradable stents.

Part 1 of this review discusses the current status of coronary stents and examines some of the unresolved issues surrounding their implantation in contemporary practice. Part 2 will review the vast array of new coronary stents that are currently undergoing evaluation in pre-clinical and clinical trials.

From the Department of Interventional Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands. Drs. Garg and Serruys report that they have no relationships to disclose.

Manuscript received December 9, 2009; revised manuscript received June 1, 2010, accepted June 15, 2010.

The Need for Coronary Stents and the Early Period

There is no dispute that POBA was a pioneering treatment; however, its success was hindered by the problems of acute vessel closure and restenosis (4–6). These problems lead to the development of a second revolutionary treatment, the coronary stent, which was first implanted by Sigwart et al. (3) in 1986 (Fig. 1) (7). This bare metal, self-expanding stent, known as the "Wall" stent was able to provide a scaffold that prevented acute vessel closure and late constrictive recoil (3). Although these initial stents proved effective as "bailout" devices in cases of abrupt or threatened vessel closure, thereby reducing rates of emergency coronary artery bypass surgery (CABG) (8), development was ultimately hampered by the risk of subacute thrombotic coronary artery occlusion, which was observed in up to 18% of cases within 2 weeks of implantation (9). This novel, stent-specific hazard prompted the use of complex anticoagulation regimens that were associated with increased bleeding and prolonged hospitalization (10). Overall, the early success and complication rates seen with these initial coronary stents were not always competitive with those of routine POBA.

Coronary stenting only became a widely accepted technique after the publication of the landmark BENESTENT (Belgian Netherlands Stent) trial (11) and the STRESS (Stent Restenosis Study) (12), together with evidence indicating that stenting was safe in the absence of anticoagulation therapy with the use of dual antiplatelet therapy (DAPT) (13–15) and/or adequate stent deployment (16).

By 1999, coronary stenting was performed in 84.2% of PCI procedures (17); however, despite their obvious advantages, there were associated problems and concerns. Most notably, and in addition to the risk of subacute thrombosis, which has already been alluded to, an iatrogenic problem emerged in the form of in-stent neointimal hyperplasia (18–20). This intrastent growth of scar tissue, which was

Abbreviations and Acronyms

ACS = acute coronary syndrome
BMS = bare-metal stent(s)
CABG = coronary artery bypass grafting
CAD = coronary artery disease
CI = confidence interval
CoCr = cobalt chromium
CTO = chronic total occlusion
DAPT = dual antiplatelet therapy
DES = drug-eluting stent(s)
EES = everolimus-eluting stent(s)
FDA = Food and Drug Administration
HR = hazard ratio
ISA = incomplete stent apposition
ISR = in-stent restenosis
IVUS = intravascular ultrasound
MACE = major adverse cardiovascular events
MI = myocardial infarction
MVD = multivessel disease
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stent(s)
POBA = plain old balloon angioplasty
RR = relative risk
SES = sirolimus-eluting stent(s)
ST = stent thrombosis
STEMI = ST-segment elevation myocardial infarction
SVG = saphenous vein graft
TLR = target lesion revascularization
TVR = target vessel revascularization
UPLMS = unprotected left main stem
ZES = zotarolimus-eluting stent(s)

the result of proliferation and migration of vascular smooth muscle cells, and as demonstrated in Figure 2 was directly linked to stent implantation, resulted in restenosis rates of 20% to 30% (21). It was the attempts to minimize this in-stent neointimal hyperplasia, and thereby reduce rates of repeat revascularization, that ultimately lead to the development of another revolutionary treatment: the DES. The dramatic reduction in restenosis rates seen with the use of these DES compared with BMS (22–26) has been the major driving force behind the exponential growth of PCI as a treatment for patients with coronary artery disease (CAD). After the outstanding results from the early pivotal trials with DES, there was an increased confidence to use PCI, so that its use has expanded to lesions subsets that were only previously considered suitable for CABG (27–29). This increased confidence lead to a rapid and unprecedented uptake in their use, so that by 2005, 80% to 90% of all revascularization procedures in the U.S. were performed using a DES (30). In 2006, concerns were raised over the safety profile of these stents (31–33), resulting in an immediate worldwide downturn in their use. These concerns proved a vital stimulus to focus research, and have ultimately lead to the development of newer stents and improved safety, resulting in a resurgence in the use of DES; however, current rates (~75%) are still below those of 2005 (34).

DES Initial Phase: "The Rosy Period"

Sirolimus-eluting stents (SES). In the late 1990s, numerous preclinical studies reported that sirolimus (previously called rapamycin), a macrolide antibiotic that was approved for use as an immunosuppressant to prevent organ rejection, was able to inhibit the cytokine- and growth-factor–mediated proliferation of lymphocytes and smooth muscle cells, resulting in reduced neointimal proliferation (Fig. 3) (35–38). Despite its promise, problems remained over the ability to locally deliver sirolimus at an appropriate and sustained concentration necessary to inhibit neointimal proliferation. Failures with both oral administration and local delivery using special delivery balloons led to the development of a coronary stent with a drug coating, the DES. The first human DES implant was performed by J. Eduardo Sousa in Sao Paulo in December 1999 at the start of the 2 first-in-man studies that recruited a total of 45 patients and reported minimal in-stent neointimal proliferation through to 12-month follow-up (39–41). This research culminated in the development and commercial launch of the stainless steel Cypher SES (Cordis, Warren, New Jersey), the specification of which is summarized in Table 1. The Cypher SES was initially evaluated in the pivotal RAVEL (Randomized Study With the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions) study, which randomly assigned 238 patients with relatively low risk lesions to treatment with the Cypher SES or BMS controls. At 1-year follow-up, the rate of binary stenosis was 0.0% and 26.6% for patients treated with Cypher SES and BMS, respectively (42). These results were subsequently confirmed in the much larger SIRIUS (Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions) trial that enrolled 1,058 patients with more complex lesions than were seen in the RAVEL study. This study again demonstrated significantly lower rates of target lesion revascularization (TLR) and major adverse cardiovascular events (MACE) after treatment with the Cypher SES compared with BMS controls at 9-month, 2-year, and now 5-year follow-up (43–45).

After these initial randomized studies, which ultimately lead to regulatory approval, the performance of the Cypher stent has been assessed in: 1) different patient types, for example, diabetic patients; 2) different clinical settings, including primary PCI for ST-segment elevation myocardial infarction (STEMI); and 3) different lesion types including chronic total occlusions (CTO), saphenous vein grafts (SVG), small coronary vessels, and complex lesions. The results of the most important randomized controlled trials comparing SES and BMS in these different clinical settings are summarized in Table 2 (42–75). As clearly demonstrated, when compared with BMS, the use of SES results in significant reductions in angiographic in-stent late loss, in-stent angiographic (binary) restenosis, and repeat revascularization at both short- and long-term follow-up, with results consistent across numerous different patient and lesion types. Furthermore, meta-analyses of patient data from the initial approval trials reaffirms the sustained advantage of SES over BMS in terms of reduced repeat revascularization, together with comparable rates of death and myocardial infarction (MI) at long-term follow-up (Table 3) (22–26,76).

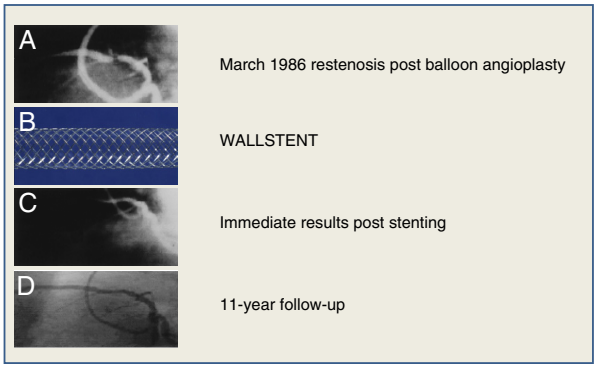


Figure 1 **First Human Coronary Stent Implantation, March 1986**

(A) A restenotic lesion after balloon angioplasty. **(B)** The self-expanding WALLSTENT. **(C)** Immediate results after stenting. **(D)** Angiographic results at 11-year follow-up. Reproduced with permission from Carrie et al. (7).

In addition to randomized data, registries have evaluated the performance of the Cypher stent in the setting of the real-world. The first of these registries was the single-center RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) registry, which enrolled 508 consecutive patients who were treated with the Cypher SES irrespective of lesion complexity. Running concurrently with the RESEARCH registry was the multicenter ARTS-II (Arterial Revascularization Therapies Study) registry, which assessed the Cypher stent in 607 patients with 2- and 3-vessel CAD. Results from both registries at short- and long-term follow-up, which now extends to 4 and 5 years,

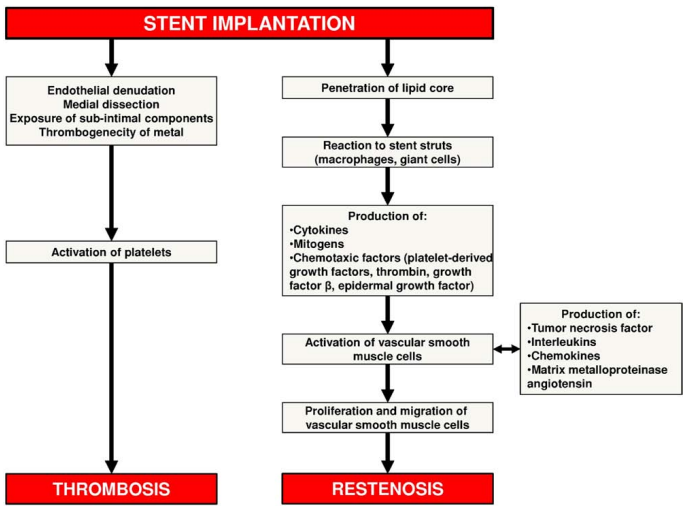


Figure 2 **Pathway Leading to In-Stent Restenosis After Stent Implantation**

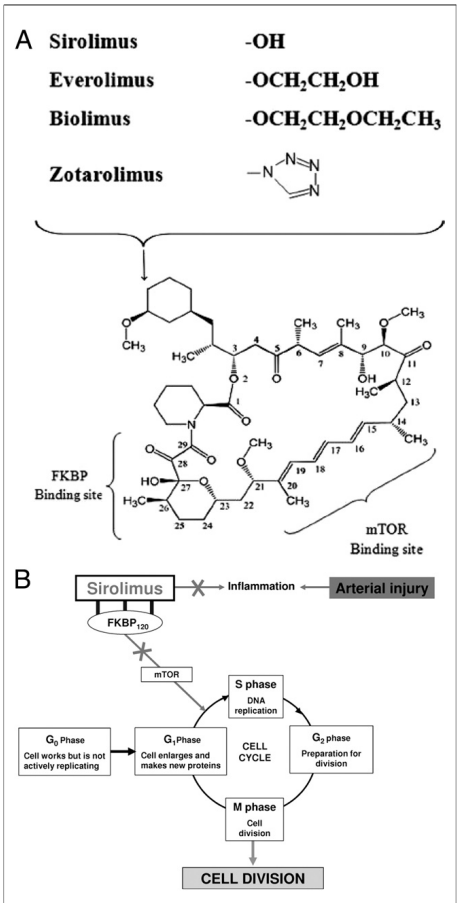


Figure 3 Sirolimus

(A) The chemical structure of the macrocylic lactone group of antiproliferative drugs. **(B)** The mode of action of sirolimus: sirolimus binds to the FK-binding protein 12 (FKBP12), which in turn inhibits the mammalian target of rapamycin (mTOR) pathway. This subsequently prevents the downregulation of the cell division kinase inhibitor $p27^{kip1}$, thereby inhibiting cell division between phases G1 and S1 of the cell cycle. Sirolimus has a wide dose range, is cytostatic as opposed to cytotoxic, and has additional anti-inflammatory properties through its inhibition of interleukin-2, which reduces T- and B-cell activation. DNA = deoxyribonucleic acid.

respectively, for the RESEARCH and ARTS-II registries (Fig. 4) (77), mirrors those from other registries and the previously noted randomized studies and meta-analyses, by continuing to demonstrate significantly lower rates of

Table 1 Specifications of the Food and Drug Administration-Approved Drug-Eluting Stents

Stent	Drug (Concentration [$\mu g/cm^2$])	Drug Mechanism	Polymer	Polymer Thickness, μm	Release Kinetics, 28 Days	Metal	Geometry	Strut Thickness, μm	Crimped Profile, mm*	Maximum Cell C/D, mm*
CYPHER	Sirolimus (140)	Inhibits mTOR, cytostatic	Polyethelyne co-vinyl acetate and poly-n-butyl methacrylate	12.6	80%	SS	Closed cell	140	1.198	9.5/3.0
TAXUS Express	Paclitaxel (100)	Microtubule inhibitor, cell cycle arrest in G0/G1 and G2/M	Poly(styrene-b-isobutylene-b-styrene)	16.0	<10%	SS	Open cell	132	1.245	11.9/3.8
TAXUS Liberté	Paclitaxel (100)	Microtubule inhibitor, cell cycle arrest in G0/G1 and G2/M	Poly(styrene-b-isobutylene-b-styrene)	16.0	<10%	SS	Hybrid	97	1.219	13.7/4.4
Endeavor	Zotarolimus (100)	Inhibits mTOR, cytostatic	Phosphorylcholine	4.1	95%†	CoCr	Open cell	91	1.130	19.8/6.3
Xience V	Everolimus (100)	Inhibits mTOR, cytostatic	Polyvinylidene fluoride co-hexafluoropropylene and poly-n-butyl methacrylate	7.6	80%	CoCr	Open cell	81	1.055	12.6/4.0

*Based on a 3-mm stent. †Drug release at 14 days.
C/D = circumference/diameter; CoCr = cobalt chromium; mTOR = mammalian target of rapamycin; SS = stainless steel.

Table 2 Summary of Major Randomized Trials of SES Versus BMS in Different Clinical Settings

Trial or First Author (Ref. #)	No. of Patients	Clinical Setting	Follow-Up, Months	In-Stent Late Loss (SES vs.), mm	Binary In-Stent Restenosis (SES vs.), %	MACE (SES vs.), %	Death (SES vs.), %	MI (SES vs.), %	TLR (SES vs.), %	Definite/ Probable ST (SES vs.), %
RAVEL (42,46)	SES (n = 120) vs. BMS (n = 118)	Elective simple lesions	6*/12†	−0.01 vs. 0.80‡	0.0 vs. 26.6‡	5.8 vs. 28.8‡	1.7 vs. 1.7	3.3 vs. 4.2	0.0 vs. 23.7§	0.0 vs. 1.7
			60	NA	NA	25.8 vs. 35.2§	12.1 vs. 7.1	8.9 vs. 6.9	10.3 vs. 26.0‡	1.7 vs. 2.5
C-SIRIUS (47)	SES (n = 50) vs. BMS (n = 50)	Canadian approval trial	8*/9†	0.12 vs. 1.02‡	0.0 vs. 45.5‡	4.0 vs. 18.0	0.0 vs. 0.0	2.0 vs. 4.0	4.0 vs. 18.0‖	2.0 vs. 2.0
E-SIRIUS (48)	SES (n = 175) vs. BMS (n = 177)	Elective long lesions, small vessels, overlapped stents	8*/9†	0.20 vs. 1.05‡	3.9 vs. 41.7‡	8.0 vs. 22.6‡	1.1 vs. 0.6	4.6 vs. 2.3	4.0 vs. 20.9‡	1.1 vs. 0.0
SIRIUS (43,45)	SES (n = 163) vs. BMS (n = 159)	U.S. pivotal approval trial	8*/12†	0.17 vs. 1.00‡	3.2 vs. 35.4‡	8.3 vs. 23.2‡	1.3 vs. 0.8	3.0 vs. 4.2	4.9 vs. 20.2‡‖	0.4 vs. 1.1
			60	NA	NA	20.3 vs. 33.5‡	8.4 vs. 8.4	6.2 vs. 6.5	9.4 vs. 24.2‡‖	1.2 vs. 1.8
DIABETES (49,51)	SES (n = 80) vs. BMS (n = 80)	Diabetes	9*/24†	0.09 vs. 0.67‡	3.9 vs. 31.7‡	12.8 vs. 41.3‡¶	2.6 vs. 3.8¶	3.8 vs. 8.8	7.7 vs. 35.0‡‖	3.8 vs. 2.5#
			48	NA	NA	NA	4.1 vs. 6.5¶	4.1 vs. 10.4	8.1 vs. 37.7‡	3.8 vs. 3.8#
DESSERT (52)	SES (n = 75) vs. BMS (n = 75)	Diabetes	8*/12†	0.14 vs. 0.96‡	3.6 vs. 38.8‡	22.1 vs. 44.0§	4.4 vs. 2.9	16.2 vs. 20.0	5.9 vs. 30.0‡	1.4 vs. 1.5
SCORPIUS (53)	SES (n = 98) vs. BMS (n = 102)	Diabetes	8*/12†	0.22 vs. 0.99‡	8.8 vs. 42.1‡	NA	5.3 vs. 4.1	4.3 vs. 5.2	5.3 vs. 21.1‡	2.1 vs. 2.1
Diaz de la Llera et al. (54)	SES (n = 60) vs. BMS (n = 60)	STEMI	12	NA	NA	6.7 vs. 11.1	5.0 vs. 3.6	6.7 vs. 5.4 (Death+MI)	0.0 vs. 5.7**	3.4 vs. 1.8#
MISSION! (55,56)	SES (n = 158) vs. BMS (n = 152)	STEMI	9*/12†	0.19 vs. 0.95‡	2.3 vs. 22.6‡	NA	1.3 vs. 2.6	5.7 vs. 9.2	3.2 vs. 11.2§	1.3 vs. 2.0
			36	NA	NA	NA	4.4 vs. 6.6	7.6 vs. 11.2	6.3 vs. 12.5	3.1 vs. 2.0
PASEO (57,58)	SES (n = 90) vs. BMS (n = 90)	STEMI	12	NA	NA	11.1 vs. 24.4§	3.3 vs. 6.7	4.4 vs. 6.7	3.3 vs. 14.4§	0.0 vs. 1.1††
			48	NA	NA	36.7 vs. 21.1§	7.8 vs. 12.2	8.9 vs. 13.3	5.6 vs. 21.1§	1.1 vs. 2.2††
SESAMI (59,60)	SES (n = 160) vs. BMS (n = 160)	STEMI	12	0.18 vs. 0.85§	9.3 vs. 21.3§	6.8 vs. 16.8§	1.8 vs. 4.3	1.8 vs. 1.8	4.3 vs. 11.2§‖	1.2 vs. 0.6††
			36	NA	NA	12.7 vs. 21.0§	3.2 vs. 5.0	2.5 vs. 2.5	7.0 vs. 13.5§‖	1.9 vs. 1.3††
STRATEGY (61,62)	SES (n = 87) vs. BMS (n = 88)	STEMI	8	0.22 vs. 0.60‡	7.5 vs. 28§	18.4 vs. 31.8§	8.0 vs. 9.1	6.9 vs. 9.1	5.7 vs. 20.5§	0.0 vs. 2.3#
			60	NA	NA	29.9 vs. 43.2	18.0 vs. 16.0	22.0 vs. 25.0 (Death+MI)	10.3 vs. 26.1§**	7.0 vs. 8.0‡‡
TYPHOON (63,64)	SES (n = 355) vs. BMS (n = 357)	STEMI	8*/12†	0.14 vs. 0.83‡	3.5 vs. 20.3§	5.9 vs. 14.6‡	2.3 vs. 2.2	1.1 vs. 1.4	5.6 vs. 13.4‡‖	2.4 vs. 3.6
			48	NA	NA	NA	4.0 vs. 6.4	4.8 vs. 4.0	7.2 vs. 15.2§	4.4 vs. 4.8
Pache et al. (65)	SES (n = 250) vs. BMS (n = 250)	Elective all-comers	6*/12†	0.14 vs. 0.94‡	8.3 vs. 25.5‡	13.6 vs. 22.4§**	2.8 vs. 2.0	4.6 vs. 2.8	7.2 vs. 18.8‡**	0.8 vs. 0.4
PRISON II (66,68)	SES (n = 100) vs. BMS (n = 100)	Chronic total occlusion	6*/12†	0.05 vs. 1.09‡	7.0 vs. 36.0‡	5.0 vs. 24.0‡	0.0 vs. 1.0	2.0 vs. 3.0	5.0 vs. 21.0§	2.0 vs. 0.0‡‡
			60	NA	NA	12.0 vs. 36.0‡	5.0 vs. 5.0	8.0 vs. 7.0	12.0 vs. 30.0§	8.0 vs. 3.0‡‡
GISSOC II-GISE (69)	SES (n = 78) vs. BMS (n = 74)	Chronic total occlusion	8*/24†	0.20 vs. 1.57‡	8.2 vs. 67.7‡	17.6 vs. 50.0‡	2.7 vs. 1.3	2.7 vs. 5.1	8.1 vs. 44.9‡	1.4 vs. 1.3
SES-SMART (70,71)	SES (n = 129) vs. BMS (n = 128)	Small vessels	8	0.16 vs. 0.90‡	4.9 vs. 49.1‡	9.3 vs. 31.3‡‖§§	0.0 vs. 1.6	1.6 vs. 7.8§	7.0 vs. 21.1§‖	0.8 vs. 3.1#
			24	NA	NA	12.6 vs. 33.1‡‖§§	0.8 vs. 3.9	1.6 vs. 10.2§	7.9 vs. 29.9‡‖	0.8 vs. 3.1#
SCANDSTENT (72,73)	SES (n = 163) vs. BMS (n = 159)	Complex disease	6*/7†	0.02 vs. 1.01‡	2.0 vs. 30.6‡	4.3 vs. 29.9‡	0.6 vs. 0.6	1.2 vs. 3.1	2.5 vs. 29.3‡‖	0.6 vs. 3.8
			36	NA	NA	12.3 vs. 37.6‡	5.6 vs. 1.9	3.7 vs. 9.6	4.9 vs. 33.8‡‖	1.2 vs. 4.4
RRISC (74,75)	SES (n = 38) vs. BMS (n = 37)	Saphenous vein grafts	6	0.38 vs. 0.79§	11.3 vs. 30.6§	15.8 vs. 29.7	2.6 vs. 0.0	2.6 vs. 0.0	5.3 vs. 21.6§	0.0 vs. 0.0
			32	NA	NA	57.9 vs. 40.5	28.9 vs. 0.0‡	18.4 vs. 5.4	23.7 vs. 29.7	5.0 vs. 0.0††

Differences are nonsignificant unless indicated. Stent thrombosis defined per Academic Research Consortium definitions, unless indicated. All trial acronyms are listed in the Online Appendix. *Angiographic follow-up. †Clinical follow-up. ‡$p < 0.001$. §$p < 0.05$. ‖Ischemia driven. ¶Cardiac. #Protocol-defined ST. **Target vessel revascularization. ††Definite ST only. ‡‡Definite, probable, and possible. §§Major adverse cardiovascular and cerebrovascular events.

BMS = bare-metal stent(s); MACE = major adverse cardiovascular events (a composite of death, myocardial infarction, and target lesion revascularization); MI = myocardial infarction; NA = not available; SES = sirolimus-eluting stent(s); ST = stent thrombosis; STEMI = ST-segment elevation myocardial infarction; TLR = target lesion revascularization.

Table 3 Rates of Death, MI, and TLR From Recent Meta-Analyses of DES Compared to BMS

First Author (Ref. #)	Number of Patients	Longest Follow-Up, yrs	Death (DES vs. BMS)	MI (DES vs. BMS)	TLR (DES vs. BMS)
SES vs. BMS					
Stettler et al. (22)	8,646 (4,643 SES, 4,003 BMS)	4	HR: 1.0	HR: 0.81*	HR: 0.3†
Stone et al. (24)	1,748 (878 SES, 870 BMS)	4	6.7% vs. 5.3%	6.4% vs. 6.2%	7.8% vs. 23.6%†
Kastrati et al. (26)	4,958 (2,486 SES, 2,472 BMS)	5	6.0% vs. 5.9%	9.7% vs. 10.2%‡	HR: 0.43§†
PES vs. BMS					
Stettler et al. (22)	8,330 (4,327 PES, 4,003 BMS)	4	HR: 1.03	HR: 1.0	HR: 0.42†
Stone et al. (24)	3,513 (1,755 PES, 1,758 BMS)	4	6.1% vs. 6.6%	7.0% vs. 6.3%	10.1% vs. 20.0%†
Other					
Stettler et al. (22)	8,970 (4,643 SES, 4,327 PES)	4	HR: 0.96	HR: 0.83*	HR: 0.70*
Kirtane et al. (76), on-label			HR: 1.05	HR: 1.03	HR: 0.54†
Kirtane et al. (76), off-label	9,470 (4,867 DES, 4,603 BMS)	5	HR: 0.84	HR: 0.83	HR: 0.42†

Differences nonsignificant unless indicated. *$p < 0.05$. †$p < 0.001$. ‡Combined death or MI. §Combined death, MI, or TVR.
DES = drug-eluting stent(s); HR = hazard ratio; PES = paclitaxel-eluting stent(s); TVR = target vessel revascularization; other abbreviations as in Table 2.

MACE and TLR after the use of the Cypher SES compared with historical BMS controls (77–81).

Paclitaxel-eluting stents (PES). The TAXUS PES (Boston Scientific, Natick, Massachusetts) was developed almost simultaneously with the SES, gaining regulatory approval ~12 months later (Table 1, Fig. 5). Its evaluation has followed a pattern similar to that of the SES, and its first assessment, in the randomized TAXUS I study, reported no binary restenosis at 6-month follow-up (82). Subsequent randomized studies, the most important of which are summarized in Table 4, have demonstrated a significantly lower rate of late loss, angiographic binary restenosis, and repeat revascularization with

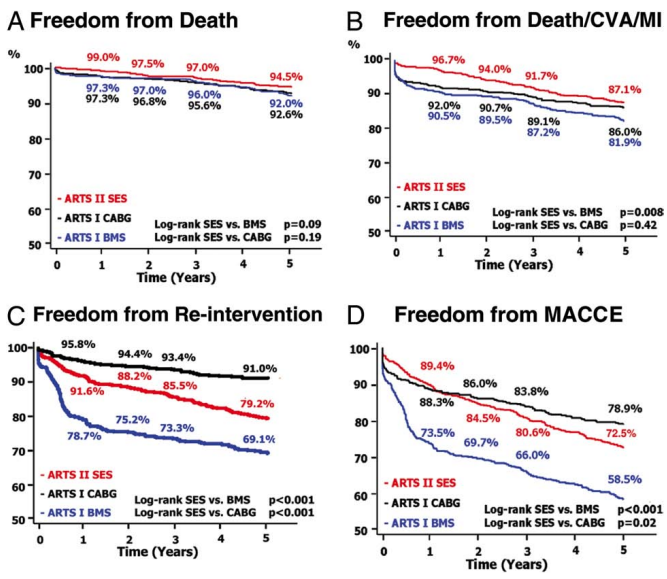


Figure 4 Long-Term Clinical Outcomes of SES, BMS, and CABG in ARTS I and II

Long-term clinical outcomes compared for patients treated with sirolimus-eluting stents (SES **[red lines]**), bare-metal stents (BMS **[blue lines]**), and coronary artery bypass graft surgery (CABG **[black lines]**) in the ARTS (Arterial Revascularization Therapy Studies) I and II (77). Kaplan-Meier estimates for freedom from **(A)** death, **(B)** death, cerebrovascular accident (CVA), and myocardial infarction (MI), **(C)** repeat revascularization, and **(D)** overall major adverse cardiovascular and cerebrovascular events (MACCE). Reproduced with permission from Serruys et al. (77).

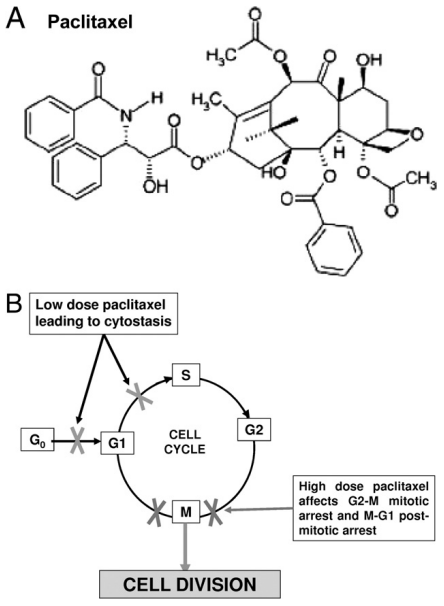


Figure 5 Paclitaxel

(A) The chemical structure and **(B)** mode of action of paclitaxel, an extract derived from the bark of the *Taxus brevifolia* (Pacific Yew) tree. Paclitaxel inhibits smooth muscle cell proliferation through the stabilization of microtubules, and thereby inhibits cell division.

PES compared with BMS that is consistent across different patient groups including those with simple lesions, STEMI, lesions in the unprotected left main stem (UPLMS), and complex lesions (57,82–96). In addition, patient-level meta-analysis of the initial PES approval trials has confirmed the comparable safety and superior efficacy of PES compared with BMS out to 4-year follow-up (Table 3) (22,24).

In a fashion similar to the SES, the TAXUS PES stent has been assessed in an unrestricted single-center registry that used the PES as the default stent for all PCI in 576 consecutive real-world patients. Two-year results from the T-SEARCH (Taxus Stent Evaluated at Rotterdam Cardiology Hospital) registry demonstrate similar efficacy in terms of suppression of neointimal growth and reduction of restenosis when compared with historical controls treated with SES (97,98).

TAXUS EXPRESS VERSUS TAXUS LIBERTÉ. The first PES to be approved by the Food and Drug Administration (FDA) was the TAXUS PES Express stent. This was subsequently superseded by the TAXUS PES Liberté stent, which was designed to be more deliverable and conformable and to provide a more homogenous drug distribution (99). Table 1 summarizes the main physical properties of both stents, both of which have the same polymer and dose of paclitaxel; however, the Liberté stent has a more uniform cell geometry (Fig. 6) (99), allowing more enhanced and uniform drug delivery, thinner struts (97 μm vs. 132 μm), a smaller profile, and separate stent designs depending on stent diameter. Stents with a diameter of 2.25 to 2.5 mm have a 2-cell design, whereas stents with a diameter >2.75 mm have a 3-cell design. The superiority of the Liberté stent was confirmed through the multicenter noninferiority TAXUS ATLAS (TAXUS Liberté-SR Stent for the Treatment of De Novo Coronary Artery Lesion) clinical trial, which enrolled 871 patients treated with the TAXUS Liberté stent who were compared with a historical population of patients treated with the TAXUS Express-SR stent from the TAXUS IV and V trials (99). In spite of similar inclusion criteria, patients receiving the Liberté stent had treatment for significantly more complex baseline lesions. Nevertheless, the primary end point of 9-month target vessel revascularization (TVR) occurred in 7.0% and 8.0% of patients treated with the Express and Liberté stents, respectively, achieving the pre-specified criteria for noninferiority ($p = 0.049$). There were no significant differences in other clinical outcomes.

Two additional multicenter studies confirmed the improved outcomes with the newer Liberté stent. These were the TAXUS ATLAS Small Vessels study and the TAXUS ATLAS Long Lesions study.

The TAXUS ATLAS Small Vessels study, which compared the performance of the 2.25-mm TAXUS Liberté stent in 261 patients with 75 historical controls from the TAXUS V study who had had a lesion treated with a single 2.25-mm TAXUS Express stent (100). In addition to meeting the noninferiority primary end point of 9-month in-segment diameter stenosis, compared with the Express stent, the Liberté stent was shown to significantly reduce the rate of 9-month angiographic restenosis (18.5% vs. 32.7%, $p = 0.02$) and TLR at 12 months (6.1% vs. 16.9%, $p = 0.004$). Moreover, at 3-year follow-up, the use of the TAXUS Liberté led to a significant reduction in TLR (10.0% vs. 22.1%, $p = 0.008$) and MACE (19.5% vs. 32.4%, $p = 0.03$), together with a numerically lower composite of death/stroke and MI (6.5% vs. 7.4%, $p = 0.79$) (101).

The TAXUS ATLAS Long Lesions study compared the performance of the 38-mm long TAXUS Liberté stent in 150 patients with lesions between 26 mm and 34 mm in length with that of 145 historical control patients from the TAXUS IV and V studies with similar length lesions treated with a least 1 Express stent (100). In addition to meeting the noninferiority primary end point of 9-month in-segment diameter stenosis, compared with the Express stent, the Liberté stent was also shown to significantly reduce the risk of MI at both 12-month follow-up (1.4% vs.

Table 4 Summary of Major Randomized Trials of PES Versus BMS in Different Clinical Settings

Trial or First Author (Ref. #)	No. of Patients	Clinical Setting	Follow-Up, Months	In-Stent Late Loss (PES vs.), mm	Binary In-Stent Restenosis (PES vs.), %	MACE (PES vs.), %	Death (PES vs.), %	MI (PES vs.), %	TLR (PES vs.), %	Definite/Probable ST (PES vs.), %
TAXUS-I (82)	PES (n = 31) vs. BMS (n = 30)	Simple lesions	6*/12†	0.36 vs. 0.71	0.0 vs. 10.4	3.3 vs. 10.0‡	0.0 vs. 0.0	0.0 vs. 0.0 (Q-wave only)	0.0 vs. 10.0§	0.0 vs. 0.0
TAXUS-II Slow release (83,84)	PES (n = 131) vs. BMS (n = 136)	Simple lesions	6*/12†	0.31 vs. 0.79‖	2.3 vs. 17.9‖	10.9 vs. 22.0¶#	0.0 vs. 1.5	2.4 vs. 5.3	4.7 vs. 12.9¶	0.7 vs. 0.0**
			60	NA	NA	20.4 vs. 27.6‡††	2.4 vs. 1.5††	4.7 vs. 7.1	10.3 vs. 18.4¶	2.7 vs. 0.8**
TAXUS-II Moderate release (83,84)	PES (n = 135) vs. BMS (n = 134)	Simple lesions	6*/12†	0.30 vs. 0.77‖	4.7 vs. 20.2‖	9.9 vs. 21.4¶#	0.0 vs. 0.0	3.8 vs. 5.4	3.8 vs. 16.0¶	0.7 vs. 0.0**
			60	NA	NA	15.1 vs. 27.6‡¶††	1.6 vs. 1.5††	5.3 vs. 7.1	4.5 vs. 18.4‖	1.7 vs. 0.8**
TAXUS-IV (85,86)	PES (n = 662) vs. BMS (n = 652)	Pivotal approval trial	9	0.39 vs. 0.92‖	5.5 vs. 24.4‖	8.5 vs. 15.0‖†††‡	2.4 vs. 2.2	3.5 vs. 3.7	3.0 vs. 11.3‖‡‡	0.8 vs. 1.1
			60	NA	NA	24.0 vs. 32.0‡‖††	10.0 vs. 11.2	7.2 vs. 7.4	9.1 vs. 20.5‖‡‡	2.1 vs. 2.3
TAXUS-V (87,88)	PES (n = 577) vs. BMS (n = 579)	Complex lesions	9	0.49 vs. 0.90‖	13.7 vs. 31.9‖	15.0 vs. 21.2¶†††‡	0.5 vs. 0.9††	5.4 vs. 4.6	8.6 vs. 15.7¶‡‡	0.7 vs. 0.7**
			60	NA	NA	NA	10.2 vs. 8.5	9.3 vs. 5.6¶	17.0 vs. 23.2¶‡‡	2.4 vs. 1.5¶
TAXUS-VI (89,90)	PES (n = 219) vs. BMS (n = 227)	Long complex lesions	9	0.39 vs. 0.99‖	9.1 vs. 32.9‖	16.4 vs. 22.5	0.0 vs. 0.9††	8.2 vs. 6.2	6.8 vs. 18.9‖	0.5 vs. 0.9**
			60	NA	NA	31.3 vs. 27.8#††	2.8 vs. 3.2††	11.2 vs. 8.2	14.6 vs. 21.4¶	0.9 vs. 0.9**
HORIZONS-AMI (91,92)	PES (n = 2,257) vs. BMS (n = 749)	STEMI	13*/12†	0.41 vs. 0.82‖	8.2 vs. 21.0‖	8.0 vs. 7.9§§	3.5 vs. 3.5	3.6 vs. 4.4	4.3 vs. 7.2¶‡‡	3.1 vs. 3.3
			24	NA	NA	11.0 vs. 11.2§§	4.3 vs. 5.2	5.7 vs. 6.1	6.8 vs. 11.6‖‡‡	4.1 vs. 4.1
PASEO (57,58)	PES (n = 90) vs. BMS (n = 90)	STEMI	12	NA	NA	11.1 vs. 24.4¶	4.4 vs. 6.7	3.3 vs. 6.7	4.4 vs. 14.4¶	1.1 vs. 1.1‖‖
			48	NA	NA	21.1 vs. 36.7¶	8.9 vs. 12.2	7.8 vs. 13.3	6.7 vs. 21.1¶	1.1 vs. 2.2‖‖
PASSION (93,95)	PES (n = 310) vs. BMS (n = 309)	STEMI	12	NA	NA	8.8 vs. 12.8†‡‡	4.6 vs. 6.5	1.7 vs. 2.0	5.3 vs. 7.8	1.4 vs. 2.3
			60	NA	NA	18.3 vs. 22.0†‡‡	8.9 vs. 11.5††	6.5 vs. 4.3	7.3 vs. 10.5	3.9 vs. 3.4
Erglis et al. (96)	PES (n = 53) vs. BMS (n = 50)	UPLMS	6	0.22 vs. 0.60‖	5.7 vs. 22.0¶	13.2 vs. 30.0	1.9 vs. 2.0	9.4 vs. 14.0	1.9 vs. 16.0¶	0.0 vs. 0.0

Differences are nonsignificant unless stated. Stent thrombosis as per Academic Research Consortium definition, unless indicated. All trial acronyms are listed in the Online Appendix. *Angiographic follow-up. †Clinical follow-up. ‡Major adverse cardiovascular events a composite of death, MI, TVR, and ST. §Percutaneous revascularization only. ‖$p < 0.001$. ¶$p < 0.05$. #Major adverse cardiovascular events a composite of death, MI, and TVR. **Protocol-defined ST. ††Cardiac death. ‡‡Ischemia driven. §§Major adverse cardiovascular events a composite of death, MI, stroke, and ST. ‖‖Definite ST only.

UPLMS = unprotected left main stem; other abbreviations as in Tables 2 and 3.

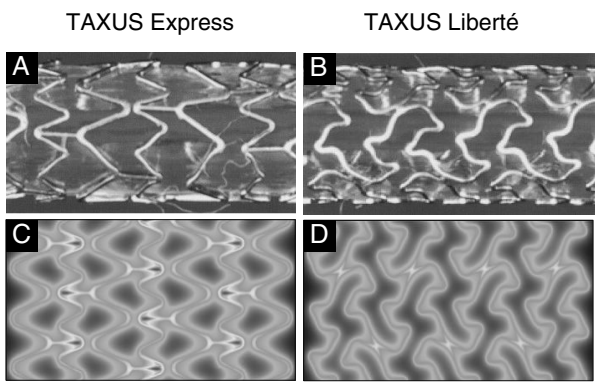


Figure 6 **TAXUS Express and TAXUS Liberté Stents**

(A and B) The difference in stent strut distribution between the TAXUS Express and TAXUS Liberté stents. Reproduced with permission from Turco et al. (99). **(C and D)** Computer simulations illustrating the more uniform drug distribution achieved with the TAXUS Liberté stent. **Blue** indicates areas of low paclitaxel concentration, whereas **red** indicates areas of high paclitaxel concentration. Image courtesy of Boston Scientific, Natick, Massachusetts.

6.5%, p = 0.002) and 3-year follow-up (2.9% vs. 10.4%, p = 0.01). Moreover, at 3-year follow-up, the use of the Liberté stent led to a 78% reduction in cardiac death (1.5% vs. 6.7%, p = 0.03), with no reported stent thrombosis (ST) (101).

SES versus PES. Several randomized studies, which are summarized in Table 5, have formally compared outcomes between patients treated with SES or PES for: 1) unselected patients populations; 2) specific patient groups such as diabetic patients or patients with STEMI; and 3) specific lesion types such as UPLMS lesions, long lesions, or lesions in small vessels (102–117). Of note, results at short-term angiographic follow-up demonstrate superior reductions in late loss and binary restenosis with the use of SES; however, long-term angiographic follow-up, which is limited to the SIRTAX (Sirolimus Eluting Versus Paclitaxel Eluting Stents for Coronary Revascularization) study, indicates a greater delayed late loss with SES in that, at 5 years, there was no longer a significant difference in late loss between SES and PES (107). With respect to clinical outcomes, a meta-analysis of 16 randomized trials of SES versus PES, which included 8,695 patients and, where possible, patient-level data, reported significant reductions in TLR (hazard ratio [HR]: 0.74, 95% confidence interval [CI]: 0.63 to 0.87, p < 0.001) and ST (HR: 0.66, 95% CI: 0.46 to 0.94, p = 0.02) with SES, whereas no significant differences in death (HR: 0.92, 95% CI: 0.74 to 1.13, p = 0.43), or MI (HR: 0.84, 95% CI: 0.69 to 1.03, p = 0.10) were noted at a median of 2-year follow-up (118).

Angiographic measures of DES effectiveness. As suggested by the discussion in the preceding text, angiographic measures such as late lumen loss and binary angiographic stenosis are commonly used surrogates of clinical effectiveness in DES trials (119). Of the 2, binary angiographic stenosis appears a more favorable variable as it requires a single measurement and not, as in the case of late loss, 2 separate measurements several months apart. In addition, the relationship between late loss and TLR is dependent on vessel size, with more late loss being accommodated in larger vessels before triggering a TLR (so-called headroom); conversely, binary angiographic stenosis is independent of vessel size (120).

The relationship between late loss and the risk of binary restenosis has been described as monotomic; in other words, incremental changes in late loss are associated with a predictable increased risk of binary restenosis (121). Conversely, a curvilinear relationship has been described between late lumen loss and TLR, namely, the increased risk of TLR is not linear over the entire range of late lumen loss (122). Using data from the TAXUS IV trial, Ellis et al. (122) demonstrated that the normally low risk of TLR is only significantly increased once late lumen loss reaches a threshold >0.5 to 0.6 mm. This nonlinear relationship serves to explain why significant differences in late loss during follow-up do not invariably translate into differences in clinical outcomes. For example, in the REALITY (Comparison of the Cypher Sirolimus Eluting and the Taxus Paclitaxel Eluting Stent Systems Trial), the significantly higher late lumen loss at 8 months with PES (PES vs. SES: 0.31 mm vs. 0.09 mm, p < 0.001) did not translate into any significant difference in restenosis rate (PES 11.1% vs. SES 9.6%, p = 0.31) or TLR (PES 6.1% vs. SES 6.0%, p > 0.99) at 12 months (105). Moreover, because of this

Table 5 Summary of Major Randomized Trials (>100 Patients in Each Group) Comparing SES to PES in Different Clinical Settings

Trial (Ref. #)	No. of Patients	Clinical Setting	Follow-Up, Months	In-Stent Late Loss (SES vs. PES), mm	Binary In-Stent Restenosis (SES vs. PES), %	MACE (SES vs. PES), %	Death (SES vs. PES), %	MI (SES vs. PES), %	TLR (SES vs. PES), %	Definite/Probable ST (SES vs. PES), %
DES-DIABETES (102,103)	SES (n = 200) vs. PES (n = 200)	Diabetic patients	9	0.13 vs. 0.53*	3.4 vs. 18.2*	2.0 vs. 8.0†	0.0 vs. 0.5	0.5 vs. 0.5	2.0 vs. 7.5†	0.5 vs. 0.0
			24	NA	NA	3.5 vs. 12.5†	0.0 vs. 1.5	0.5 vs. 1.0	3.5 vs. 11.0†	1.0 vs. 0.0
ISAR-DIABETES (104)	SES (n = 125) vs. PES (n = 125)	Diabetic patients	9	0.19 vs. 0.46*	4.9 vs. 13.6†	NA	3.2 vs. 4.8	4.0 vs. 2.4	6.4 vs. 12.0	0.0 vs. 0.1
REALITY (105)	SES (n = 701) vs. PES (n = 685)	Unselected	8‡/12§	0.09 vs. 0.31*	7.0 vs. 8.3	10.7 vs. 11.4‖	2.3 vs. 1.3	5.1 vs. 6.0	6.0 vs. 6.1	0.7 vs. 1.9¶
SIRTAX (106,107)	SES (n = 503) vs. PES (n = 509)	Unselected	8‡/9§	0.12 vs. 0.25*	3.2 vs. 7.5†	6.2 vs. 10.8†‖#	1.0 vs. 2.2	2.8 vs. 3.5	4.8 vs. 8.3†#	2.0 vs. 1.8
			60	0.30 vs. 0.37	NA	21.3 vs. 24.2	10.9 vs. 9.4	6.6 vs. 6.9	14.9 vs. 17.9	4.6 vs. 4.1
SORT-OUT II (108)	SES (n = 1,065) vs. PES (n = 1,065)	Unselected	18	NA	NA	10.0 vs. 11.6‖**	3.8 vs. 3.9	4.2 vs. 5.1	4.5 vs. 5.9	2.6 vs. 2.8
TAXi (109,110)	SES (n = 102) vs. PES (n = 100)	Unselected	6	NA	NA	6.0 vs. 4.0	0.0 vs. 0.0	2.0 vs. 3.0	2.0 vs. 1.0	1.0 vs. 0.0¶
			36	NA	NA	17 vs. 11	7.0 vs. 3.0	3.0 vs. 6.9	5.0 vs. 1.0	2.0 vs. 2.0¶
PROSIT (111,112)	SES (n = 154) vs. PES (n = 154)	STEMI	6‡/12§	0.19 vs. 0.43†	5.0 vs. 12.0	5.8 vs. 11.7 (+ST)	3.2 vs. 5.8	0.0 vs. 1.9	2.6 vs. 6.5	0.0 vs. 1.3¶
			36	NA	NA	12.3 vs. 18.8** (+ST)	6.5 vs. 10.4	2.6 vs. 3.9	3.9 vs. 8.4**	0.6 vs. 1.9
ISAR-LEFT MAIN (113)	SES (n = 305) vs. PES (n = 302)	UPLMS	6–8‡/24§	NA	19.4 vs. 16.0	20.6 vs. 21.3	8.7 vs. 10.4	4.6 vs. 5.4	10.7 vs. 9.2	1.0 vs. 0.3
LONG-DES II (114)	SES (n = 250) vs. PES (n = 250)	Long lesions	6	0.09 vs. 0.45*	2.9 vs. 11.7†	12.0 vs. 17.2	0.8 vs. 0.0	8.8 vs. 10.8	2.4 vs. 7.2†	0.8 vs. 0.0¶
ISAR-SMART 3 (115)	SES (n = 180) vs. PES (n = 180)	Small vessels, nondiabetic	6–8‡/12§	0.25 vs. 0.56*	8.0 vs. 14.9†	5.0 vs. 5.6 (Death/MI)	1.7 vs. 2.2	3.9 vs. 3.3	6.6 vs. 14.7†	0.0 vs. 0.0 (30 days)
ISAR-DESIRE (116)	SES (n = 100) vs. PES (n = 100)	In-stent restenosis	6	0.10 vs. 0.26†	11.0 vs. 18.5	NA	2.0 vs. 1.0	1.0 vs. 2.0	8.0 vs. 19.0†**	NA
ISAR-DESIRE 2 (117)	SES (n = 225) vs. PES (n = 225)	SES in-stent restenosis	6–8‡/12§	0.40 vs. 0.38	19.0 vs. 20.6	20.4 vs. 19.6	3.4 vs. 4.5	2.7 vs. 1.8	16.6 vs. 14.6	0.4 vs. 0.4††

Differences are nonsignificant unless indicated. Stent thrombosis Academic Research Consortium definition unless indicated. All trial acronyms are listed in the Online Appendix. *$p < 0.001$. †$p < 0.05$. ‡Angiographic follow-up. §Clinical follow-up. ‖Cardiac death. ¶Protocol-defined ST. #Ischemia driven. **Target vessel revascularization. ††Definite only.

Abbreviations as in Tables 2, 3, and 4.

relationship, late lumen loss is regarded as having only limited use in isolation in the assessment of clinical effectiveness among different DES, particularly if absolute levels are low.

Benefits of DES. Extensive data exist confirming the benefits of DES in terms of reduced rates of restenosis compared with BMS. Results from the largest meta-analysis to date, which included >18,000 patients from 38 DES trials, indicated a reduction in TLR of 70% ($p < 0.0001$) with the use of SES, and 58% ($p < 0.001$) with the use of PES, when compared with BMS out to 4 years of follow-up (Table 3) (22). This corresponded to a number needed to treat, to prevent a single revascularization, of only 7 and 8 patients for SES and PES, respectively. Several other similar meta-analyses have also been performed, and their results are summarized in Table 3 (23–26).

Importantly, these impressive results are not only confined to the select patients treated for on-label indications, but also have consistently been reproduced in registries and randomized controlled trials that have included those with patients receiving DES for off-label indications (76,78,123). Of note, a recent large meta-analysis by Kirtane et al. (76) that included >9,000 patients suggests that the benefit in terms of reduced restenosis from DES use appears to be at least as great as in patients treated for off-label indications (HR: 0.46, 95% CI: 0.34 to 0.52, $p < 0.01$) as opposed to on-label indications (HR: 0.54, 95% CI: 0.48 to 0.62, $p < 0.01$).

Risks of DES. MORTALITY. The concerns that DES increased mortality stemmed from the presentation and publication of 4 studies. 1) A meta-analysis performed by Nordmann et al. (31) using aggregate trial data from 17 randomized studies of patients treated with SES, PES, and BMS that demonstrated a statistically significant increase in noncardiac mortality between 2 and 3 years after SES implantation. 2) The single-center BASKET-LATE (Basel Stent Kosten Effektivitats Trial), which randomly assigned 746 unselected patients to either SES or BMS, and reported a higher rate of death and MI between 7 and 18 months after the index PCI among patients treated with SES compared with BMS (adjusted HR: 2.2, $p = 0.03$). No significant difference was seen in the rates of ST or thrombosis-related events between groups; however, ultimately the study was underpowered to detect ST events, and limited angiographic evidence was available to confirm that events were actually due to ST (124). 3) The pooled analysis of published data from the Cypher SES trials, RAVEL, SIRIUS, E-SIRIUS (European-Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions), and C-SIRIUS (Canadian-Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions) by Camenzind et al. (32), that showed a statistically significant 2.4% increased risk of death and Q-wave MI with the use of SES compared with BMS (6.3% vs. 3.9%, $p = 0.03$). Much criticism was directed at the use of the peculiar end point of death and Q-wave MI, and the use of aggregate trial data. A subsequent analysis of the same studies by Spaulding et al. (23) using patient-level data indicated that there were no significant differences in death/MI between groups (11.4% SES vs. 10.1% BMS, $p = 0.4$). 4) The 3-year results of SCAAR (Swedish Angiography and Angioplasty Registry), which reported results from ~20,000 patients treated with BMS or DES between 2003 and 2004, and demonstrated a higher overall risk of death for patients receiving DES (adjusted relative risk [RR]: 1.18; 95% CI: 1.04 to 1.35) (33). Subsequent extended analyses to incorporate data from 2005, however, demonstrated a 31% reduction in events during the first 6 months with DES, and no difference in events between DES and BMS during long-term follow-up. That may have been the result of DES use increasing from 22% to 53% of PCI procedures from 2003 to 2005, together with operators traversing the learning curve with DES, and thereby selecting lesions and patients more appropriately, and being more meticulous with ensuring adequate stent deployment, and compliance to DAPT (125). Most recently, data from the registry, extended to include new patients treated in 2006 and now including just under 48,000 patients, showed a similar long-term incidence of death or MI among DES and BMS patients. Moreover, DES were also shown to have a reduced rate of restenosis among high-risk patients (125,126).

In the aftermath of these studies, which caused widespread concern, several patient-based meta-analysis were performed that reassuringly demonstrated the overall comparable outcomes between DES and BMS in terms of death and MI, at both short- and long-term follow-up (Table 3). The largest of these studies, by Stettler et al. (22), reported a similar risk of death for patients treated with SES, PES, or BMS; the risk of MI, although comparable between PES and BMS ($p = 0.99$), was significantly lower with SES compared with BMS ($p = 0.03$) (22). Additional meta-analyses were performed at a similar time by Stone et al. (24), Spaulding et al. (23), Kastrati et al. (26), and Mauri et al. (25), and now more recently by Kirtane et al. (76). All reiterated the safety of DES by demonstrating the absence of any significantly increased risk of death and/or MI with the use of DES compared with BMS.

In addition to the data from randomized controlled trials, observation data comparing DES to BMS have been published from numerous registries, which in total include >400,000 patients. The largest single registry published to date includes 262,700 patients from the Medicare registry and demonstrates lower rates of adjusted and unadjusted death, MI, and repeat revascularization after treatment with DES compared with BMS out to 30 months of follow-up (123). A similar advantage in favor of DES was also reported by Kirtane et al. (76) in a meta-analysis of >30 registries, which included >180,000 patients followed up for 12 to 48 months. These data reflect some of inherent differences between randomized studies and observation studies, which provide a better reflection of real-world practice and, owing to the large numbers of patients recruited, may be able to detect differences in infrequent events. Conversely, however, they can be affected by a

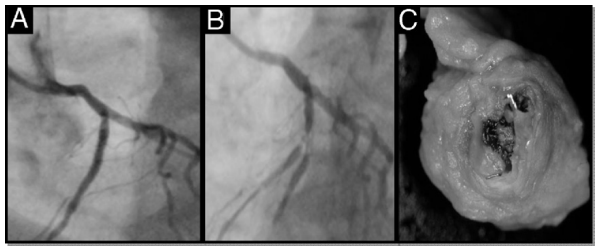


Figure 7 **Stent Thrombosis**

(A) Drug-eluting stent implantation in the proximal left anterior descending artery, complicated by **(B)** stent thrombosis occurring 7 months later, shortly after discontinuation of dual antiplatelet therapy. **(C)** Gross pathology example of stent thrombosis.

selection bias and/or incomplete risk adjustment due to unmeasured baseline population differences, factors that may account for the previously noted reductions in mortality and MI.

Off-label indications. The current on-label indications for DES use, as approved by the U.S. FDA are limited to simple lesions: for SES, de novo lesions ≤30 mm in length in native coronary arteries with reference vessel diameters of 2.5 to 3.5 mm, and for PES de novo lesions ≤28 mm in native coronary arteries 2.5 to 3.75 mm in diameter. It follows that off-label indications represent a higher-risk population with more complex lesion morphologies and unstable clinical presentations.

One of the criticisms of early DES trials was that they enrolled stable patients treated with DES for on-label indications. For example, the meta-analyses by Stettler et al. (22), Stone et al. (24), Spaulding et al. (23), Kastrati et al. (26), and Mauri et al. (25) included patients who were treated for essentially stable de novo lesions, which had a mean lesion length of 23 to 24 mm, a mean vessel diameter of 2.7 mm, and were suitably treated with an average of 1.2 to 1.4 stents. There were concerns that the comparative results between DES and BMS seen in these studies did not reflect real-world practice in which 70% to 75% of DES are implanted for off-label indications (127,128).

Unfortunately, the lack of any dedicated trials comparing off-label DES and BMS added to these concerns, and the FDA Circulatory System Devices Advisory Panel that met in December 2006 concluded that there was a need for a comprehensive assessment of the safety and efficacy of off-label DES use (129). This prompted numerous studies, many of which were observational, that ultimately demonstrated that the use DES for off-label indications was associated with poorer clinical outcomes in terms of death, MI, and repeat revascularization when compared with DES use for on-label indications (127,130–132). Of equal importance are the results from registries and randomized controlled trials that suggest that, for off-label indications, the use of a DES is no worse than the use of a BMS (76,133–136), with some studies, such as the Medicare and STENT (Strategic Transcatheter Evaluation of New Therapies) registry actually demonstrating significantly improved outcomes with the use of a DES (123,131). These findings suggest that the overall poor outcome with off-label use is most likely related to patient or lesions characteristics, rather than to specific shortcomings of DES.

ST. ST has emerged as 1 of the major safety concerns with stenting in today's clinical practice (Fig. 7). Fortunately, it is a rare, but it remains a devastating unpredictable event that has a significant morbidity and mortality (137); the clinical consequences are highly dependent on the myocardial area at risk, its viability, the degree of recruitable collaterals, and the speed of reperfusion therapy. The overall prognosis from ST is poor: 10% to 30% of patients with definite ST will die, whereas a proportion will experience an unexpected out-of-hospital death.

Early anecdotal reports of ST occurring in the months and years after implantation of a DES (138–140) were substantiated by subsequent studies reporting an annual risk of ST ranging from 0.2% in post-marketing surveillance registries, to 0.5% in trials of multivessel PCI (141–144). The infrequent nature of ST, together with concerns regarding mortality among patients treated with DES, lead to large collaborative meta-analyses, performed using the standardized Academic Research Consortium (ARC) definitions, that demonstrated similar rates of overall ST between DES and BMS (Table 6) (22–26,145). In particular, no difference between DES and BMS was seen for early ST (<30 days) or late ST (30 days to 1 year); however, significantly higher rates of very late ST (>1 year) were seen with DES. Furthermore, registry data from the Rotterdam-Bern group (n = 8,146), the SCAAR (Swedish Angiography and Angioplasty Registry) registry (n = 21,717), and the Pinto Slottow et al. registry (n = 8,000) have all indicated that the risk of very late ST persists at an annual rate of between 0.36% and 0.6%/year to at least 5 years after

Table 6 Rates of Overall, Early, Late, and Very Late Stent Thrombosis From Recent Meta-Analyses Comparing DES to BMS

First Author (Ref. #)	No. of Patients	Longest Follow-Up, yrs	Overall ST, DES vs. BMS	Early ST, DES vs. BMS	Late ST, DES vs. BMS	Very Late ST, DES vs. BMS
SES vs. BMS						
Spaudling et al. (23)*	1,748 (878 SES, 870 BMS)	4	3.6% vs. 3.3%	0.5% vs. 0.5%	0.3% vs. 1.3%†	2.8% vs. 1.7%
Stettler et al. (22)*	8,646 (4,643 SES, 4,003 BMS)	4	HR: 1.00	HR: 1.02	HR: 1.14	HR: 1.43
Stone et al. (24)‡	1,748 (878 SES, 870 BMS)	4	1.2% vs. 0.6%	0.5% vs. 0.1%	0.1% vs. 0.5%	0.6% vs. 0.0%†
Kastrati et al. (26)‡	4,958 (2,486 SES, 2,472 BMS)	5	HR: 1.09	—	—	0.6% vs. 0.05%†
PES vs. BMS						
Stettler et al. (22)*	8,330 (4,327 PES, 4,003 BMS)	4	HR: 1.38	HR: 0.95	HR: 1.61	HR: 3.57
Stone et al. (24)‡	3,513 (1,755 PES, 1,758 BMS)	4	1.3% vs. 0.9%	0.5% vs. 0.6%	0.2% vs. 0.1%	0.7% vs. 0.2%†
Mauri et al. (25)*	2,797 (1,400 PES, 1,397 BMS)	4	3.2% vs. 3.5%	0.5% vs. 0.5%	0.9% vs. 0.9%	1.8% vs. 2.1%
Other						
Stettler et al. (22)*	8,970 (4,643 SES, 4,327 PES)	4	HR: 0.71§	HR: 1.05§	HR: 0.68§	HR: 0.39§
Roukoz et al. (145)‡	10,727 (5.534 DES, 5,193 BMS)	5	1.4% vs. 1.3%	0.8% vs. 0.9%	0.3% vs. 0.4%	0.7% vs. 0.1%†

Difference nonsignificant unless indicated. Stent thrombosis defined by *Academic Research Council definitions or †$p < 0.05$. ‡study protocols. §SES vs. PES.
Abbreviations as in Tables 2 and 3.

DES implantation (146–150). The results at 2-year follow-up from both the ARRIVE (The TAXUS Peri-Approval Registry: A Multi-Centre Safety Surveillance) and the STENT registry indicate that the risk of ST is higher for patients treated with DES for off-label indications compared with on-label indications (130,131).

Uncertainty exists over the exact cause of ST; however, numerous factors have been implicated in increasing the risk of a ST event (Table 7). Of note, data from large-scale registries demonstrate that the multivariate predictors of ST change during follow-up (146,147,151,152). In addition to the early cessation of DAPT, numerous other procedural-related factors such as stent undersizing, lesion length >28 mm, dissection, multiple stent implantation, calcification, and small vessel diameter have been shown to be important factors in the development of early/late but not very late ST (151,152). Conversely, patient factors such as previous brachytherapy and renal failure appear to be more influential in very late ST. This variation in the cause of ST may explain the relatively higher rates of early ST when compared with late/very late ST. For example, in the Dutch Stent registry of 21,009 patients, 437 patient had documented ST of which 32.0%, 41.2%, 13.3%, and 13.5% was categorized as acute, subacute, late, and very late ST, respectively (151).

Table 7 Precipitants of Stent Thrombosis

	Precipitant of Stent Thrombosis
Patient factors	Percutaneous coronary intervention for acute coronary syndrome/ST-segment elevation myocardial infarction
	Diabetes mellitus
	Renal failure
	Impaired left ventricular function
	Premature cessation of dual anti-platelet therapy
	Clopidogrel nonresponsiveness
	Prior brachytherapy
Lesion characteristics	Lesion/stent length
	Vessel/stent diameter
	Complex Lesions (bifurcation lesions, chronic total occlusions)
Procedural factors	Inadequate stent expansion
	Incomplete stent apposition
	Stent deployment in necrotic core
Device factors	Hypersensitivity to drug coating or polymer
	Incomplete endothelialization
	Stent design

Two of the most prominent device concerns with the use of DES that deserve additional consideration are their ability to potentially delay endothelialization and induce hypersensitivity reactions through the presence of a drug polymer.

IMPAIRED ENDOTHELIALIZATION BY ANTIPROLIFERATIVE DRUGS. The antiproliferative properties of DES impair and/or delay endothelialization so that blood is exposed to thrombogenic stent struts, potentially precipitating ST (138,153–156). Animal studies using scanning electron microscopy have previously demonstrated a greater area of exposed stent struts with the use of DES (SES 3.08 mm^2, PES 3.54 mm^2) compared with BMS (0.12 mm^2) (157). More recently, human studies using optical coherency tomography have also demonstrated differences between different types of DES, with the second generation zotarolimus-eluting stent (ZES) having significantly lower rates of uncovered stent struts when compared with SES at both overlapping sites (0.06% vs. 5.4%) and nonoverlapping sites (0.03% vs. 8.7%) (158). Similar results have been reported by Kim et al. (159), whereas Barlis et al. (160) demonstrated a higher rate of near complete (>95%) strut coverage in a stent with a biodegradable polymer when compared with a stent with a durable polymer (SES [89.3% vs. 63.3%, $p = 0.03$]). Incomplete strut coverage can also be demonstrated on angioscopy, and has been seen as late as 2 years after implantation of SES (161,162). The restitution of a healthy but not hyperproliferative endothelial lining remains a target of ongoing current research.

POLYMER. Conventionally, DES are coated with permanent polymers that facilitate drug release and remain long after drug elution is complete. These permanent polymers can cause delayed healing, impaired stent strut endothelialization, and a hypersensitivity reaction, which can culminate in ST (153,157,163–165) Data from histopathology studies also indicate that these nonerodable polymers can precipitate ST by inducing localized vascular inflammation, hypereosinophilia, thrombogenic reactions, and apoptosis of smooth muscle cells (164–166). Of note, the Cypher SES is coated in a nonerodable poly(ethylene co-vinyl acetate) and poly(n-butyl methacrylate) polymer that has been shown to induce granulomatous and hypersensitivity reactions in animal models and humans (167,168). Similarly, the first-generation TAXUS PES stent has a durable poly(styrene-b-isobutylene-b-styrene) polymer that is associated with medial necrosis, positive remodeling, and excessive fibrin deposition, which likely contribute to the deleterious pathologic changes that can be seen with the TAXUS stent (168).

The potential of these first-generation stents to cause ST due to a permanent polymer has led to extensive research into developing new polymers. These developments have led to the second-generation DES that have more biocompatible nonerodable polymers, which have been shown in animal studies to have a greater degrees of re-endothelialization compared with first-generation stents (157). Research has also led to the design of the newer DES that are described in Part Two of this article, and have biodegradable polymers, novel coatings, or are completely polymer free.

DURATION OF ANTIPLATELET THERAPY. Although the clinical value and cost effectiveness of long-term clopidogrel (up to 12 months) with BMS after PCI for acute coronary syndrome (ACS) is well established (169–171), the optimal duration of DAPT after DES implantation remains an issue of contention. Central to the discussion are repeated studies that demonstrate that premature (<1 year) discontinuation of DAPT is 1 of the most significant independent predictors of ST (142,151,172,173), with poor patient compliance, surgery, bleeding complications, poor patient education, allergy to clopidogrel, and cost the most frequently cited reasons for cessation (146,172). It was this association between "early" discontinuation of DAPT and ST that led guidelines' authorities and the U.S. FDA advisory panel to recommend 12-month DAPT after DES implantation for all patients without contraindications and bleeding risk (128,174). However, these recommendations were made in the absence of any prospective randomized trials evaluating whether prolonged DAPT actually reduced rates of ST.

This association of cessation of DAPT and ST is complicated by studies that demonstrated that discontinuation of clopidogrel is only a major independent predictor of ST in the first 6 months after PCI, and not beyond. The median time interval for a ST event after the discontinuation of clopidogrel has been shown to be 9 days (interquartile range 5.5 to 22.5) within the first 6 months of the PCI, compared with 104.3 days (interquartile range 7.4 to 294.8) for the period after (173,175). Further complicating the issues are a lack of randomized data and reliance on observational studies, some of which indicate that discontinuing clopidogrel after 6 months does not increase the risk of ST (175,176), whereas others demonstrate that long-term DAPT might be associated with reductions in death and MI (177,178). Other important facts to consider are that <1% of patients who discontinue DAPT experience a ST (179), whereas ST events commonly occur among patients who are still receiving DAPT (173). For example, in the Rotterdam-Bern study, 87% of patients with early ST and 23% of patients with late ST were still taking DAPT at the time of the event (146). Further clouding matters is a possible hyperthrombotic rebound phenomena after clopidogrel discontinuation. That has been suggested by, among others, Ho et al. (180), who observed a clustering of adverse events in the 90-day period after the cessation of clopidogrel in 3,137 ACS patients who were treated either medically or with PCI.

Current registry data assessing long-term use of DAPT show conflicting results. Park et al. (181) reported no benefit in terms of reduced clinical outcomes or ST events in 2,851 patients treated with DES who received DAPT for >12 months. More recently, however, the smaller TYCOON (Two-Year Clopidogrel Need Study) registry has reported more positive results among 443 patients treated with DES who received DAPT for 12 months (n = 173) or 24 months (n = 274). At 4-year follow-up, there was no difference in clinical outcomes; however, significantly lower rates of very late ST (2% vs. 0%, p = 0.03) and overall ST (3% vs. 0.4%, p = 0.02) were seen in the group receiving prolonged DAPT. A major limitation of the study was failure to assess the potentially adverse effects of prolonged DAPT in these patients (182).

It is hoped that several on-going randomized trials will provide additional data to help establish the optimal duration of DAPT. The ISAR-SAFE (Intracoronary Stenting and Angiographic Results: Safety And Efficacy of 6 Months Dual Anti-platelet Therapy After Drug Eluting Stenting) study and the OPTIMIZE (Optimized Duration of Clopidogrel Therapy Following Treatment With the Endeavor Zotarolimus-Eluting Stent (ZES) in the "Real-World") study are both currently randomizing patients treated with DES to either standard therapy of 12 months of DAPT or shorter periods of DAPT ranging from 3 months (OPTIMIZE) or 6 months (ISAR-SAFE) (183,184). Conversely, the DAPT (Dual Anti-Platelet Therapy Trial) will compare outcomes of >20,000 patients treated with BMS and DES who are randomly allocated to DAPT therapy for either 12 or 30 months (185).

These concerns may be rendered immaterial if the initial promise from newer antiplatelet agents, which have recently been assessed in randomized controlled trials, is maintained (Fig. 8). Prasugrel represents a novel antiplatelet agent

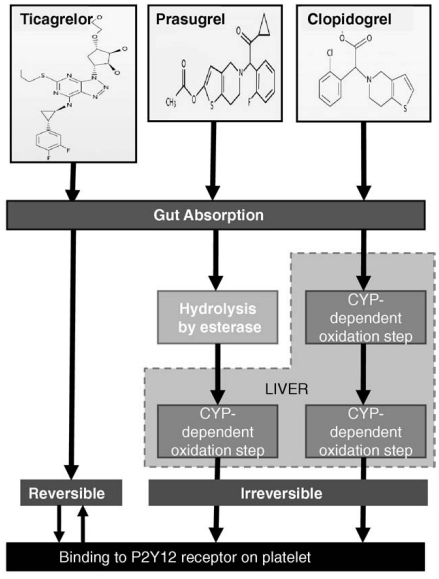


Figure 8 Activation of Clopidogrel, Prasugrel, and Ticagrelor

Clopidogrel, prasugrel, and ticagrelor are all absorbed from the gut. Ticagrelor is active immediately, and binds in a reversible fashion to the $P2Y_{12}$ receptor on the platelet. Prasugrel is first hydrolyzed by esterases, before undergoing hepatic CYP-mediated oxidation to produce the active metabolite that binds irreversibly to the $P2Y_{12}$ receptor on the platelet for the duration of the platelet's life. Clopidogrel requires 2 oxidation steps within the liver before binding irreversibly to the $P2Y_{12}$ receptor.

that is a more effective inhibitor of the $P2Y_{12}$ platelet adenosine diphosphate receptor, compared with both ticlopidine and clopidogrel. This results in its antiplatelet activity peaking 60 min after oral administration, compared with 2 to 6 h with clopidogrel (186). In the recent TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38) trial that randomized >13,000 patients with ACS, use of prasugrel was associated with a significant reduction in the primary end point (a composite of cardiac death/nonfatal MI/nonfatal stroke), and rates of MI, TVR, and ST ($p < 0.001$ for all), when compared with standard therapy with clopidogrel. Of note, the risk of major life-threatening and fatal bleeding was significantly higher with prasugrel (187). A pre-specified substudy analysis involving >12,000 patients who received a stent reported significantly reduced rates of ST in patients receiving prasugrel (1.13% vs. 2.35%, HR: 0.80, $p = 0.03$), with at least as great a reduction in ST seen in patients treated with a DES (HR: 0.36) compared with a BMS (HR: 0.52) (188).

Ticagrelor is a cyclopentyl triazolopyrimidine and functions as an orally active reversible inhibitor of the platelet adenosine diphosphate receptor $P2Y_{12}$. In the recently published PLATO (Platelet Inhibition and Patient Outcomes) study, use of ticagrelor compared with clopidogrel in 18,624 patients with ACS resulted in a 16.0% reduction in the primary end point, which was a composite of death from vascular causes, MI, or stroke (9.8% vs. 11.7%, HR: 0.84; 95% CI: 0.77 to 0.92; $p < 0.001$). Moreover, rates of ST among patients receiving a stent were also significantly lower in those treated with ticagrelor compared with clopidogrel (1.3% vs. 1.9%, $p = 0.009$). Rates of major bleeding were comparable; however, patients treated with ticagrelor had high rates of non-CABG–related major bleeding (4.5% vs. 3.8%, $p = 0.03$), which included more instances of fatal intracranial bleeding (189,190). Conversely, patients treated with ticagrelor had a lower risk of CABG major bleeding, which is the likely consequence of its reversibility that enables it to dissipate before surgery.

CLOPIDOGREL RESISTANCE/NONRESPONDERS. In recent times, resistance to aspirin and/or clopidogrel, which may occur in as many as 44% of patients (191,192), has emerged as a potential risk factor for adverse cardiac events, particularly ST (193–195). The underlying mechanism of this nonresponsiveness is not completely understood, but is likely to occur through a combination of clinical, cellular, and genetic factors, together with potential drug interactions (196).

The assessment of clopidogrel resistance has been advanced after developments in patient tests. Importantly, several studies in patients undergoing elective or urgent PCI have reported a correlation between the reactive platelet response to adenosine diphosphate, assessed using the point-of-care assay VerifyNow (Accumetrics, San Diego, California), and clinical outcomes ranging from periprocedural MI to 1-year MACE (197–201). These results indicate the potential importance of platelet function testing; however, in the absence of large-scale clinical trials, these tests can only be regarded as research tools at present.

Despite the potential to identify patients with clopidogrel resistance, no definitive treatment has been fully established, and in view of the potentially fatal consequences, this represents a major clinical problem. Simple measures include ensuring adequate patient compliance and evaluating possible drug interactions. Additional strategies that have been suggested include the following. 1) Use an increased maintenance dose of clopidogrel of 150 mg/day, which may improve clinical outcomes without significantly increasing bleeding (202,203). This treatment for clopidogrel resistance is currently being assessed in the randomized GRAVITAS (Gauging Responsiveness With A VerifyNow assay—Impact on Thrombosis and Safety) study (204). Further anecdotal support for this strategy is provided by

the PCI cohort in the randomized CURRENT–OASIS 7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events–Optimal Anti-platelet Strategy for Interventions) study, which has recently reported the safety and clinical benefits of administering 150 mg/day clopidogrel for 7 days after PCI in patients with ACS or STEMI treated before PCI with a 600-mg loading dose of clopidogrel. The use of the higher dose of clopidogrel led to significant reductions in both definite ST and MI at 30-day follow-up, without any significant increase in stroke or major, fatal, or CABG-related bleeding (205,206). 2) Use additional antiplatelet agents such as glycoprotein IIb/IIIa inhibitors during PCI, and cilostazol, a phosphodiesterase III inhibitor, during maintenance (207–209). 3) Use alternative $P2Y_{12}$ receptor antagonists such as prasugrel or ticagrelor.

Operator technique. The importance of operator technique in ensuring adequate stent deployment cannot be overstated in maximizing the benefit and minimizing the risk associated with stent implantation. Specifically, suboptimal or incomplete stent expansion is associated with increased rates of restenosis and TVR, and is a possible precipitant of ST (16,151,210–212).

One of the most common causes of suboptimal stent deployment is stent undersizing, which is aggravated by the use of direct stenting, and by relying solely on coronary angiography to assess stent size together with the underuse of intravascular ultrasound (IVUS). Previous studies demonstrate that reference vessel diameters vary significantly depending on the method of measurement used. For example, Briguori et al. (213) reported a difference between IVUS and angiography of >1.0 mm in 71% and 49% of cases with vessel size diameters <2.75 mm and >2.75 mm, respectively.

As alluded to, IVUS has an important role to play in optimizing stent implantation that extends beyond just minimizing the risk of stent undersizing. Intravascular ultrasound is considerably more accurate than angiography in determining in-stent dimensions, identifying incomplete stent apposition (ISA), and stent-edge dissections.

CLINICAL IMPLICATIONS. Studies indicate that the main clinical consequences of stent underexpansion are restenosis, ST, and stent fracture.

RESTENOSIS. In BMS studies, minimum stent area was identified as the single most powerful predictor of in-stent restenosis (ISR), with an inverse correlation between post-procedural minimum stent area and both angiographic restenosis and TVR (214,215). After the arrival of DES and the subsequent reduction in TVR, less importance was given to adequate stent deployment. Importantly, observational studies have indicated that not only is minimum stent area still an independent predictor of ISR in patients having DES, but also that the rate of stent underexpansion with DES may be as high as 30% (216–218). This finding reiterates the importance of maximizing final minimal stent area/diameter with noncompliant balloon inflation, thereby reducing suboptimal stent deployment, which may result in improved clinical outcomes. Unfortunately, at present, no randomized data exist investigating this with DES.

Figure 9 Stent Malapposition

Stent malapposition is seen from the 11 o'clock to 9 o'clock position using Fourier domain optical coherence tomography (Terumo Corp., Tokyo, Japan). Reproduced with permission from Okamura et al. (222).

ST. Minimum stent area and suboptimal stent expansion represent major post-procedural predictors of ST (211,219,220). Retrospective data from Fuji et al. (211) indicate that lesions leading to ST after successful implantation of a SES stent more often have stent underexpansion, a small minimum stent area, and a residual edge stenosis. The importance of IVUS assessment after stent deployment is reaffirmed by registry data from >7,000 patients treated with BMS indicating that only approximately one-fifth of patients experiencing subacute ST had an optimum PCI result as assessed by IVUS. Moreover, analysis of these thrombosed stents indicates inadequate lumen dilation (final lumen <80% reference lumen), edge dissection, ISA, and plaque prolapse in 78%, 17%, 9%, and 4% of cases, respectively (221).

Incomplete stent apposition can be acute if detected at the time of the procedure, or late if detected at follow-up (Fig. 9) (222). Acute ISA can resolve itself, or if detected at the time of stent implantation, can be treated immediately with balloon dilation. Late ISA can be persistent (present after procedure and at follow-up) or acquired, if only detected on follow-up (223). Some studies (219) but not all (224,225) have suggested that ISA is associated with an increased risk of ST. Moreover, a recent meta-analysis has demonstrated that the risk of late acquired ISA is significantly higher for DES compared with BMS (OR: 4.36, 95% CI: 1.74 to 10.94), whereas the risk of late/very late ST is significantly higher for patients with ISA when compared

with patients who do not have ISA (OR: 6.51, 95% CI: 1.34 to 34.91) (226).

This difference in ISA between DES and BMS may be due to the effect of the antiproliferative drug on the vessel wall, causing positive remodeling, or a result of the decrease in plaque volume behind the stent struts (227). It has also been demonstrated using optical coherence tomography in patients before PCI and at 9-month follow-up that lesions with plaque rupture, thrombus, lipid-rich plaque, and thin-capped fibroatheroma have a greater incidence of ISA than do patients not having those features at baseline (83% vs. 30%, $p < 0.001$) (228).

It remains unclear exactly how ISA leads to ST. It may be the result of chronic inflammation and delayed healing, causing tissue necrosis and erosion around the stent (153). The link between inflammation, ISA, and ST has been reaffirmed by a histopathology study of ST eosinophil counts demonstrating that not only is very late ST associated with a greater degree of inflammation than other types of ST (early, late, BMS), but also eosinophil counts appear to correlate with the degree of ISA (167). Finally, ISA may serve as a trigger for thrombosis by allowing fibrin and platelet deposition behind stent struts (229).

Stent fracture. Stent fracture remains an uncommon late complication of DES implantation (230,231) whose true incidence among first-generation DES remains unknown; however, rates of 1% to 2%, 1% to 7.7%, and as high as 29% have been reported in randomized, observational, and autopsy studies, respectively (232–235). Notably, the majority of stent fractures have been reported with the Cypher SES, whereas stent fractures with TAXUS PES and BMS have been seen very rarely. This difference may be related to the increased radio-opacity of the Cypher SES, its closed cell design, and/or the greater neointimal coverage seen with the PES and BMS that may strengthen and stabilize the struts to withstand the mechanical forces that result in stent fracture. Overall, stent fractures can range from a single strut fracture (grade I) through to multiple strut fractures (grade V).

There are a number of suspected causes for stent fractures that include both mechanical and lesion-based factors.

MECHANICAL FACTORS. Stent fracture may be the consequence of an excessive mechanical vessel wall stress that occurs from extreme repetitive contraction and flexion of the vessel (233). Of note, this may actually be a protective mechanism for stress relief within the vessel.

LESION FACTORS. Predictors for stent fractures have included lesions located in the right coronary artery and/or lesions in very tortuous or severely calcified vessels. Additional factors increasing the risk of stent fracture include implantation of long and/or overlapping stents (Fig. 10), underlying diffuse disease, SVG, and treatment of CTO (230,235–237). In a recent autopsy study, longer stent length, use of the Cypher stent, and longer stent duration were all identified as independent predictors of stent fracture (235).

Patients with stent fractures may remain asymptomatic; however, they may present with ACS, ST, or recurrent angina due to clinical restenosis; overall, 70% to 80% of patients with a stent fracture will present with ISR or ST (230,231,233,238). The extent of symptoms appears to be related to the grade of the stent fracture, with few symptoms occurring as a result of grade I to grade IV stent factures, whereas grade V stent fractures are associated with the most adverse clinical events (235). There are no data on definitive treatment; however, repeat PCI, which is the current preferred strategy, appears to provides prompt symptom relief (230,231). Some suggest treatment using a short stent, together with extending DAPT beyond 12 months (239).

Coronary artery aneurysms. Coronary artery aneurysms are a rare complication of stenting, whose true incidence, clinical course, and treatment are largely unknown (Fig. 11). Nevertheless, studies report an incidence between 0.3% and 6.0% after DES and BMS implantation (240). There are a number of postulated causes for these coronary artery aneurysms, some of which are specific for DES. In general, mechanical causes include the use of oversized balloons or stents, high-pressure balloon inflations, and atherectomy—all of which can cause residual dissection and deep arterial wall injury eventually leading to aneurysm formation (241–243). Of note for DES, the elution of antiproliferative drugs and/or presence of a polymer can lead to delayed re-endothelialization, inflammatory changes in the medial wall, ISA, and hypersensitivity reactions, all of which can result in coronary artery aneurysm formation (240). Data on coronary aneurysms are derived mainly from case reports indicating a variable clinical course that is similar irrespective of whether the aneurysm is after BMS or after DES implantation. In particular, aneurysms have been detected from as early as 3 days after DES implantation (244) and as late as 9 years after BMS implantation (245).

Coronary artery aneurysms can be associated with restenosis (246), whereas turbulent and sluggish blood flow in the area of the aneurysm, coupled with a metallic stent, can predispose patients to the risk of ST and/or distal embolization (247,248). Currently, there are no definitive data on the best management of patients with coronary artery aneurysms, treatment of which is complicated by some aneurysms resolving spontaneously (249), whereas others lead to life-threatening complications. In addition to the use of long-term DAPT to minimize the risks of ST, therapeutic options that can be considered include the use of coils and cardiac surgery.

Second-Generation DES

The initial coronary stents were composed of 316L stainless steel since this material is radio-opaque and provides adequate radial strength to maintain arterial scaffolding with minimal acute recoil. An alternative to stainless steel is cobalt chromium (CoCr), which exhibits superior radial

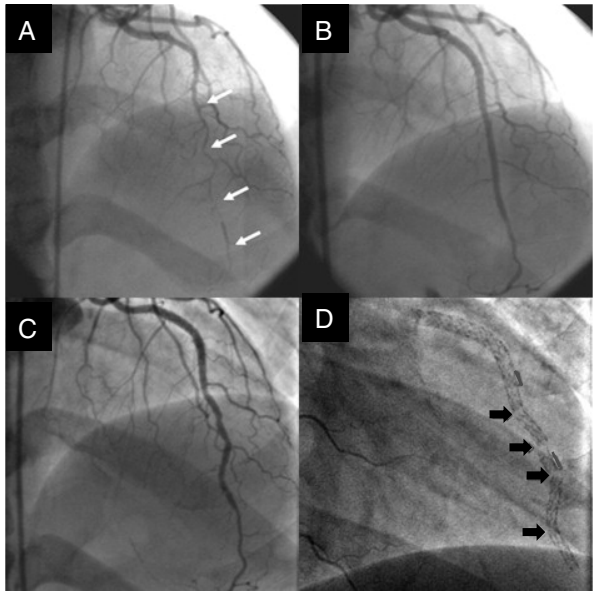


Figure 10 **Stent Fracture**

(A) A long, diffusely diseased left anterior descending artery is treated with 3 sirolimus-eluting stents **(white arrows)**. **(B)** The initial angiographic result is excellent; however, at **(C)** 3-months' follow-up, an irregular appearance is seen, and is the result of **(D)** 4 stent fractures **(black arrows)** occurring adjacent to regions of stent overlap **(red lines)**. Reproduced with permission from Popma et al. (236).

strength and improved radio-opacity, allowing for thinner stent struts that may reduce restenosis (250–252). Thinner struts can also lead to a reduction in device profile and, hence, an improvement in stent deliverability to the target lesion. The 2 second-generation DES that are currently approved by the U.S. FDA utilize CoCr, and elute "limus" drugs with the aid of more biocompatible polymers than are found on the first-generation DES.

Endeavor ZES. The second-generation Endeavor ZES (Medtronic, Minneapolis, Minnesota) uses the CoCr Driver stent platform loaded with a permanent "biomimetic" phosphorylcholine polymer (Table 1), which although not biodegradable is biostatic and biocompatible, being a natural component of the cell membrane. The polymer, which releases ~95% of the sirolimus analogue, zotarolimus, within 14 days of stent deployment, causes less inflammation compared with the polymers on the Cypher SES stent.

Both animal studies and in vivo studies using angioscopy and optical coherence tomography have shown a greater endothelial coverage of struts with ZES compared with SES and PES (157,253–255). Angioscopy has demonstrated levels of neointimal coverage with ZES that are superior to that SES and comparable to that seen with BMS (253). Similarly, the mean percentage of covered struts seen by optical coherency tomography 3 months after implantation of ZES, SES, and BMS has been reported in separate studies as 99.9%, 85%, and 99.9%, respectively (254,255).

Clinical data on ZES are available from the Real-World E-Registry, and from numerous other trials ranging from the first-in-man ENDEAVOR I study to randomized trials comparing ZES to BMS, SES, and PES (Table 8) (256–269). Data from the "all-comers" E-Registry at 12 months of follow-up, and a pre-specified subgroup of patients who had extended follow-up for 2 years in the E-Five (Endeavor Stent Registry) study, demonstrate comparable outcomes between the randomized ENDEAVOR studies and real-world patients.

The superiority of ZES compared with BMS was demonstrated in the 1,197-patient, randomized ENDEAVOR II study, which reported significantly lower in-stent late loss and angiographic binary restenosis at 9-month follow-up with ZES, together with significantly lower TLR out to 5 years of follow-up. Rates of death, MI, and ST remained comparable between both stents throughout follow-up (258,259).

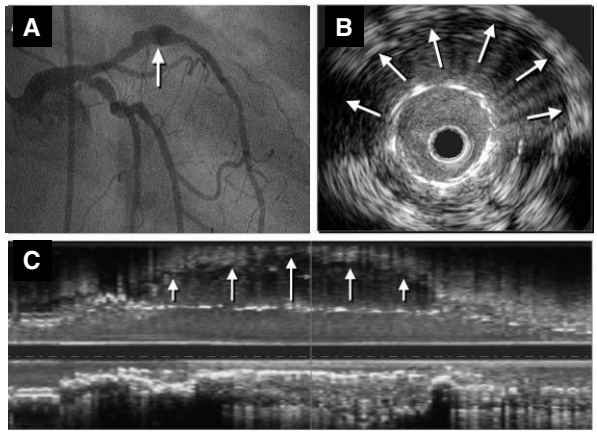


Figure 11 **Coronary Artery Aneurysms**

A coronary aneurysm **(white arrows)** is seen on **(A)** coronary angiography and on **(B)** cross-sectional and **(C)** longitudinal intravascular ultrasound. The aneurysm has led to extensive stent malapposition **(B and C)**. Reproduced with permission from Alfonso et al. (246).

In the comparison with other DES, data have indicated a relatively poorer performance of ZES compared with PES and SES at short-term follow-up, as indicated by significantly higher late loss and numerically greater TLR (260,264). Results at longer follow-up have been more reassuring after the observed reductions in the absolute difference in TLR between ZES and SES/PES. For example, in the ENDEAVOR III study, the 2.8% absolute difference in TLR between ZES and SES at 1 year was reduced to 1.6% at 5 years (260,262), whereas in the ENDEAVOR IV study, the absolute difference in TLR between ZES and PES was 1.3% and 0.5% at 1 year and 3 years, respectively (264,265). Although at only medium-term follow-up, these results suggest the absence of the "late-catch" phenomenon with ZES.

Conflicting results have been observed when comparing ZES to SES and PES for early and late ST; however, despite this, a consistent benefit has been seen with ZES in terms of reduced very late ST (Fig. 12). Although these current trials are underpowered to detect differences in ST, these inconsistencies with ZES serve to reaffirm data that indicate the lack of association between in-stent late loss and ST (270); moreover, they reiterate the complex pathophysiology underlying ST. The only adequately powered study that will provide definitive data on the safety and efficacy between ZES and SES is the fully enrolled PROTECT (Patient Related Outcomes With Endeavor Versus Cypher Stenting Trial) study. This study has randomly assigned 8,800 "all-comers" patients to treatment with either the ZES or SES, and will report a primary end point of definite/probable ST at 3-year follow-up (271).

Xience V everolimus-eluting stent (EES). The Xience V EES (Abbott Vascular, Santa Clara, California) consists of the Multilink Vision CoCr platform with a nonerodable biocompatible polymer and 100 $\mu g/cm^2$ everolimus, a synthetic derivative of sirolimus (40-O-[2-hydroxyethyl]-rapamycin). The 6- to 8-μm-thick polymer is composed of acrylic and fluorinated polymers and releases ~80% of the drug within 30 days, with nearly all the drug released within 4 months (Table 1). This stent is also marketed by Boston Scientific as the Promus stent. In the U.S., the Abbott supply agreement for the Promus stent continues until 2012 when the Promus stent will be replaced by the Promus Element stent.

Clinical data consist of both real-world registries, and randomized trials comparing EES to BMS and PES. Results have consistently demonstrated the safety and efficacy of the EES, together with low rates of ST out to long-term follow-up (Table 9) (272–282).

In brief, the randomized SPIRIT (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System) II, III, IV studies and the COMPARE (Second-Generation Everolimus-Eluting and Paclitaxel-Eluting Stents in Real-Life Practice) study have all compared EES and PES. Two-year follow-up of the SPIRIT II study was the first study to demonstrate "delayed" restenosis with everolimus, a phenomenon previously observed with other DES (283,284); however, this did not appear to have any detrimental effect on clinical outcomes. In fact, at 3-year follow-up, a greater absolute difference in cardiac death, MI, TLR, and MACE in favor of EES was observed when compared with results at both 1- and 2-year follow-up

Table 8 The Most Prominent Randomized Trials and Registries of the Second-Generation ZES

Trial (Ref. #)	No. of Patients	Follow-Up, Months	In-Stent Late Lumen Loss (ZES vs.), mm	Binary In-Stent Restenosis (ZES vs.), %	Death (ZES vs.), %	Myocardial Infarction (ZES vs.), %	Target Lesion Revascularization (ZES vs.), %	TVF (ZES vs.), %	Definite/Probable ST (ZES vs.), %
Randomized trials									
ENDEAVOR I (256,257)	ZES (n = 100)	12	0.61	5.4	0.0	1.0	2.0	2.0	1.0
		60	—	—	4.1	1.0	3.1	5.2	1.0
ENDEAVOR II (258,259)	ZES (n = 598) vs. BMS (n = 599)	9	0.61 vs. 1.03*	9.4 vs. 33.5*	1.2 vs. 0.5	2.7 vs. 3.9	4.6 vs. 11.8*†	7.9 vs. 15.1*	0.5 vs. 1.2
		60	—	—	6.2 vs. 7.6	3.8 vs. 4.8	7.5 vs. 16.3*†	15.4 vs. 24.4*	0.9 vs. 1.7
ENDEAVOR III (260,262)	ZES (n = 323) vs. SES (n = 113)	8‡/9§	0.60 vs. 0.15*	9.2 vs. 2.1‖	0.6 vs. 0.0	0.6 vs. 3.5‖	6.3 vs. 3.5†	12.0 vs. 11.5	0.0 vs. 0.0
		60	—	—	5.2 vs. 13.0‖	1.0 vs. 4.6‖	8.1 vs. 6.5†	17.9 vs. 18.5	0.7 vs. 0.9
ENDEAVOR IV (264,265)	ZES (n = 773) vs. PES (n = 775)	8‡/12§	0.67 vs. 0.42*	13.3 vs. 6.7	1.1 vs. 1.1	1.6 vs. 2.7	4.5 vs. 3.2†	6.6 vs. 7.2¶	0.9 vs. 0.1
		36	—	—	4.0 vs. 4.5	2.2 vs. 4.9‖	6.5 vs. 6.0†	12.4 vs. 16.1	1.1 vs. 1.6
ZEST (266)	ZES (n = 880) vs. SES (n = 880) vs. PES (n = 880)	12	—	—	0.7 vs. 0.8 vs. 1.1	5.3 vs. 6.3 vs. 7.0	4.9 vs. 1.4 vs. 7.5*	—	0.7 vs. 0.0 vs. 0.8‖
SORT-OUT III (267)	ZES (n = 1,162) vs. SES (n = 1,170)	9	—	—	2.0 vs. 2.0	1.4 vs. 0.5‖	4.0 vs. 1.0*†	—	1.1 vs. 0.2‖#
		18	—	—	4.4 vs. 2.7‖	2.1 vs. 0.9‖	6.1 vs. 1.7*†	—	1.1 vs. 0.5#
Registry data									
E-Registry (268)	ZES (n = 7,832)	12	—	—	2.4	1.6	4.5	7.2	1.1
E-Five Registry (269)	ZES (n = 2,116)	12	—	—	1.7	1.2	4.5	6.7	0.6
		24	—	—	2.9	1.5	5.1	7.9	0.7

Differences nonsignificant unless indicated. All trial acronyms are listed in the Online Appendix. *$p < 0.001$. †Ischemia-driven. ‡Angiographic follow-up. §Clinical follow-up. ‖$p < 0.05$. ¶$p < 0.001$ for noninferiority. #Definite only.
ST = stent thrombosis; TVF = target vessel failure (a composite of cardiac death, target vessel myocardial infarction, or target vessel revascularization); ZES = zotarolimus-eluting stent; other abbreviations as in Tables 2 and 3.

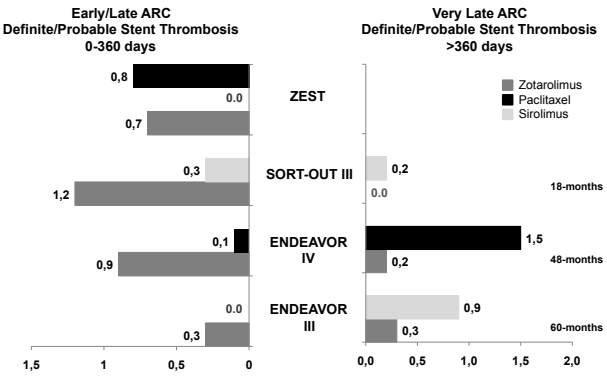


Figure 12 Rates of Stent Thrombosis Comparing ZES to SES or PES

Rates of early/late and very late definite/probable stent thrombosis in randomized trials comparing the Endeavor zotarolimus-eluting stent (ZES **[blue bars]**) to either the sirolimus-eluting stent (SES **[red bars]**) or paclitaxel-eluting stent (PES **[green bars]**). Rates of early/late stent thrombosis are consistently higher with the ZES; however, conversely, very late stent thrombosis rates are consistently lowest with ZES. No differences are significant. ARC = Academic Research Consortium.

(Fig. 13) (275). Similarly, in the larger SPIRIT III study, the benefit of EES over PES increased during follow-up, and at 3 years, use of EES lead to significant reductions in target vessel failure, target lesion failure, and MACE (278). Recently, 2 important randomized studies assessing EES have reported 12-month outcomes. The SPIRIT IV study, which enrolled 3,690 patients, represents the largest randomized trial comparing 2 DES; and the COMPARE study, which recruited 1,800 patients, was the first randomized all-comers trial of the EES (279,281). Both studies demonstrated significantly superior efficacy and safety with EES compared with PES. In addition, whereas nonsignificantly lower rates of ST have been observed in the SPIRIT II and III studies, the SPIRIT IV and COMPARE studies were the first to demonstrate a significant reduction in ST between 2 DES. At 12-month follow-up, rates of definite/probable ST for EES and PES were 0.29% versus 1.06% ($p = 0.003$), and 0.7% versus 2.6% ($p = 0.002$) in the SPIRIT IV and COMPARE studies, respectively.

Some have suggested that the superiority of EES has only been demonstrated because it has not been compared with the SES, which historically is regarded as the most efficacious first-generation DES (22,105,106). Important data on this issue will be provided by the EXCELLENT (Efficacy of Xience/Promus Versus Cypher in Reducing Late Loss After Stenting) study, which plans to randomize 1,400

Table 9 The Most Prominent Randomized Trials and Registries of the Second-Generation EES

Trial (Ref. #)	No. of Patients	Follow-Up, Months	In-Stent Late Lumen Loss (EES vs.), mm	Binary In-Stent Restenosis (EES vs.), %	Death (EES vs.), %	Myocardial Infarction (EES vs.), %	Target Lesion Revascularization (EES vs.), %	MACE (EES vs.), %	Definite/ Probable ST (EES vs.), %
SPIRIT FIRST (272,273)	EES (n = 27) vs. BMS (n = 29)	6	0.10 vs. 0.87*	0.0 vs. 25.9†	0.0 vs. 0.0	3.8 vs. 0.0	3.8 vs. 21.4‡	7.7 vs. 21.4	0.0 vs. 0.0
		60	—	—	0.0 vs. 7.4	8.3 vs. 0.0	8.3 vs. 28.0‡	16.7 vs. 28.0	0.0 vs. 0.0
SPIRIT II (274,276)	EES (n = 223) vs. PES (n = 77)	6	0.11 vs. 0.36*	1.3 vs. 3.5	0.0 vs. 1.3	0.9 vs. 3.9	2.7 vs. 6.5	2.7 vs. 6.5	0.5 vs. 1.3
		48	—	—	4.9 vs. 9.9	3.6 vs. 7.5	5.9 vs. 12.7	7.7 vs. 16.4	1.0 vs. 3.0
SPIRIT III (277,278)	EES (n = 669) vs. PES (n = 333)	8§/12‖	0.16 vs. 0.30†	2.3 vs. 5.7	1.2 vs. 1.2	2.8 vs. 4.1	3.4 vs. 5.6	6.0 vs. 10.3†	1.1 vs. 0.6
		36	—	—	2.6 vs. 4.1	3.7 vs. 6.3	5.4 vs. 8.9‡	9.1 vs. 15.7†	1.3 vs. 1.7
SPIRIT IV (279)	EES (n = 2,458) vs. PES (n = 1,229)	12	—	—	1.0 vs. 1.3	1.9 vs. 3.1†	2.5 vs. 4.6†‡	4.2 vs. 6.9*‡	0.3 vs. 1.1†
SPIRIT V (280)	EES (n = 2,663)	12	—	—	1.7	3.5	1.9	5.3	0.65
		24	—	—	3.0	4.4	3.0	7.5	0.79
COMPARE (281)	EES (n = 897) vs. PES (n = 903)	12	—	—	2.0 vs. 1.6	2.8 vs. 5.3†	2.0 vs. 5.3*	6.2 vs. 9.1†	0.7 vs. 2.6†

Differences nonsignificant unless indicated. All trial acronyms are listed in the Online Appendix. *$p < 0.001$. †$p < 0.05$. ‡Ischemia driven. §Angiographic follow-up. ‖Clinical follow-up.
EES = everolimus-eluting stent(s); other abbreviations as in Tables 2 and 3.

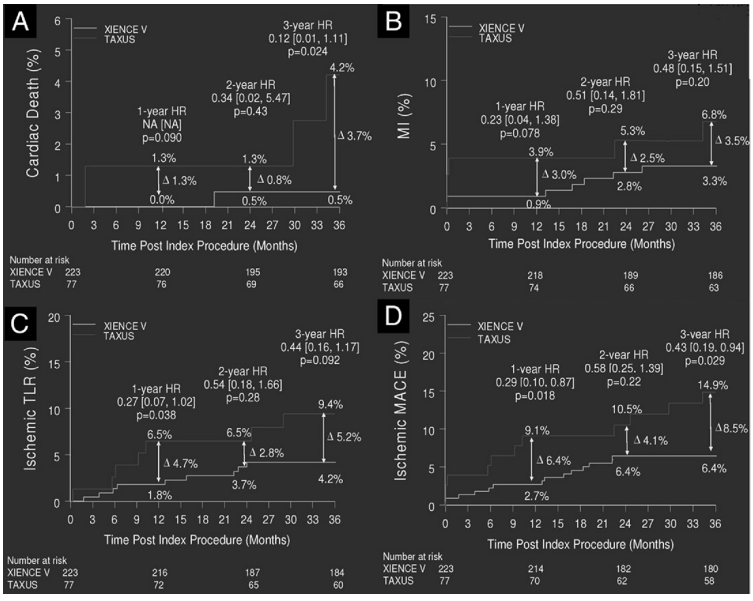


Figure 13 **Clinical Outcomes in the SPIRIT II Trial**

The delayed restenosis observed with the XIENCE V everolimus-eluting stent (EES **[white lines]**) between 1 year and 2 years may explain the reduction in the absolute difference in **(A)** cardiac death, **(B)** myocardial infarction (MI), **(C)** ischemic target lesion revascularization (TLR), and **(D)** ischemic major adverse cardiovascular events (MACE) seen between EES and the TAXUS paclitaxel-eluting stent (PES **[red lines]**) at 2-year follow-up. However, events rates remained lower with EES, and a much larger absolute difference between both stents was observed at 3-year follow-up. Reproduced with permission from Garg et al. (275). HR = hazard ratio.

patients to treatment with either EES or SES (285). The study will also investigate the optimal duration of DAPT by comparing outcomes in patients randomly assigned to 6 months or 12 months of DAPT.

The Xience PRIME EES, which represents the latest development of the Xience V stent, has recently gain regulatory approval in Europe. This modified EES has a CoCr platform; however, this is mounted on a new enhanced stent delivery system that enables the stent to be more flexible and deliverable. Furthermore, the stent balloon has higher rate burst pressures, and shorter balloon tapers to minimize the risk of edge dissections. The stent is being evaluated in the prospective, multicenter, nonrandomized SPIRIT PRIME study in 500 patients at 75 hospital centers, with the aim of gaining U.S. FDA approval.

Issues of Today

Role of BMS in Contemporary Practice

Despite the benefits of DES, there is still a role for BMS in the management of patients with CAD. Although reports indicate that DES are used in >75% of PCI procedures in the U.S. (34), their use varies widely from hospital to hospital, and in some U.S. states, DES use is actually less than BMS use. For example, recent data indicate that only 49% of PCI cases in Arkansas used a DES, with rates dropping down to 35% for rural hospitals (286). Irrespective of the specific reasons for this disparity, this report confirms the BMS are still used in contemporary practice. Ultimately, the decision to implant a BMS is guided by both clinical and economic factors.

Clinical justification for stent selection. The overall net clinical benefit of a stent can be summarized after considering the stent's beneficial and adverse effects. The benefits of DES are their significant reduction in repeat revascularization compared with use of a BMS, whereas their adverse effects relate to the increased risk of very late ST and the requirement for prolonged DAPT (22–26). Importantly, the net benefit cannot be assessed by simply determining the difference between these 2 outcomes, as they both have a different incidence and clinical consequence. For example, in a study by Stone et al. (287), the rate of ST and TLR was

3.1% (DES:BMS 1.4:1) and 12.3% (DES:BMS 0.47:1), respectively, whereas the rate of death and MI within 7 days for these events was 91.1% for ST and 3.5% for TLR. Therefore, to assess the overall net clinical benefit, actual mortality must be considered. Extensive data exist to confirm that DES not only significantly reduce restenosis compared with BMS, but do so without increasing the risk of mortality or MI. Thus, the overall net clinical benefit favors DES.

It must be appreciated, however, that this benefit in favor of DES is not universal, and in certain patients and lesions this net benefit may ultimately favor a BMS. The advantage of a DES in terms of reducing restenosis is dependent on lesion characteristics, and the observed benefit is greater in lesions at higher risk for restenosis. For example, the absolute difference in rates of repeat revascularization between DES and BMS for lesions in vessels <3 and >3 mm in diameter in the BASKET trial at 3-year follow-up was 9.1% and 2.0%, respectively (288). Similarly, in the Ontario registry, Tu et al. (289) reported a significantly lower rate of TVR with the use of DES compared with BMS among diabetic patients who had lesions that were >20 mm long in vessels <3 mm in diameter (DES vs. BMS 7.2% vs. 17.6%, HR: 0.38, 95% CI: 0.24 to 0.60, $p < 0.001$; number needed to treat to prevent TVR = 10). Conversely, no significant different in TVR was seen between DES and BMS when patients were not diabetic and had lesions <20 mm long in vessels >3 mm in diameter (DES vs. BMS 5.3% vs. 5.9%, HR: 0.87, 95% CI: 0.52 to 1.47, $p = 0.61$; number needed to treat to prevent TVR = 167) (289). The risk of ST is also variable and may be increased for patients who are not willing to, or are unlikely to, comply with DAPT, or for patients awaiting elective surgery (146,172). Therefore, for patients whose risk of restenosis is relatively low (i.e., nondiabetic, large vessel >3 mm in diameter), and/or the risk of ST is relatively high (inability to comply with long-term DAPT), a BMS maybe more appropriate. Ultimately, an evaluation of the overall risk/benefit ratio should play a key role in the clinical decision whether to implant a BMS or DES.

Cost effectiveness. Unfortunately, the discussion of stent selection cannot be made without considering the cost effectiveness of both therapies, in view of the additional initial expense associated with using a DES. Numerous cost-effectiveness analyses have been performed with conflicting results. Of note, many studies group patients treated with different DES together as 1 population, which ultimately can affect the accuracy of cost-effectiveness calculations for individual stents.

Some studies indicate that DES may be cost effective or even cost saving with specific patients, such as those who have lesions with a high risk for restenosis such as diabetic patients, long lesions, and lesions in vessels with small diameters. In the BASKET study, for example, DES were more effective and less expensive for vessels <3.0 mm diameter. For vessels >3.0 mm diameter, although the overall cost per quality-adjusted life-year gained was €39,641 ($59,392), subgroup analysis revealed that the cost per quality-adjusted life-year gained was €6,863 ($10,282) for off-label use, €3,471 ($5,200) for lesions ≥24 mm in length, and €300 ($450) for patients ≥65 years of age (290). Conversely, other studies report an incremental cost-effectiveness ratio of >200,000 Canadian dollars per quality-adjusted life year—indicating DES are not cost effective (291).

Importantly, the use of angiographic follow-up in randomized controlled trials and a short period of follow-up are 2 major factors that can bias results in favor of DES. Nevertheless, a recent systematic review evaluated 19 different cost-effectiveness studies that mainly reported results at 1 year, and concluded that the cost effectiveness of DES was unfavorable compared with that of BMS. That was primarily because, although the use of DES was associated with a higher initial cost (€700 [$1,060]), they did not increase life expectancy, produced only a small relative reduction in rates of repeat procedures, and led to only a short duration of improved quality of life (291).

Further data suggesting DES are not cost effective come from analysis at 1 year of the outcomes from patients in France enrolled in the TYPHOON (Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated With Balloon Angioplasty), which reported the mean aggregate 1-year costs were €1,142 ($1,711) higher per patient in the SES group compared with the BMS group. The incremental cost-effectiveness ratio was €7,321 ($10,972) per TVR avoided (292).

By restricting follow-up to 1 year, previous cost-effectiveness studies have the potential to miss accounting for the costs incurred with very late ST, thereby introducing bias against BMS. To investigate the impact of long-term follow-up, Bischof et al. (293) performed an analysis using a Markov model to speculate on the cost effectiveness of using DES in the U.S. Medicare setting at 1 to 3 years of follow-up. Their results suggested that DES were not cost effective compared with BMS when used in unselected patients with CAD in the setting of Medicare (293).

In the United Kingdom, the National Institute of Clinical Excellence has taken into account the differences in cost between DES and BMS, and the differences in the risk of restenosis for specific lesions. Therefore, they have recommended DES in cases where lesions are >15 mm in length, in vessels <3.0 mm in diameter, provided the cost difference between BMS and DES is £300 or less (€330 [$500]) (294).

The increasing development of DES in the developing world and the expiry of the patent for sirolimus are both likely to lead to reductions in the cost of DES, completely altering the cost-effectiveness evaluations that have previously been performed.

Diabetes Mellitus

Diabetic patients are known to have an aggressive form of atherosclerosis with less favorable long-term survival after PCI compared with that of nondiabetic patients. Moreover, diabetes mellitus is frequently identified as an independent predictor of ISR (295,296), although the underlying mechanisms for this are poorly understood. Implicated factors include the greater degree of the vascular inflammation and endothelial dysfunction seen in diabetic patients (297,298) together with poor glycemic control (299) and insulin resistance that can aggravate restenosis through the direct growth factor-like effect of insulin on vascular smooth muscle and neointimal cells (300).

BMS versus DES. **REGISTRY DATA.** The most recent registry data come from the MDACR (Massachusetts Data Analysis Center Registry) and the SCAAR registry, which have reported results for 5,051 and 19,004 diabetic patients, respectively. The MDACR, which reported the results of propensity-matched diabetic patients treated with either BMS or DES, demonstrated significantly lower rates of death, MI, and repeat revascularization with DES at 3-year follow-up (301). The SCAAR registry only assessed patients treated with DES and demonstrated that, overall, patients with diabetes were at higher risk of restenosis compared with nondiabetic patients. Interestingly, this was only true for patients treated with SES and ZES; the rate of restenosis for patients treated with PES was not influenced by diabetic status. Ultimately, no mortality difference was demonstrated between the different DES (302).

RANDOMIZED DATA. The evaluation of diabetic patients with the use of DES is hampered by the distinct lack of dedicated randomized trials. At present, only 10 randomized trials enrolling 1,662 patients have been conducted with DES to specifically assess outcomes in diabetic patients: 4 Cypher SES versus BMS, 5 Cypher SES versus TAXUS PES, and 1 Cypher SES versus ZES (49–53,102–104,303–308). There are no dedicated randomized trials assessing the performance of EES in diabetics, and data are derived from the diabetic patient subgroup (n = 1,185; 786 EES, 399 PES) of the SPIRIT IV trial (279) and the diabetic subgroup of the SPIRIT V study, which randomly assigned 324 patients to EES (n = 215) or PES (n = 104) (309). Similarly, the only data comparing ZES and PES are derived from 477 diabetic patients (241 ZES, 236 PES) in a subgroup analysis of the ENDEAVOR IV study (310).

SAFETY. Pooled analyses of diabetic subgroups from randomized trials comparing SES to BMS and PES to BMS among diabetic patients have demonstrated conflict results. Spaulding et al. (23) reported significantly higher mortality with the use of SES compared with BMS at 4-years follow-up (12.2% vs. 4.4%, p = 0.004); however, the authors acknowledge that this result may have been a play of chance, particularly in view of the small number of actual deaths in the diabetic subgroup (SES 23 vs. BMS 10). At the same length of follow-up, Kirtane et al. (311) reported comparable mortality between PES and BMS (PES 8.4% vs. BMS 10.3%, p = 0.61), and reassuringly, a collaborative network analysis by Stettler et al. (312) that included 3,850 patients demonstrated no significant difference in mortality between SES, BMS, and PES in the treatment of diabetic patients who received DAPT for >6 months.

Among different DES, no differences in mortality or MI have been noted. A recent meta-analysis (313) of 5 dedicated randomized trials comparing SES to PES—the ISAR-DIABETES (Intracoronary Stenting and Angiographic Results: Do Diabetic Patients Derive Similar Benefit From Paclitaxel-Eluting and Sirolimus-Eluting Stents?), DES-DIABETES (Drug-Eluting Stents in Patients With Diabetes Mellitus), and DiabeDES (Diabetes and Drug Eluting Stent) trials, and studies by Kim et al. (303) and Tomai et al. (307)—that in total enrolled 1,069 patients, with follow-up of as long as 2 years, reported no significant difference between SES and PES with respect to mortality (OR: 0.78, 95% CI: 0.30 to 2.07) or the risk of MI (OR: 0.88, 95% CI: 0.33 to 2.38). No significant differences in mortality, MI, or ST were reported at 12-month follow-up between either ZES and PES, or between EES and PES in the SPIRIT IV study. In the SPIRIT V diabetic cohort, treatment with EES led to a significantly lower risk of the composite of cardiac death/MI (3.7% vs. 9.6%, p = 0.04), which was driven by the significantly lower rate of MI with EES (309). The rate of ST was 0.0% for EES and 1.9% for PES.

EFFICACY. Clinical data indicate the superior performance of the SES with respect to BMS and both PES and ZES. The 4 dedicated randomized trials comparing SES to BMS (DECODE [A Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent in the Treatment of Diabetics Patients With Native Coronary Artery Lesions], SCORPIUS [German Multicenter Randomized Single Blind Study of the CYPHER Sirolimus-Eluting Stent in the Treatment of Diabetic Patients With De Novo Native Coronary Artery Lesions], DESSERT [Diabetes Drug-Eluting Sirolimus Stent Experience in Restenosis Trial], and DIABETES [Diabetes and Sirolimus-Eluting Stent]) have collectively enrolled ~600 patients, and have all demonstrated significant reductions in their primary end point of in-segment late loss at between 6 and 9 months of follow-up. Furthermore, although not powered to detect differences in clinical outcomes, they have also all shown significant reductions in TLR at follow-up of between 8 and 48 months.

Similarly, 4 of the 5 dedicated randomized trials comparing SES to PES have demonstrated significant reductions in in-segment late loss for SES compared with PES. With respect to reintervention, no significant difference has been shown in any of the individual trials apart from the DES-DIABETES study, which reported a somewhat unexpected 75% reduction in reintervention at 2 years for SES

compared with PES (SES 3.5% vs. PES 11%, OR: 0.25, 95% CI: 0.08 to 0.77, p = 0.004). Meta-analysis of these 5 trials, which include a total of 1,069 patients with follow-up of as long as 2 years, has indicated that overall treatment with SES is associated with significant reductions in restenosis (OR: 0.29, 95% CI: 0.18 to 0.47) and reintervention (OR: 0.47, 95% CI: 0.28 to 0.77), compared with PES (313).

The DiabeDES III study is the only randomized comparison involving treatment with ZES. This study randomly allocated 127 diabetic patients to either ZES or SES, and demonstrated significantly lower late lumen loss with SES (0.14 mm vs. 0.74 mm, $p < 0.001$) at 10-month follow-up (308). In the subgroup of diabetic patients returning for angiographic follow-up in the ENDEAVOR IV study (n = 86), a trend toward higher in-stent late loss was seen in patients treated with ZES compared with SES (0.81 vs. 0.56, p = 0.073), whereas no notable differences in 1-year TLR were seen (310). Similarly, in the SPIRIT IV study, despite significant reductions at 1 year in TLR, TVR, MACE, and target vessel failure among nondiabetic patients treated with EES compared with PES, no significant differences in any of these outcomes were seen among diabetic patients (279). In the SPIRIT V study, EES was shown to be noninferior and subsequently superior to PES with respect to in-stent late loss at 9 months (0.19 mm vs. 0.39 mm, $p_{noninferority} < 0.0001$, $p_{superiority} = 0.0001$); rates of repeat revascularization remained comparable between both stents (309). Some of these results are at variance with the meta-analysis by Kastrati et al. (313), and therefore, reiterate that there is presently no clear evidence to indicate that "limus"-based DES are superior to paclitaxel in the treatment of coronary lesions in diabetic patients.

DES versus CABG for diabetic patients. The CARDia (Coronary Artery Revascularization in Diabetes Trial) is the only randomized trial comparing the management of diabetes with multivessel disease (MVD) between CABG and PCI; however, because of poor recruitment, it was discontinued early after enrolling only 510 of the desired 600 patients, and is therefore largely underpowered. The ultimately negative noninferiority trial found no significant difference in 1-year mortality (3.2% PCI vs. 3.3% CABG, p = 0.83) or the 1-year composite clinical end point of death, nonfatal MI, or nonfatal stroke (10.2% for PCI vs. 11.8% for CABG); however, repeat revascularization was required more frequently in the PCI group (9.9% vs. 2.0%, p = 0.001). Although PCI was performed with DES in only 71% of cases, even these patients had higher rates of repeat revascularization when compared with CABG (7.3% vs. 2.0%, p = 0.013) (314).

More recently, the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) study, although not a dedicated randomized trial of diabetic patients, did enroll 452 diabetic patients (221 CABG, 231 PCI). Results demonstrated a higher rate of major adverse cardiovascular and cerebrovascular events (MACCE) for patients treated with PCI that was mainly driven by significant higher rates of repeat revascularization. Overall, the presence of diabetes increased mortality for both revascularization strategies (315). Further information about the optimal treatment for diabetic patients with MVD will be known with the results of the ongoing FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial (316).

STEMI

Invasive reperfusion therapy has improved the prognosis of patients with STEMI (317,318), and new recommendations from the American College of Cardiology/American Heart Association (ACC/AHA) indicate that DES are a reasonable alternative to BMS for these patients (319). There have been concerns, however, that the use of DES in this setting may predispose to a higher risk of ST (143,320,321), which may result from the following: 1) the trapping of thrombus behind stent struts and subsequent thrombus resolution, which can lead to an increased risk of ISA; 2) the protrusion of stent struts into underlying necrotic core due to overlying plaque rupture; 3) a delay in arterial healing (e.g., greater incomplete stent strut endothelialization and persistent fibrin deposition) that has been recognized at the culprit site in patients with STEMI compared with patients treated for stable angina (322); and 4) high risk of adverse events for patients noncompliant to DAPT, as suggested by results from the PREMIER (Prospective Registry Evaluating Myocardial Infarction: Events and Recovery) study, which reported a significantly increased 11-month mortality among the 13.6% of patients who discontinued DAPT 30 days after their revascularization for ACS or STEMI (172).

Clinical data on outcomes from primary PCI are limited at present by the short duration of follow-up in most studies. The largest randomized primary PCI trial to date, the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) study, has reported angiographic data and clinical outcomes at 13 and 24 months, respectively, among 3,006 STEMI patients treated with PES or BMS. At 13 months, there were significant reductions in in-stent late loss and binary restenosis with PES (91). At 24 months of clinical follow-up, the use of PES was associated with significant reductions in the respective primary and second efficacy end point of ischemia-driven TLR ($p < 0.001$) and ischemic TVR ($p < 0.001$). In addition, there were no significant differences at 24 months between PES and BMS in the primary safety end point, a composite of death, MI, stroke or ST (PES 11.0% vs. BMS 11.2%, p = 0.90), or all-cause mortality, cardiac death, reinfarction, or definite/probable ST (92).

A previous meta-analysis by Kastrati et al. (323) of 2,786 patients undergoing primary PCI reported no significant difference in terms of death, MI, or ST between BMS or DES, and significant reductions in the risk of reintervention

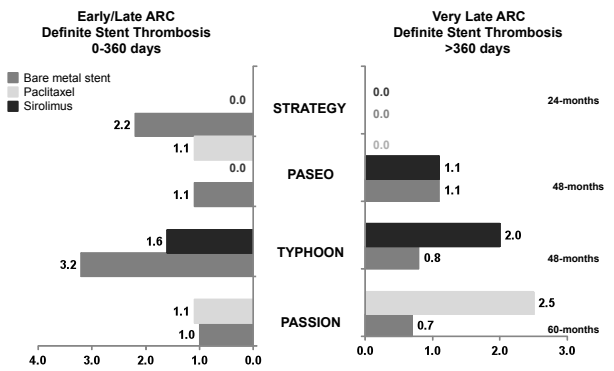


Figure 14 Rates of Stent Thrombosis Comparing DES to BMS

Rates of early/late and very late definite stent thrombosis (ST) in randomized trials comparing paclitaxel-eluting stents **(green bars)** and sirolimus-eluting stents **(red bars)** to bare-metal stents **(blue bars)** among patients undergoing primary percutaneous coronary intervention at long-term follow-up. Although no differences are significant, the rates of early/late ST are numerically higher with bare-metal stents, whereas the rates of very late ST are numerically greater with drug-eluting stents. ARC = Academic Research Consortium.

with DES (HR: 0.38, 95% CI: 0.29 to 0.50, $p < 0.001$). Unfortunately, follow-up was limited to 2 years (323).

More recently, Brar et al. (324) performed a much larger meta-analysis of 13 randomized trials that included 7,352 patients followed up for a maximum of 2 years. Results again demonstrate no significant difference between BMS and DES in terms of mortality (RR: 0.89, 95% CI: 0.70 to 1.14), MI (RR: 0.82, 95% CI: 0.64 to 1.05), and ST (RR: 0.97, 95% CI: 0.73 to 1.28), whereas the use of DES led to a significant reduction in repeat TVR (RR: 0.44, 95% CI: 0.35 to 0.55, $p < 0.001$). Notably, this benefit in reduced TVR was consistent in patients irrespective of whether DAPT was given for <6 months or >6 months, or whether follow-up was for 1 year or >1 year. Another important observation was that the benefit seen with DES treatment was greater for patients at highest risk of restenosis (324). A concurrent meta-analysis of 18 registries that included >26,000 patients was performed by the same group, and has shown similar results, with comparative outcomes in terms of death and MI between DES and BMS and significant reductions in terms of repeat revascularization with DES at up to 3-year follow-up (324).

Long-term follow-up data (≥4 years) that are available from 1 registry and 4 randomized studies have shown conflicting results. The randomized TYPHOON study, the PASEO (Paclitaxel or Sirolimus-Eluting Stent Versus Bare Metal Stent in Primary Angioplasty) study, and the STRATEGY (Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent Versus Abciximab and Bare Metal Stent in Myocardial Infarction) study, which all randomly assigned STEMI patients to treatment with either DES and BMS, have all shown positive results in favor of using DES with respect to reduced rates of repeat revascularization, and comparable safety at between 4- and 5-year follow-up (58,62,64). Specifically, the TYPHOON study, which randomly allocated 715 STEMI patients to treatment with either BMS or SES, demonstrated no significant differences in rates of death, cardiac death, and MI at 4-year follow-up, whereas rates of TLR and TVR were significantly lower in the SES group. With respect to ST, although the overall rate was comparable between groups (SES 3.6% vs. BMS 4.0%, $p = 0.82$), very late ST was numerically higher with SES (2.0% vs. 0.8%) (Fig. 14) (64). These results need to be interpreted with caution, considering the extensive exclusion criteria used during enrollment (only 35% of screened patients were enrolled) (63) and that complete follow-up was available for only 70% of patients.

At variance with these results are data from a large single-center registry of 1,738 patients by Kukreja et al. (325) and the 5-year follow-up results of the 619-patient PASSION (Paclitaxel-Eluting Stent Versus Conventional Stent in Myocardial Infarction With ST-Segment Elevation) randomized trial (95). Kukreja et al. (325) reported no overall significant differences between DES (SES, $n = 185$; PES, $n = 1,022$) and BMS ($n = 531$) in all-cause mortality (BMS 16.4% vs. SES 11.4% vs. PES 12.9%) or repeat revascularization (8.0% vs. 7.0% vs. 6.9%, respectively) at a median follow-up of 1,185 days. Moreover, although there were no differences in overall, early, or late ST rates, there were no cases of very late ST in the BMS group compared with a rate of 2.7% and 0.9%, respectively, in the SES group ($p = 0.001$) and the PES group ($p = 0.03$).

Similarly, in the PASSION study, which had considerably fewer exclusion criteria compared with the TYPHOON study and enrolled 60% of patients who were screened, no significant differences were observed in overall MACE, mortality, reinfarction, and TLR between patients treated with PES or BMS out to 5-year follow-up. Overall rates of definite/probable ST were comparable (PES 3.9% vs. BMS 3.4%, p = 0.85); however, rates of late/very late ST were approximately 3 times higher among patients treated with PES (3.2% vs. BMS 1.1%, p = 0.09) (Fig. 14). Again, these results must interpreted with caution considering the relatively small sample size and the lack of power to detect differences in ST.

Multivessel CAD

The debate over the optimal method of revascularizing patients with MVD has raged for many years and continues to this day. The importance of this patient subgroup cannot be under estimated considering the increasing age and multiple comorbidities of patients currently being investigated for CAD, and the correspondingly higher number of patients with MVD ultimately requiring revascularization (326). Historically, CABG has been the accepted treatment for MVD (327); however, advances in the percutaneous treatment of CAD have made PCI a more attractive alternative (28,77,328). Despite this, observational data from real-world practice indicate that for two-thirds of patients with complex CAD, cardiac surgery remains the preferred method of revascularization, findings that have been supported by a recent prospective randomized trial (28,329).

BMS versus CABG. A meta-analysis of the 4 randomized trials comparing outcomes at 5-year follow-up in patients with MVD treated with either a BMS or CABG showed a similar rate of the composite of death, stroke, and MI (PCI 16.7% vs. CABG 16.9%; HR: 1.04, 95% CI: 0.86 to 1.27, p = 0.69); a numerically higher rate of stroke with CABG (PCI 3.1% vs. CABG 3.9%; HR: 1.16, 95% CI: 0.73 to 1.83, p = 0.54); and a significantly higher rate of repeat revascularization with the use of a BMS (29.0% vs. 7.9%; HR: 0.23, 95% CI: 0.18 to 0.29; p < 0.001) (330). A much larger meta-analysis by Bravata et al. (331) that included 23 randomized controlled trials comparing PCI (POBA or BMS; n = 5,019) with CABG (n = 4,944) showed that despite a significantly higher rate of procedure-related stroke after CABG (1.2% vs. 0.6%, p = 0.002), and more frequent repeat revascularization after PCI (absolute risk difference 24% at 1 year and 33% at 5 years), there was no difference in survival between percutaneous and surgical intervention. More recently, Hlatky et al. (332) performed a collaborative analysis using patient data from trials comparing POBA and BMS to CABG and reported somewhat similar findings, with significantly higher stroke rates at 90 days after CABG, significantly higher repeat revascularization after PCI, and no overall significant difference in terms of mortality at a median of 5.9 years of follow-up (PCI 15% vs. CABG 16%, HR: 0.91, 95% CI: 0.82 to1.02, p = 0.12).

BMS versus DES. The development of DES led to significant reductions in the rates of restenosis and repeat revascularization when compared with BMS. Consequently, if PCI is selected, there is little debate over whether to use a DES or a BMS; in fact, some would argue that patients with MVD where a DES cannot be used should be offered surgical revascularization. Currently, no dedicated prospective randomized trials have been performed comparing DES and BMS for patients specifically with MVD, and data supporting the use of DES in these patients, as opposed to BMS, come from the extrapolation of data from registries, nondedicated trials, and subgroup analyses. The ARTS-II study recruited 607 patients with 2- or 3-vessel disease treated with DES, who were then compared with patients with 2- or 3-vessel disease treated with BMS who were recruited in the ARTS-I study. At 5-year follow-up, there was no significant difference in survival (DES 94.5% vs. BMS 92.0%), whereas the use of DES led to significant reductions in repeat revascularizations (20.8% vs. 30.9%, p < 0.001) and overall MACCE (27.5% vs. 41.5%, p < 0.001) (Fig. 4) (77).

At variance with these results is the risk-adjusted outcomes among 60,000 patients undergoing PCI or CABG in the New York cardiac registry (333). Results suggested a significantly higher risk-adjusted survival among the CABG group (HR: 0.64, 95% CI: 0.56 to 0.74), with the difference being most pronounced in patients with 3-vessel disease and proximal left anterior descending artery disease. Complete risk adjustment was impossible to achieve, particularly as clinical judgment could not be adjusted for in this complex cohort of patients.

DES versus CABG. Data comparing the outcomes in patients with MVD treated with DES and CABG were initially derived from the addition of DES arms to the initial BMS-CABG trials, to allow a comparison of outcomes between DES and historical CABG cohorts. This was performed in the ARTS-II study, which at 5 years again demonstrated no significant difference in survival between DES and CABG (DES 94.5% vs. CABG 92.6%), but significantly higher rates of repeat revascularization (20.8% vs. 9.0%, p < 0.001) and MACCE (27.5% vs. 21.1%, p = 0.02) with the use of DES (Fig. 4) (77). A similar approach was performed in the ERACI-III (Argentine Randomized Study: Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Multi-vessel Disease) study, which added 225 DES patients to the 500 patients (225 BMS, 225 CABG) in the ERACI-II study. At 1-year follow-up, freedom from adverse events was significantly greater among patients treated with DES (88.0% vs. 80.5% CABG, p = 0.038), whereas at 3-year follow-up, event rates were equal (77.3%, p = 1.0). This convergence was largely driven by the significantly higher TVR in the PCI cohort at 3 years (5.8% vs. 14.2%, p < 0.002). Of note, mortality was highest in the

cohort treated with CABG at both 1-year follow-up (3.1% vs. 7.6%, RR: 0.41, 95% CI: 0.17 to 0.97) and 3-year follow-up (5.7% vs. 9.8%, RR: 0.59, 95% CI: 0.31 to 1.14) (334).

Observation data, again from the New York cardiac registry, of 17,400 patients reported similar rates of unadjusted survival at 18 months between DES and CABG in patients with 3-vessel (93.7% vs. 93.4%, p = not significant) and 2-vessel (95.0% vs. 94.9%, p = not significant) disease. However, after adjustment of variables that are difficult to adjust for, such as the judgment of the treating physician, outcomes in favor of CABG were obtained (94.0% vs. 92.7%, p = 0.03; and 96.0% vs. 94.6%, p = 0.003 for 3- and 2-vessel disease, respectively) (335,336).

The only randomized data comparing DES to CABG in patients with MVD comes from the previously discussed CARDia trial, and the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) study (28,314). The SYNTAX study was a large, prospective, multicenter, "all-comers" trial that assessed outcomes in 1,800 patients with either left main (705 patients: PCI 357, CABG 348) or 3-vessel disease (1,095 patients: PCI 546, CABG 549) randomly allocated to treatment with either PCI (with PES) or CABG (28). The all-comers study design and the use of the SYNTAX score allowed the study to address the important limitations of previously conducted randomized trials comparing PCI and CABG. These limitations included patient selection; for example, in studies comparing BMS to CABG, only 4% of those initially screened were eventually randomized (330), with a common exclusion being patients with impaired left ventricular function (327). Second, all patients with MVD are not the same, and the previous trials did not include any methods of categorizing the extent of MVD or the lesion complexity to allow results to be put into context and stratified according to disease severity.

Among patients with triple-vessel disease, the overall respective rates of death (4.1% vs. 6.5%; p = 0.07), cardiac death (2.3% vs. 4.5%; p = 0.05), stroke (2.3% vs. 1.7%; p = 0.47), MI (2.8% vs. 6.1%; p = 0.009), repeat revascularization (7.5% vs. 17.4%; p < 0.001), and MACCE (14.4% vs. 23.8%; p < 0.001) favored CABG at 2-year follow-up. Moreover, as shown in Figure 15, when outcomes are stratified according to disease complexity using the SYNTAX score, outcomes between PCI and CABG are only comparable among patients in the lowest SYNTAX score tercile (≤22) (337).

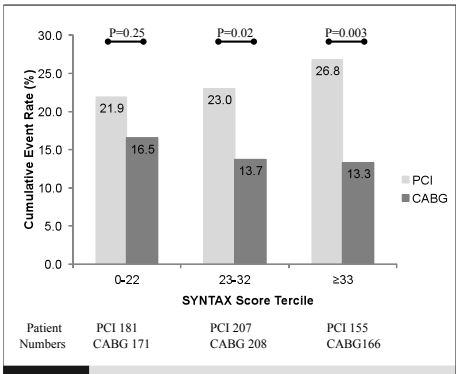


Figure 15 **MACCE Among Patients With Triple-Vessel Disease in the SYNTAX Trial**

The rates of major adverse cardiovascular and cerebrovascular events (MACCE [a composite of death, stroke, myocardial infarction, and repeat revascularization]) at 2-year follow-up among patients with triple-vessel disease treated with percutaneous coronary intervention (PCI **[blue bars]**) or coronary artery bypass graft surgery (CABG **[red bars]**) in the SYNTAX trial. For patients with a SYNTAX score between 0 and 22, PCI offers a suitable alternative to CABG (339).

UPLMS Disease

Using PCI for UPLMS disease was deemed inappropriate according to the 2009 ACC/AHA appropriateness criteria for coronary revascularization, which was in line with guidelines from the U.S. and Europe that both gave PCI for UPLMS a Class III indication for patients suitable for CABG (338,339). However, despite these guidelines, in 2006, approximately one-quarter of UPLMS disease was still treated by PCI (329). More recently, a white paper that includes a comprehensive review of the literature was published in this *Journal*, and suggests that in specific patients and lesions, PCI may offer a suitable alternative to CABG (340). Following on from this, the 2009 focused update on PCI published by the ACC/AHA has upgraded PCI for UPLMS to a Class IIb indication, and it may be considered for appropriate patients, namely, those with coronary anatomy that is associated with a low risk of procedural complication if treated by PCI and/or clinical conditions that predict an increased risk of adverse surgical outcomes (319). Unfortunately, current studies assessing outcomes in UPLMS stenting are limited by being largely observational with relatively short follow-up.

BMS versus DES. In brief, at present there is only 1 randomized trial comparing outcomes between DES and BMS for PCI of UPLMS (96). Erglis et al. (96) enrolled 103 patients randomly assigned to PCI with either PES or BMS and reported, as expected, that at 6-month follow-up, the use of DES leads to significant reductions in repeat revascularization when compared with BMS without exposing patients to any additional risk of death, MI, or ST. Further comparisons between BMS and DES in UPLMS PCI, from largely nonrandomized, observational studies with follow-up ranging from 6 months to 3 years, report similar findings. These results, however, must be taken in the context of the observational nature of the studies involved and the subsequent limitations that encompasses, such as patient selection and a lack of statistical power to demonstrate differences in events and ST (340).

SES versus PES. Three studies have assessed the outcomes of UPLMS PCI between patients treated with SES

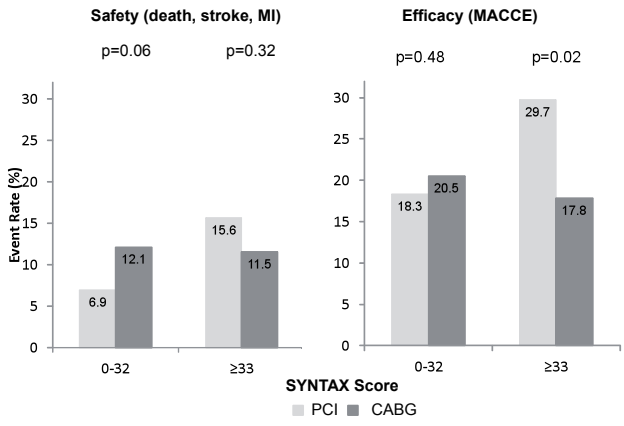


Figure 16 MACCE Among Patients With Left Main Disease in the SYNTAX Trial

The rates of safety (death, stroke, and myocardial infarction [MI]) and efficacy (major adverse cardiovascular and cerebrovascular events [MACCE], a composite of death, stroke, MI, and repeat revascularization) among patients with left main disease treated with percutaneous coronary intervention (PCI **[blue bars]**) or coronary artery bypass graft surgery (CABG **[red bars]**) in the SYNTAX trial. For SYNTAX scores between 0 and 32, PCI appears to be as safe and efficacious as CABG; for scores of 33 and above, CABG is superior (347).

and PES (113,341,342). The 607-patient ISAR-LEFT MAIN (Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions) study represents the only dedicated randomized study, and at 1 year, there was no significant difference in the primary end point, a composite of death, MI, or TLR, between SES or PES (PES 13.6% vs. SES 15.8%, p = 0.44) (113). In addition, angiographic restenosis at 6- to 9-month follow-up (PES 16.0% vs. SES 19.4%, p = 0.30), mortality (PES 10.7% vs. SES 8.7%, p = 0.64), and UPLMS-specific TLR (PES 9.2% vs. SES 10.7%, p = 0.47) at 2-year follow-up, together with ST were all comparable between SES and PES. Longer follow-up is available from subgroup analyses of the DELFT (Drug-Eluting Stent for Left Main) registry and MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) registry. At 3-year follow-up, both studies demonstrated similar adjusted rates of death, MI, and TVR, and comparable ST (341,342).

PCI versus CABG. Consistent with the previous discussion on MVD, PCI in patients with UPLMS has shown similar safety outcomes, and consistently higher rates of repeat revascularization compared with CABG. The nonrandomized MAIN-COMPARE registry that enrolled 2,240 patients (1,138 CABG and 1,102 who had PCI: 318 BMS, 784 DES) is the largest single study comparing PCI to CABG to date. At 3-year follow-up, outcomes among a propensity-matched cohort of patients were comparable in terms of death (HR: 1.18 for PCI, 95% CI: 0.77 to 1.80, p = 0.45) and MACCE (HR: 1.10 for PCI, 95% CI: 0.75 to 1.62, p = 0.61), whereas repeat revascularization was significantly higher in the PCI group (HR: 4.76, 95% CI: 2.80 to 8.11, p < 0.001), with DES performing much better than BMS (26). At 5-year follow-up, overall results were unchanged (343). Of note, similar findings have also been reported out to 3-year follow-up in a meta-analysis of 3,773 patients with UPLMS undergoing revascularization by PCI or CABG (344).

The UPLMS subgroup from the SYNTAX trial (357 PCI, 348 CABG) represents the largest cohort of patients randomized to either PCI or CABG. In the overall UPLMS group at 2 years, 22.9% and 19.3% of patients treated with PCI and CABG, respectively, reached the primary end point of MACCE (p = 0.27), a composite of mortality (PCI 5.6% vs. CABG 6.2%, p = 0.77), MI (5.5% vs. 4.1%, p = 0.45), stroke (0.9% vs. 3.7%, p = 0.01), and repeat revascularization (17.3% vs. 10.4%, p = 0.01).

The stratification of outcomes according to the SYNTAX score has demonstrated that for patients with scores between 0 and 32, PCI with PES may be safer and as efficacious as CABG, whereas for patients with scores ≥33, CABG offers a safer and more efficacious treatment, albeit at a higher risk of stroke (Fig. 16). In the overall SYNTAX study population, 421 of the 1,212 patients with UPLMS disease had a SYNTAX score between 0 and 32, indicating that approximately one-third of patients with UPLMS are suitable for PCI (345).

The results from the SYNTAX trial have fuelled the debate with respect to the management of UPLMS disease, and prompted the first dedicated UPLMS trial, the EXCEL (Evaluation of Xience Prime Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) study, which will randomize 2,500 patients to revascularization with either the Xience V PRIME EES or CABG. The trial aims to commence enrollment in late 2010 (346).

CTO

CTOs are encountered in ~15% to 30% of patients referred for coronary angiography, and generally regarded as 1 of the few remaining challenges for interventional cardiologists (347). They are associated with lower procedural success rates compared with nonocclusive lesions, with inability to cross the CTO with a wire as the most commonly cited reason for procedural failure (347).

Successful percutaneous recanalization of a CTO, compared with a failed attempt, offers the benefit of a reduction in symptoms, improved left ventricular function, and improved survival (348–351). For example, the 376-patient multicenter TOAST-GISE (Total Occlusion Angioplasty Study–Società Italiana di Cardiologia Invasiva) study reported significant reductions in mortality (1.05% vs. 7.23%, $p = 0.005$), and a greater rate of angina-free survival (88.7% vs. 75.0%, $p = 0.008$) among patients with successful CTO-PCI compared with patients who had an unsuccessful CTO-PCI attempt at 12-month follow-up (348). The long-term prognostic benefits of successful versus unsuccessful CTO intervention at both 5- and 10-year follow-up have also been demonstrated by Hoye et al. (351) (93.5 vs. 88.0%, $p = 0.02$) and Suero et al. (350) (73.5% vs. 65.1%, $p = 0.001$), respectively. In contrast, however, Prasad et al. (352), who reviewed outcomes over 25 years in a single center, reported that an unsuccessful procedure was not an independent predictor of long-term mortality; whereas de Labriolle et al. (353) also reported that patients with a successful CTO procedure had no survival benefit compared with patients having an unsuccessful procedure.

DES versus BMS. After successful recanalization of a CTO, studies demonstrate consistent improvements in clinical outcomes after implantation of a DES compared with a BMS that have been predominantly driven through reductions in repeat revascularization (66–69,354–360).

Randomized data are limited to the PRISON II (Primary Stenting of Totally Occluded Native Coronary Arteries II) study and the GISSOC II-GISE (Gruppo Italiano di Studio sullo Stent nelle Occlusioni Coronariche II–Società Italiana di Cardiologia Invasiva) study, which both compared outcomes of patients with a CTO treated with BMS or SES. The use of SES compared with BMS led to significant reductions in TLR and TVR, and comparable rates of death, MI, and ST at follow-up ranging from 6 months (PRISON II), to 24 months (GISSOC II-GISE), and out to 5 years (PRISON II) (Table 2) (66–69).

Numerous registries have also reported data from CTO subgroups, and results demonstrate a consistent significant reduction in TLR and MACE after use of DES compared with BMS at short-term follow-up of between 6 and 18 months (357–360). At longer-term follow-up, and consistent with the randomized studies, De Felice et al. (360) reported the maintenance of this advantage with DES out to 3 years among 283 patients treated with SES/PES ($n = 124$) or BMS ($n = 159$). Conversely, no significant differences in TLR or MACE were observed among 140 patients (SES 76, BMS 64) in the CTO subgroup of the RESEARCH registry at either 3- or 5-year follow-up (361,362).

A recent meta-analysis of all these studies, which included >4,000 patients with a CTO treated with either a DES ($n = 2,390$) or BMS ($n = 2,004$), confirms the superiority of DES in terms of significantly improved efficacy and comparable safety compared with BMS at a mean of 22 months of follow-up (363). It is noteworthy that a strong trend toward a higher rate of ST was observed in the DES-treated cohort (RR: 2.79, 95% CI: 0.98 to 7.97, $p = 0.06$).

SVG

SVGs have a limited durability; however, they are still frequently used as conduits in CABG. Their subsequent failure due to atherosclerosis is the most common cause of recurrent ischemia in surgically revascularized patients. Unfortunately, the optimal method of repeat revascularization in these patients is not clearly established. Repeat surgical revascularization exposes patients to an increased risk of morbidity and mortality compared with their primary operation, without evidence of prognostic gain (364,365). Moreover, PCI for SVG is associated with suboptimal results due to high rates of periprocedural MI and high rates of restenosis requiring TLR (366). The high rates of periprocedural MI are thought to relate to the poor development of fibrous caps in the SVG atheroma (367) that increases the likelihood of embolization during stent implantation. The incidence of these periprocedural MIs is reduced after the use of embolic protection devices (368–370); however, despite this, and their class I recommendation for use when technically feasible (174), analysis of the ACC National Cardiovascular Data Registry suggests that they are used in only ~22% of SVG PCI (371).

Unlike native vessel lesions, the clear clinical benefits of DES over BMS have been slow to materialize in patients with SVG. Currently there is a paucity of data investigating the benefits of BMS over DES, and what data are available, are largely retrospective (372).

Randomized data. There have been only 2 small dedicated, randomized studies comparing DES to BMS in SVG intervention, which in total have included 155 patients (74,75,373). At short-term follow-up of 6 and 18 months, respectively, both the single-center RRISC (Reduction of Restenosis in Saphenous Vein Grafts With Cypher

Sirolimus-Eluting Stent) trial, and the multicenter SOS (Stent or Surgery) study reported, as expected, significant reductions in binary restenosis and TLR after use of DES compared with BMS, together with comparable rates of death and MI (74,373). Long-term data to a median of 32 months are only available in the RRISC trial, and demonstrates catch-up in the repeat revascularization rates in patients treated with DES (75). Moreover, there was a significant increase in late mortality among patients treated with SES as compared with patients treated with BMS (29% vs. 0%, $p < 0.001$) (75). Because of their small sample sizes, both studies were very underpowered to detect true differences in clinical events.

Registry data. Twenty registries have reported results in patients with SVG PCI, including a total of 5,172 patients (3,091 DES, 2,081 BMS), with outcomes reported between 6 and 34 months of follow-up. Results have been inconsistent, with some reporting advantages for DES over BMS, (131,374–378), and some reporting no difference (379–382). The largest study to date, a subgroup of the large multicenter STENT study, has recently reported 2-year propensity score matched outcomes for 1,000 patients treated with DES or BMS. At 9-month follow-up, the use of DES was associated with significantly reduced rates of MACE (14% vs. 21%, $p = 0.001$), a lower composite of death or MI (8.7% vs. 14%, $p = 0.006$), and a lower rate of TVR (HR: 0.36, $p < 0.001$) and ST (HR: 0.22, $p = 0.009$). At 2 years, DES-treated patients had significantly better survival, whereas significant reductions in overall MACE and TVR were only noted after adjustment (383).

All trials are summarized in a recently published systematic review (372), which concluded that in comparison to BMS, DES are safe (with the exception of the RRISC trial), and offer consistently reduced late loss and angiographic stenosis. Definitive data are still needed and will be partly obtained from the results of 3 on-going randomized multicenter prospective trials. In the absence of these data, however, for the time being, current results suggest that DES offer an advantage over BMS in terms of reduced restenosis and the need for TLR.

ISR

The introduction of DES led to a significant reduction in the rates of restenosis; however, they have not been able to eliminate it, resulting in a minority of patients returning with symptoms ranging from the gradual recurrence of angina pectoris to acute presentations with ACS (384,385). Numerous factors have been suggested as the underlying mechanism of this ISR, and these include: 1) biological factors such as resistance to antiproliferative drugs and hypersensitivity reactions; 2) mechanical factors such as stent fractures, polymer peeling, and nonuniform stent strut distribution or drug deposition; and 3) technical factors, including incomplete stent expansion, geographical miss, and barotraumas to unstented segments.

BMS ISR. Historically, numerous therapies have been used in the management of ISR after BMS implantation including POBA, atherectomy, and repeat stenting. Although all these modalities produced satisfactory immediate results, their utilization was hindered by a frequent need for a subsequent repeat revascularization procedure. To address this problem, vascular brachytherapy was introduced as an adjunctive therapy after successful POBA, with subsequent randomized studies confirming that this combination was highly effective at reducing the high rates of repeat TVR after treatment of BMS ISR (386,387). The use of brachytherapy soon fell out of favor, however, not only because of procedural logistics such as the expensive equipment, but also because of results at long-term follow-up, which raised concerns over ST and demonstrated a reduction in efficacy over time with subsequent delayed restenosis and a late TVR catch-up response (388). Perhaps the most important factor, however, in the downfall of brachytherapy was the emergence of DES.

Several studies have compared the performance of DES with brachytherapy in patients with BMS ISR. All studies, ranging from nonrandomized pilot studies to the large randomized SISR (Sirolimus-Eluting Stents Versus Vascular Brachytherapy for In-Stent Restenosis) study and the TAXUS V ISR study (PES vs. brachytherapy), which individually enrolled ~400 patients, have shown a consistent benefit with treatment using DES (SES or PES) compared with brachytherapy (389–395). Of note, at long-term follow-up in the TAXUS V ISR study, a greater absolute difference in TLR was seen at 2-year follow-up in favor of PES (9-month ΔTLR 7.6% vs. 24-month ΔTLR 11.5%), without any compromise on safety (392). Similarly, in the SISR study, the significant reduction in TLR with the use of SES that was observed at 12 months was maintained out to 3-year follow-up (394).

Concurrent with the comparison between DES and brachytherapy, DES have also been compared with POBA in the treatment of ISR after BMS implantation. The first of such studies was the ISAR-DESIRE (Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for In-Stent Restenosis) study that randomly assigned 300 patients with BMS ISR to treatment with SES, PES, and POBA (116). At 6-month follow-up, treatment with DES had led to significantly lower rates of in-segment angiographic stenosis (POBA 44.6% vs. SES 14.3% vs. PES 21.7%, $p < 0.05$ for SES and PES vs. POBA), whereas at 12 months, use of DES led to significantly lower rates of TVR (POBA 33% vs. SES 8% vs. PES 19%, $p < 0.05$ for SES and PES vs. POBA). Overall, rates of mortality and MI were comparable through to 12-month follow-up. A secondary analysis compared outcomes between stents, and demonstrated no significant difference between SES and PES in the rate of angiographic restenosis ($p = 0.19$), whereas use of SES

lead to significantly lower rates of TVR compared with PES ($p = 0.02$).

This advantage of DES over POBA appears to be preserved long-term, as indicated by the results of the RIBS-II (Restenosis Intra-stent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting) study that randomly allocated 150 patients with BMS ISR to treatment with SES or POBA. At 1-year follow-up (12% vs. 31%, $p < 0.005$) and 4-year follow-up (24% vs. 35%, $p = 0.02$), treatment with SES had led to a significantly lower rate of MACE, with comparable rates of death, MI, and ST. Of note, SES implantation was shown to be an independent predictor of event-free survival (396,397).

DES ISR. ISR with DES is likely to become an increasing problem, considering the expanding use of DES in contemporary practice. At present, it is estimated that there are >200,000 cases of DES ISR annually in the U.S. alone (398). Despite this, however, the optimal treatment strategy for this condition remains to be established. The lessons learned from the treatment of BMS ISR suggest that the most appropriate treatment lies with repeat stenting, rather than with brachytherapy and POBA, and this is further supported by the more focal nature of DES ISR, which is a somewhat easier morphological pattern to treat compared with BMS restenosis (399). Other treatment options besides stenting include surgical revascularization for extreme cases and the use of more novel therapies such as drug-eluting balloons, which are discussed in more detail in Part 2 of this supplement.

If stenting is selected, a question that remains under discussion is whether DES ISR should be treated with a DES eluting the same antiproliferative drug or a different class of drug. That has recently been investigated in the ISAR-DESIRE II study, which randomly allocated 450 patients with ISR after SES implantation to treatment with repeat SES implantation or PES (117). At 6-month angiographic follow-up, there were no significant differences in late loss (SES 0.40 mm vs. PES 0.38 mm, $p = 0.85$) or binary restenosis (19.6% vs. 20.6%, $p = 0.69$). Similarly, at 12-month clinical follow-up, rates of death, MI, TLR, and ST were also all comparable between treatment strategies. Therefore, patients with SES ISR can be equally effectively treated with repeat SES implantation or PES; however, it is not known whether these results are applicable to ISR occurring after implantation of a second-generation DES. Importantly, the late loss observed after SES implantation was considerably higher than that seen in other studies of SES (Tables 2 and 5), suggesting that patients experiencing SES ISR may be hyporesponsive to the antiproliferative effects of SES. It follows that further investigation is required into the problem of ISR after DES implantation to establish a definitive treatment strategy.

Conclusions

Coronary stents are an essential component of contemporary percutaneous revascularization. The introduction of DES led to significant reductions in restenosis, and although their use is associated with an increased risk of late ST, no additional risk of mortality has been demonstrated. The improved outcomes with DES have led to expanding indications for PCI, which is now an accepted treatment for diabetic patients and patients with complex CAD. The persisting concerns over ST have led to improvements in stent design, and although the second-generation DES have demonstrated early improvements in safety, great anticipation remains over the newer stent technology, which is explored in Part 2: Looking Forward.

Reprint requests and correspondence: Dr. Patrick W. Serruys, Department of Interventional Cardiology, Ba583a, Thoraxcenter, Erasmus Medical Center, 's-Gravendijkwal 230, Rotterdam 3015 CE, the Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl.

REFERENCES

1. Dotter CT, Judkins MP. Transluminal treatment of arteriosclerotic obstruction. Description of a new technic and a preliminary report of its application. Circulation 1964;30:654–70.
2. Gruntzig A. Transluminal dilatation of coronary-artery stenosis. Lancet 1978;1:263.
3. Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med 1987;316:701–6.
4. Gruntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. N Engl J Med 1979;301:61–8.
5. de Feyter PJ, de Jaegere PP, Serruys PW. Incidence, predictors, and management of acute coronary occlusion after coronary angioplasty. Am Heart J 1994;127:643–51.
6. Sigwart U, Urban P, Golf S, et al. Emergency stenting for acute occlusion after coronary balloon angioplasty. Circulation 1988;78:1121–7.
7. Carrie D, Elbaz M, Andrieu M, Cantie P, Fourcade J, Puel J. Ten-year clinical and angiographic follow-up of coronary wallstent. Am J Cardiol 2000;85:95–8.
8. Roubin GS, Cannon AD, Agrawal SK, et al. Intracoronary stenting for acute and threatened closure complicating percutaneous transluminal coronary angioplasty. Circulation 1992;85:916–27.
9. Serruys PW, Strauss BH, Beatt KJ, et al. Angiographic follow-up after placement of a self-expanding coronary-artery stent. N Engl J Med 1991;324:13–7.
10. van Domburg RT, Foley DP, de Jaegere PP, et al. Long term outcome after coronary stent implantation: a 10 year single centre experience of 1000 patients. Heart 1999;82 Suppl 2:II27–34.
11. Serruys PW, de Jaegere P, Kiemeneij F, et al., for the Benestent Study Group. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med 1994;331:489–95.
12. Fischman DL, Leon MB, Baim DS, et al., for the Stent Restenosis Study Investigators. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. N Engl J Med 1994;331:496–501.
13. Barragan P, Sainsous J, Silvestri M, et al. Ticlopidine and subcutaneous heparin as an alternative regimen following coronary stenting. Catheter Cardiovasc Diagn 1994;32:133–8.
14. Schomig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med 1996;334:1084–9.
15. Cutlip DE, Leon MB, Ho KK, et al. Acute and nine-month clinical outcomes after "suboptimal" coronary stenting: results from the STent Anti-thrombotic Regimen Study (STARS) registry. J Am Coll Cardiol 1999;34:698–706.
16. Colombo A, Hall P, Nakamura S, et al. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. Circulation 1995;91:1676–88.

17. Serruys PW, Kutryk MJ, Ong AT. Coronary-artery stents. N Engl J Med 2006;354:483–95.
18. Karas SP, Gravanis MB, Santoian EC, Robinson KA, Anderberg KA, King SB III. Coronary intimal proliferation after balloon injury and stenting in swine: an animal model of restenosis. J Am Coll Cardiol 1992;20:467–74.
19. Gordon PC, Gibson CM, Cohen DJ, Carrozza JP, Kuntz RE, Baim DS. Mechanisms of restenosis and redilation within coronary stents—quantitative angiographic assessment. J Am Coll Cardiol 1993;21:1166–74.
20. Hoffmann R, Mintz GS, Dussaillant GR, et al. Patterns and mechanisms of in-stent restenosis. A serial intravascular ultrasound study. Circulation 1996;94:1247–54.
21. Moliterno DJ. Healing Achilles—sirolimus versus paclitaxel. N Engl J Med 2005;353:724–7.
22. Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet 2007;370:937–48.
23. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:989–97.
24. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. N Engl J Med 2007;356:998–1008.
25. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl J Med 2007;356:1020–9.
26. Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:1030–9.
27. Seung KB, Park DW, Kim YH, et al. Stents versus coronary-artery bypass grafting for left main coronary artery disease. N Engl J Med 2008;358:1781–92.
28. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.
29. Serruys PW, Garg S. Percutaneous coronary interventions for all patients with complex coronary artery disease: triple vessel disease or left main coronary artery disease. Yes? No? Don't know? Rev Esp Cardiol 2009;62:719–25.
30. Jeremias A, Kirtane A. Balancing efficacy and safety of drug-eluting stents in patients undergoing percutaneous coronary intervention. Ann Intern Med 2008;148:234–8.
31. Nordmann AJ, Briel M, Bucher HC. Mortality in randomized controlled trials comparing drug-eluting vs. bare metal stents in coronary artery disease: a meta-analysis. Eur Heart J 2006;27:2784–814.
32. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. Circulation 2007;115:1440–55, discussion 1455.
33. Lagerqvist B, James SK, Stenestrand U, et al. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. N Engl J Med 2007;356:1009–19.
34. Maluenda G, Lemesle G, Waksman R. A critical appraisal of the safety and efficacy of drug-eluting stents. Clin Pharmacol Ther 2009;85:474–80.
35. Poon M, Marx SO, Gallo R, Badimon JJ, Taubman MB, Marks AR. Rapamycin inhibits vascular smooth muscle cell migration. J Clin Invest 1996;98:2277–83.
36. Burke SE, Lubbers NL, Chen YW, et al. Neointimal formation after balloon-induced vascular injury in Yucatan minipigs is reduced by oral rapamycin. J Cardiovasc Pharmacol 1999;33:829–35.
37. Gallo R, Padurean A, Jayaraman T, et al. Inhibition of intimal thickening after balloon angioplasty in porcine coronary arteries by targeting regulators of the cell cycle. Circulation 1999;99:2164–70.
38. Marx SO, Marks AR. Bench to bedside: the development of rapamycin and its application to stent restenosis. Circulation 2001; 104:852–5.
39. Sousa JE, Costa MA, Abizaid A, et al. Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries: a quantitative coronary angiography and three-dimensional intravascular ultrasound study. Circulation 2001;103:192–5.
40. Rensing BJ, Vos J, Smits PC, et al. Coronary restenosis elimination with a sirolimus eluting stent: first European human experience with 6-month angiographic and intravascular ultrasonic follow-up. Eur Heart J 2001;22:2125–30.
41. Sousa JE, Costa MA, Abizaid AC, et al. Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. Circulation 2001; 104:2007–11.
42. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773–80.
43. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–23.
44. Weisz G, Leon MB, Holmes DR Jr., et al. Two-year outcomes after sirolimus-eluting stent implantation: results from the Sirolimus-Eluting Stent in de Novo Native Coronary Lesions (SIRIUS) trial. J Am Coll Cardiol 2006;47:1350–5.
45. Weisz G, Leon MB, Holmes DR Jr., et al. Five-year follow-up after sirolimus-eluting stent implantation: results of the SIRIUS (Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions) trial. J Am Coll Cardiol 2009;53:1488–97.
46. Morice MC, Serruys PW, Barragan P, et al. Long-term clinical outcomes with sirolimus-eluting coronary stents: five-year results of the RAVEL trial. J Am Coll Cardiol 2007;50:1299–304.
47. Schampaert E, Cohen EA, Schluter M, et al. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). J Am Coll Cardiol 2004;43:1110–5.
48. Schofer J, Schluter M, Gershlick AH, et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). Lancet 2003;362:1093–9.
49. Sabate M, Jimenez-Quevedo P, Angiolillo DJ, et al. Randomized comparison of sirolimus-eluting stent versus standard stent for percutaneous coronary revascularization in diabetic patients: the Diabetes and Sirolimus-Eluting Stent (DIABETES) trial. Circulation 2005;112:2175–83.
50. Jimenez-Quevedo P, Sabate M, Angiolillo DJ, et al. Long-term clinical benefit of sirolimus-eluting stent implantation in diabetic patients with de novo coronary stenoses: long-term results of the DIABETES trial. Eur Heart J 2007;28:1946–52.
51. Pilar Jimenez-Quevedo. Four years follow-up of DIABETES trial. Paper presented at: i2 Summit, American College of Cardiology Scientific Sessions; March 29–31, 2009; Orlando, Florida.
52. Maresta A, Varani E, Balducelli M, et al. Comparison of effectiveness and safety of sirolimus-eluting stents versus bare-metal stents in patients with diabetes mellitus (from the Italian Multicenter Randomized DESSERT Study). Am J Cardiol 2008;101:1560–6.
53. Baumgart D, Klauss V, Baer F, et al. One-year results of the SCORPIUS study: a German multicenter investigation on the effectiveness of sirolimus-eluting stents in diabetic patients. J Am Coll Cardiol 2007;50:1627–34.
54. Diaz de la Llera LS, Ballesteros S, Nevado J, et al. Sirolimus-eluting stents compared with standard stents in the treatment of patients with primary angioplasty. Am Heart J 2007;154:164 e1–6.
55. van der Hoeven BL, Liem SS, Jukema JW, et al. Sirolimus-eluting stents versus bare-metal stents in patients with ST-segment elevation myocardial infarction: 9-month angiographic and intravascular ultrasound results and 12-month clinical outcome results from the MISSION! Intervention Study. J Am Coll Cardiol 2008;51:618–26.
56. Atary JZ, van der Hoeven BL, Liem SS, et al. Three-year outcome of sirolimus-eluting versus bare-metal stents for the treatment of ST-segment elevation myocardial infarction (from the MISSION! Intervention Study). Am J Cardiol 2010;106:4–12.
57. Di Lorenzo E, De Luca G, Sauro R, et al. The PASEO (PaclitAxel or Sirolimus-Eluting Stent Versus Bare Metal Stent in Primary Angioplasty) randomized trial. J Am Coll Cardiol Intv 2009;2:515–23.
58. Di Lorenzo E, Sauro R, Varricchio A, et al. Benefits of drug-eluting stents as compared with bare metal stent in ST-segment elevation myocardial infarction: 4 year results of the PaclitAxel or Sirolimus-Eluting stent vs bare metal stent in primary angiOplasty (PASEO) randomized trial. Am Heart J 2009;158:e43–50.

59. Menichelli M, Parma A, Pucci E, et al. Randomized trial of Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction (SESAMI). J Am Coll Cardiol 2007;49:1924–30.
60. Violini R, Musto C, De Felice F, et al. Maintenance of long-term clinical benefit with sirolimus-eluting stents in patients with ST-segment elevation myocardial infarction 3-year results of the SESAMI (Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction) trial. J Am Coll Cardiol 2010;55: 810–4.
61. Valgimigli M, Percoco G, Malagutti P, et al. Tirofiban and sirolimus-eluting stent vs abciximab and bare-metal stent for acute myocardial infarction: a randomized trial. JAMA 2005;293:2109–17.
62. Tebaldi M, Arcozzi C, Campo G, Percoco G, Ferrari R, Valgimigli M. The 5-year clinical outcomes after a randomized comparison of sirolimus-eluting versus bare-metal stent implantation in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol 2009;54:1900–1.
63. Spaulding C, Henry P, Teiger E, et al. Sirolimus-eluting versus uncoated stents in acute myocardial infarction. N Engl J Med 2006;355:1093–104.
64. Spaulding C. Four year follow-up of the TYPHOON study, a multicenter, randomised, single-blind trial to assess the use of the Cypher sirolimus eluting stent in acute myocardial infarction patients treated with balloon angioplasty. Paper presented at: EuroPCR; May 19, 2009; Barcelona, Spain. Available at: http://www.pcronline.com/Lectures/2009/4-year-follow-up-of-the-TYPHOON-study-a-randomised-trial-comparing-the-Sirolimus-eluting-stent-to-bare-metal-stents-during-PCI-for-acute-myocardial-infarction. Accessed July 14, 2009.
65. Pache J, Dibra A, Mehilli J, Dirschinger J, Schomig A, Kastrati A. Drug-eluting stents compared with thin-strut bare stents for the reduction of restenosis: a prospective, randomized trial. Eur Heart J 2005;26:1262–8.
66. Suttorp MJ, Laarman GJ, Rahel BM, et al. Primary Stenting of Totally Occluded Native Coronary Arteries II (PRISON II): a randomized comparison of bare metal stent implantation with sirolimus-eluting stent implantation for the treatment of total coronary occlusions. Circulation 2006;114:921–8.
67. Rahel BM, Laarman GJ, Kelder JC, Ten Berg JM, Suttorp MJ. Three-year clinical outcome after primary stenting of totally occluded native coronary arteries: a randomized comparison of bare-metal stent implantation with sirolimus-eluting stent implantation for the treatment of total coronary occlusions (Primary Stenting of Totally Occluded Native Coronary Arteries [PRISON] II study). Am Heart J 2009;157:149–55.
68. van den Branden BJL, Rahel BM, Laarman GJ, Kelder JC, Ten Berg JM, Suttorp MJ. Five-year clinical outcome after primary stenting of totally occluded native coronary arteries: a randomised comparison of bare metal stent implantation with Sirolimus-eluting stent implantation for the treatment of total coronary occlusions (PRISON II study). Paper presented at: EuroPCR; May 2010; Paris, France.
69. Rubartelli P, Petronio AS, Guiducci V, et al. Comparison of sirolimus-eluting and bare metal stent for treatment of patients with total coronary occlusions: results of the GISSOC II-GISE multicentre randomized trial. Eur Heart J 2010 June 20 [E-pub ahead of print].
70. Ardissino D, Cavallini C, Bramucci E, et al. Sirolimus-eluting vs uncoated stents for prevention of restenosis in small coronary arteries: a randomized trial. JAMA 2004;292:2727–34.
71. Menozzi A, Solinas E, Ortolani P, et al. Twenty-four months clinical outcomes of sirolimus-eluting stents for the treatment of small coronary arteries: the long-term SES-SMART clinical study. Eur Heart J 2009;30:2095–101.
72. Kelbaek H, Thuesen L, Helqvist S, et al. The Stenting Coronary Arteries in Non-Stress/Benestent Disease (SCANDSTENT) trial. J Am Coll Cardiol 2006;47:449–55.
73. Kelbaek H, Klovgaard L, Helqvist S, et al. Long-term outcome in patients treated with sirolimus-eluting stents in complex coronary artery lesions: 3-year results of the SCANDSTENT (Stenting Coronary Arteries in Non-Stress/Benestent Disease) trial. J Am Coll Cardiol 2008;51:2011–6.
74. Vermeersch P, Agostoni P, Verheye S, et al. Randomized double-blind comparison of sirolimus-eluting stent versus bare-metal stent implantation in diseased saphenous vein grafts: six-month angiographic, intravascular ultrasound, and clinical follow-up of the RRISC trial. J Am Coll Cardiol 2006;48:2423–31.
75. Vermeersch P, Agostoni P, Verheye S, et al. Increased late mortality after sirolimus-eluting stents versus bare-metal stents in diseased saphenous vein grafts: results from the randomized DELAYED RRISC trial. J Am Coll Cardiol 2007;50:261–7.
76. Kirtane AJ, Gupta A, Iyengar S, et al. Safety and efficacy of drug-eluting and bare metal stents: comprehensive meta-analysis of randomized trials and observational studies. Circulation 2009; 119:3198–206.
77. Serruys PW, Onuma Y, Garg S, et al. 5-Year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. J Am Coll Cardiol 2010;55:1093–101.
78. Lemos PA, Serruys PW, van Domburg RT, et al. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. Circulation 2004;109:190–5.
79. Daemen J, Kukreja N, van Twisk PH, et al. Four-year clinical follow-up of the rapamycin-eluting stent evaluated at Rotterdam Cardiology Hospital registry. Am J Cardiol 2008;101:1105–11.
80. Serruys PW, Ong ATL, Morice M-C, et al. Arterial Revascularisation Therapies Study Part II: Sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. EuroIntervention 2005;1:147–56.
81. Serruys PW, Daemen J, Morice MC, et al. Three-year follow-up of the ARTS-II—sirolimus-eluting stents for the treatment of patients with multivessel coronary artery disease. EuroIntervention 2008;3: 450–9.
82. Grube E, Silber S, Hauptmann KE, et al. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. Circulation 2003;107:38–42.
83. Colombo A, Drzewiecki J, Banning A, et al. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. Circulation 2003; 108:788–94.
84. Silber S, Colombo A, Banning AP, et al. Final 5-year results of the TAXUS II trial: a randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for de novo coronary artery lesions. Circulation 2009;120:1498–504.
85. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221–31.
86. Ellis SG, Stone GW, Cox DA, et al. Long-term safety and efficacy with paclitaxel-eluting stents: 5-year final results of the TAXUS IV clinical trial (TAXUS IV-SR: Treatment of de novo coronary disease using a single paclitaxel-eluting stent). J Am Coll Cardiol Intv 2009;2:1248–59.
87. Stone GW, Ellis SG, Cannon L, et al. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. JAMA 2005;294:1215–23.
88. Ellis SG, Cannon L, Mann T, et al. Final 5-year outcomes from the TAXUS V de novo trial: long-term safety and effectiveness of the paclitaxel-eluting TAXUS stent in complex lesions (abstr). Am J Cardiol 2009;104:135D.
89. Dawkins KD, Grube E, Guagliumi G, et al. Clinical efficacy of polymer-based paclitaxel-eluting stents in the treatment of complex, long coronary artery lesions from a multicenter, randomized trial: support for the use of drug-eluting stents in contemporary clinical practice. Circulation 2005;112:3306–13.
90. Grube E, Dawkins K, Guagliumi G, et al. TAXUS VI final 5-year results: a multicentre, randomised trial comparing polymer-based moderate-release paclitaxel-eluting stent with a bare metal stent for treatment of long, complex coronary artery lesions. EuroIntervention 2009;4:572–7.
91. Stone GW, Lansky AJ, Pocock SJ, et al. Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. N Engl J Med 2009;360:1946–59.
92. Stone GW. HORIZONS-AMI. Two-year follow from a prospective randomised trial of heparin plus glycoprotein IIb/IIIa inhibitors vs. bivalirudin and paclitaxel eluting vs. bare metal stents in STEMI.

Paper presented at: Transcatheter Cardiovascular Therapeutics; September 23, 2009; San Francisco, CA.
93. Laarman GJ, Suttorp MJ, Dirksen MT, et al. Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. N Engl J Med 2006;355:1105–13.
94. Dirksen MT, Vink MA, Suttorp MJ, et al. Two year follow-up after primary PCI with a paclitaxel-eluting stent versus a bare-metal stent for acute ST-elevation myocardial infarction (the PASSION trial): a follow-up study. EuroIntervention 2008;4:64–70.
95. Vink MA. Five-year clinical follow-up of the PASSION trial: primary PCI with a paclitaxel-eluting stent versus a bare-metal stent in acute ST-elevation myocardial infarction. Paper presented at: Annual Scientific Session/i2 Summit of the American College of Cardiology; March 16, 2010; Atlanta, Georgia.
96. Erglis A, Narbute I, Kumsars I, et al. A randomized comparison of paclitaxel-eluting stents versus bare-metal stents for treatment of unprotected left main coronary artery stenosis. J Am Coll Cardiol 2007;50:491–7.
97. Ong AT, Serruys PW, Aoki J, et al. The unrestricted use of paclitaxel- versus sirolimus-eluting stents for coronary artery disease in an unselected population: one-year results of the Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry. J Am Coll Cardiol 2005;45:1135–41.
98. Daemen J, Keiichi T, Kristensen SD, et al. Two-year clinical follow-up of the unrestricted use of the paclitaxel-eluting stent compared with the sirolimus-eluting stent as part of the Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry. EuroIntervention 2006;2:330–7.
99. Turco MA, Ormiston JA, Popma JJ, et al. Polymer-based, paclitaxel-eluting TAXUS Liberte stent in de novo lesions: the pivotal TAXUS ATLAS trial. J Am Coll Cardiol 2007;49:1676–83.
100. Turco MA, Ormiston JA, Popma JJ, et al. Reduced risk of restenosis in small vessels and reduced risk of myocardial infarction in long lesions with the new thin-strut TAXUS Liberte stent: 1-year results from the TAXUS ATLAS program. J Am Coll Cardiol Intv 2008;1:699–709.
101. Turco MA. TCT-380: TAXUS ATLAS Small Vessel and TAXUS ATLAS Long Lesion trials. Long-term benefit of TAXUS Liberté versus TAXUS Express in small vessels and long lesions. Am J Cardiol 2009;104:141D.
102. Lee SW, Park SW, Kim YH, et al. A randomized comparison of sirolimus- versus paclitaxel-eluting stent implantation in patients with diabetes mellitus. J Am Coll Cardiol 2008;52:727–33.
103. Lee SW, Park SW, Kim YH, et al. A randomized comparison of sirolimus- versus paclitaxel-eluting stent implantation in patients with diabetes mellitus: 2-year clinical outcomes of the DES-DIABETES trial. J Am Coll Cardiol 2009;53:812–3.
104. Dibra A, Kastrati A, Mehilli J, et al. Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. N Engl J Med 2005;353:663–70.
105. Morice MC, Colombo A, Meier B, et al. Sirolimus- vs paclitaxel-eluting stents in de novo coronary artery lesions. The REALITY trial: a randomized controlled trial. JAMA 2006;295:895–904.
106. Windecker S, Remondino A, Eberli FR, et al. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. N Engl J Med 2005;353:653–62.
107. Raber L. SIRTAX-LATE: five-year clinical and angiographic follow-up from a prospective randomized trial of sirolimus-eluting and paclitaxel-eluting stents. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 22, 2009; San Francisco, CA.
108. Galloe AM, Thuesen L, Kelbaek H, et al. Comparison of paclitaxel- and sirolimus-eluting stents in everyday clinical practice: the SORT OUT II randomized trial. JAMA 2008;299:409–16.
109. Goy JJ, Stauffer JC, Siegenthaler M, Benoit A, Seydoux C. A prospective randomized comparison between paclitaxel and sirolimus stents in the real world of interventional cardiology: the TAXi trial. J Am Coll Cardiol 2005;45:308–11.
110. Berger A, Stauffer JC, Seydoux C, Siegenthaler M, Benoit A, Goy JJ. Three-year follow-up of the first prospective randomized comparison between paclitaxel and sirolimus stents: the TAXi-LATE trial. Catheter Cardiovasc Interv 2007;70:163–6.
111. Lee JH, Kim HS, Lee SW, et al. Prospective randomized comparison of sirolimus- versus paclitaxel-eluting stents for the treatment of acute ST-elevation myocardial infarction: pROSIT trial. Catheter Cardiovasc Interv 2008;72:25–32.
112. Kim HS, Lee JH, Lee SW, et al. Long-term safety and efficacy of sirolimus- vs. paclitaxel-eluting stent implantation for acute ST-elevation myocardial infarction: 3-year follow-up of the PROSIT trial. Int J Cardiol 2009 Sept 25 [Epub ahead of print].
113. Mehilli J, Kastrati A, Byrne RA, et al. Paclitaxel- versus sirolimus-eluting stents for unprotected left main coronary artery disease. J Am Coll Cardiol 2009;53:1760–8.
114. Kim YH, Park SW, Lee SW, et al. Sirolimus-eluting stent versus paclitaxel-eluting stent for patients with long coronary artery disease. Circulation 2006;114:2148–53.
115. Mehilli J, Dibra A, Kastrati A, Pache J, Dirschinger J, Schomig A. Randomized trial of paclitaxel- and sirolimus-eluting stents in small coronary vessels. Eur Heart J 2006;27:260–6.
116. Kastrati A, Mehilli J, von Beckerath N, et al. Sirolimus-eluting stent or paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. JAMA 2005;293:165–71.
117. Mehilli J, Byrne RA, Tiroch K, et al. Randomized trial of paclitaxel- versus sirolimus-eluting stents for treatment of coronary restenosis in sirolimus-eluting stents: The ISAR-DESIRE 2 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 2) study. J Am Coll Cardiol 2010;55:2710–6.
118. Schomig A, Dibra A, Windecker S, et al. A meta-analysis of 16 randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary artery disease. J Am Coll Cardiol 2007;50:1373–80.
119. Popma J, Almonacid A. Angiographic markers of restenosis after drug-eluting stent implantation: surrogates for late clinical outcomes? J Interv Cardiol 2009;22 Suppl:64–71.
120. Pocock SJ, Lansky AJ, Mehran R, et al. Angiographic surrogate end points in drug-eluting stent trials: a systematic evaluation based on individual patient data from 11 randomized, controlled trials. J Am Coll Cardiol 2008;51:23–32.
121. Mauri L, Orav EJ, Kuntz RE. Late loss in lumen diameter and binary restenosis for drug-eluting stent comparison. Circulation 2005;111: 3435–42.
122. Ellis SG, Popma JJ, Lasala JM, et al. Relationship between angiographic late loss and target lesion revascularization after coronary stent implantation: analysis from the TAXUS-IV trial. J Am Coll Cardiol 2005;45:1193–200.
123. Douglas PS, Brennan JM, Anstrom KJ, et al. Clinical effectiveness of coronary stents in elderly persons: results from 262,700 Medicare patients in the American College of Cardiology-National Cardiovascular Data Registry. J Am Coll Cardiol 2009;53:1629–41.
124. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. J Am Coll Cardiol 2006;48:2584–91.
125. Serruys PW, Daemen J. The SCAAR registry or the Swedish yo-yo. EuroIntervention 2007;3:297–300.
126. James SK, Stenestrand U, Lindback J, et al. Long-term safety and efficacy of drug-eluting versus bare-metal stents in Sweden. N Engl J Med 2009;360:1933–45.
127. Win HK, Caldera AE, Maresh K, et al. Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. JAMA 2007;297:2001–9.
128. Farb A, Boam AB. Stent thrombosis redux—the FDA perspective. N Engl J Med 2007;356:984–7.
129. Shuchman M. Debating the risks of drug-eluting stents. N Engl J Med 2007;356:325–8.
130. Lasala JM, Cox DA, Lewis SJ, et al. Expanded use of the TAXUS Express Stent: two-year safety insights from the 7,500 patient ARRIVE registry programme. EuroIntervention 2009;5:67–77.
131. Brodie BR, Stuckey T, Downey W, et al. Outcomes and complications with off-label use of drug-eluting stents: results from the STENT (Strategic Transcatheter Evaluation of New Therapies) group. J Am Coll Cardiol Intv 2008;1:405–14.
132. Beohar N, Davidson CJ, Kip KE, et al. Outcomes and complications associated with off-label and untested use of drug-eluting stents. JAMA 2007;297:1992–2000.

133. Applegate RJ, Sacrinty MT, Kutcher MA, et al. "Off-label" stent therapy 2-year comparison of drug-eluting versus bare-metal stents. J Am Coll Cardiol 2008;51:607–14.
134. Ko DT, Chiu M, Guo H, et al. Safety and effectiveness of drug-eluting and bare-metal stents for patients with off- and on-label indications. J Am Coll Cardiol 2009;53:1773–82.
135. Marroquin OC, Selzer F, Mulukutla SR, et al. A comparison of bare-metal and drug-eluting stents for off-label indications. N Engl J Med 2008;358:342–52.
136. Roy P, Buch AN, Javaid A, et al. Impact of "off-label" utilization of drug-eluting stents on clinical outcomes in patients undergoing percutaneous coronary intervention. Am J Cardiol 2008;101:293–9.
137. Serruys PW, Daemen J. Are drug-eluting stents associated with a higher rate of late thrombosis than bare metal stents? Late stent thrombosis: a nuisance in both bare metal and drug-eluting stents. Circulation 2007;115:1433–9, discussion 1439.
138. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet 2004;364:1519–21.
139. Liistro F, Colombo A. Late acute thrombosis after paclitaxel eluting stent implantation. Heart 2001;86:262–4.
140. Kerner A, Gruberg L, Kapeliovich M, Grenadier E. Late stent thrombosis after implantation of a sirolimus-eluting stent. Catheter Cardiovasc Interv 2003;60:505–8.
141. Urban P, Gershlick AH, Guagliumi G, et al. Safety of coronary sirolimus-eluting stents in daily clinical practice: one-year follow-up of the e-Cypher registry. Circulation 2006;113:1434–41.
142. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293:2126–30.
143. Park DW, Park SW, Park KH, et al. Frequency of and risk factors for stent thrombosis after drug-eluting stent implantation during long-term follow-up. Am J Cardiol 2006;98:352–6.
144. Kuchulakanti PK, Chu WW, Torguson R, et al. Correlates and long-term outcomes of angiographically proven stent thrombosis with sirolimus- and paclitaxel-eluting stents. Circulation 2006;113: 1108–13.
145. Roukoz H, Bavry AA, Sarkees ML, et al. Comprehensive meta-analysis on drug-eluting stents versus bare-metal stents during extended follow-up. Am J Med 2009;122:581.e1–10.
146. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;369:667–78.
147. Wenaweser P, Daemen J, Zwahlen M, et al. Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice. 4-year results from a large 2-institutional cohort study. J Am Coll Cardiol 2008;52:1134–40.
148. Onuma Y. Incidence of late stent thrombosis up to 5 years after implantation of drug eluting stents in clinical practice. Paper presented at: Meeting of the European Society of Cardiology; August 31, 2009; Barcelona, Spain.
149. Pinto Slottow TL, Steinberg DH, Roy PK, et al. Observations and outcomes of definite and probable drug-eluting stent thrombosis seen at a single hospital in a four-year period. Am J Cardiol 2008;102: 298–303.
150. James SK, Wallentin L, Lagerqvist B. The SCAAR-scare in perspective. EuroIntervention 2009;5:501–4.
151. van Werkum JW, Heestermans AA, Zomer AC, et al. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. J Am Coll Cardiol 2009;53:1399–409.
152. Lasala JM, Cox DA, Dobies D, et al. Drug-eluting stent thrombosis in routine clinical practice: two-year outcomes and predictors from the TAXUS ARRIVE registries. Circ Cardiovasc Interv 2009;2:285–93.
153. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193–202.
154. Farb A, Burke AP, Kolodgie FD, Virmani R. Pathological mechanisms of fatal late coronary stent thrombosis in humans. Circulation 2003;108:1701–6.
155. Finn AV, Joner M, Nakazawa G, et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation 2007;115:2435–41.
156. Ong AT, McFadden EP, Regar E, de Jaegere PP, van Domburg RT, Serruys PW. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. J Am Coll Cardiol 2005;45:2088–92.
157. Joner M, Nakazawa G, Finn AV, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. J Am Coll Cardiol 2008;52:333–42.
158. Guagliumi G, Musumeci G, Sirbu V, et al. Optical coherence tomography assessment of in vivo vascular response after implantation of overlapping bare-metal and drug-eluting stents. J Am Coll Cardiol Intv 2010;3:531–9.
159. Kim J-S, Jang I-K, Kim J-S, et al. Optical coherence tomography evaluation of zotarolimus-eluting stents at 9 month follow up: comparison with sirolimus-eluting stents. Heart 2009;95:1907–12.
160. Barlis P, Regar E, Serruys PW, et al. An optical coherence tomography study of a biodegradable vs. durable polymer-coated limus-eluting stent: a LEADERS trial sub-study. Eur Heart J 2010;31: 165–76.
161. Kotani J, Awata M, Nanto S, et al. Incomplete neointimal coverage of sirolimus-eluting stents: angioscopic findings. J Am Coll Cardiol 2006;47:2108–11.
162. Awata M, Kotani J, Uematsu M, et al. Serial angioscopic evidence of incomplete neointimal coverage after sirolimus-eluting stent implantation: comparison with bare-metal stents. Circulation 2007;116: 910–6.
163. van der Giessen WJ, Lincoff AM, Schwartz RS, et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. Circulation 1996; 94:1690–7.
164. Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? Circulation 2004;109:701–5.
165. Nebeker JR, Virmani R, Bennett CL, et al. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. J Am Coll Cardiol 2006;47:175–81.
166. Virmani R, Liistro F, Stankovic G, et al. Mechanism of late in-stent restenosis after implantation of a paclitaxel derivate-eluting polymer stent system in humans. Circulation 2002;106:2649–51.
167. Cook S, Ladich E, Nakazawa G, et al. Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. Circulation 2009;120:391–9.
168. Nakazawa G, Ladich E, Finn AV, Virmani R. Pathophysiology of vascular healing and stent mediated arterial injury. EuroIntervention 2008;4 Suppl C:7–10.
169. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527–33.
170. Steinhubl SR, Berger PB, Mann JT III, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288:2411–20.
171. Weintraub WS, Mahoney EM, Lamy A, et al. Long-term cost-effectiveness of clopidogrel given for up to one year in patients with acute coronary syndromes without ST-segment elevation. J Am Coll Cardiol 2005;45:838–45.
172. Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. Circulation 2006;113:2803–9.
173. Airoldi F, Colombo A, Morici N, et al. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. Circulation 2007;116:745–54.
174. Smith SC, Jr., Feldman TE, Hirshfeld JW Jr., et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). J Am Coll Cardiol 2006;47:e1–121.
175. Schulz S, Schuster T, Mehilli J, et al. Stent thrombosis after drug-eluting stent implantation: incidence, timing, and relation to discontinuation of clopidogrel therapy over a 4 year period. Eur Heart J 2009;30:2714–21.

176. Kimura T, Morimoto T, Nakagawa Y, et al. Antiplatelet therapy and stent thrombosis after sirolimus-eluting stent implantation. Circulation 2009;119:987–95.
177. Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. JAMA 2007;297:159–68.
178. Brar SS, Kim J, Brar SK, et al. Long-term outcomes by clopidogrel duration and stent type in a diabetic population with de novo coronary artery lesions. J Am Coll Cardiol 2008;51:2220–7.
179. Serruys PW, Daemen J. Late stent thrombosis: a nuisance in both bare metal and drug-eluting stents. Circulation 2007;115:1433–9.
180. Ho PM, Peterson ED, Wang L, et al. Incidence of death and acute myocardial infarction associated with stopping clopidogrel after acute coronary syndrome. JAMA 2008;299:532–9.
181. Park D-W, Yun S-C, Lee S-W, et al. Stent thrombosis, clinical events, and influence of prolonged clopidogrel use after placement of drug-eluting stent: data from an observational cohort study of drug-eluting versus bare-metal stents. J Am Coll Cardiol Intv 2008;1:494–503.
182. Tanzilli G, Greco C, Pelliccia F, et al. Effectiveness of two-year clopidogrel + aspirin in abolishing the risk of very late thrombosis after drug-eluting stent implantation (from the TYCOON [two-year ClOpidOgrel need] study). Am J Cardiol 2009;104:1357–61.
183. Feres F. Update from ongoing DAPT studies: Brazil OPTIMIZE randomised trial. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 21, 2009; San Francisco, CA.
184. Byrne RA, Schulz S, Mehilli J, et al. Rationale and design of a randomized, double-blind, placebo-controlled trial of 6 versus 12 months clopidogrel therapy after implantation of a drug-eluting stent: the Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE) study. Am Heart J 2009;157:620–4.e2.
185. Mauri L. Updates from ongoing DAPT studies: United States: DAPT randomized trial. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 21, 2009; San Francisco, CA. Available at: http://www.tctmd.com/txshow.aspx?tid=939078&id=83980&trid=938634. Accessed October 27, 2009.
186. Van de Werf F. New antithrombotic agents: are they needed and what can they offer to patients with a non-ST-elevation acute coronary syndrome? Eur Heart J 2009;30:1695–702.
187. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.
188. Wiviott SD, Braunwald E, McCabe CH, et al. Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomised trial. Lancet 2008;371:1353–63.
189. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045–57.
190. Schomig A. Ticagrelor—is there need for a new player in the antiplatelet-therapy field? N Engl J Med 2009;361:1108–11.
191. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Identification of low responders to a 300-mg clopidogrel loading dose in patients undergoing coronary stenting. Thromb Res 2005;115:101–8.
192. Muller I, Besta F, Schulz C, Massberg S, Schonig A, Gawaz M. Prevalence of clopidogrel non-responders among patients with stable angina pectoris scheduled for elective coronary stent placement. Thromb Haemost 2003;89:783–7.
193. Snoep JD, Hovens MM, Eikenboom JC, van der Bom JG, Jukema JW, Huisman MV. Clopidogrel nonresponsiveness in patients undergoing percutaneous coronary intervention with stenting: a systematic review and meta-analysis. Am Heart J 2007;154:221–31.
194. Gurbel PA, Bliden KP, Samara W, et al. Clopidogrel effect on platelet reactivity in patients with stent thrombosis: results of the CREST Study. J Am Coll Cardiol 2005;46:1827–32.
195. Barragan P, Bouvier JL, Roquebert PO, et al. Resistance to thienopyridines: clinical detection of coronary stent thrombosis by monitoring of vasodilator-stimulated phosphoprotein phosphorylation. Catheter Cardiovasc Interv 2003;59:295–302.
196. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. J Am Coll Cardiol 2007;49:1505–16.
197. Patti G, Nusca A, Mangiacapra F, Gatto L, D'Ambrosio A, Di Sciascio G. Point-of-care measurement of clopidogrel responsiveness predicts clinical outcome in patients undergoing percutaneous coronary intervention results of the ARMYDA-PRO (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty-Platelet Reactivity Predicts Outcome) study. J Am Coll Cardiol 2008;52:1128–33.
198. Marcucci R, Gori AM, Paniccia R, et al. Cardiovascular death and nonfatal myocardial infarction in acute coronary syndrome patients receiving coronary stenting are predicted by residual platelet reactivity to ADP detected by a point-of-care assay: a 12-month follow-up. Circulation 2009;119:237–42.
199. Price MJ, Endemann S, Gollapudi RR, et al. Prognostic significance of post-clopidogrel platelet reactivity assessed by a point-of-care assay on thrombotic events after drug-eluting stent implantation. Eur Heart J 2008;29:992–1000.
200. Cuisset T, Hamilos M, Sarma J, et al. Relation of low response to clopidogrel assessed with point-of-care assay to periprocedural myonecrosis in patients undergoing elective coronary stenting for stable angina pectoris. Am J Cardiol 2008;101:1700–3.
201. de Miguel Castro A, Cuellas Ramon C, Diego Nieto A, et al. Post-treatment platelet reactivity predicts long-term adverse events better than the response to clopidogrel in patients with non-ST-segment elevation acute coronary syndrome. Rev Esp Cardiol 2009;62:126–35.
202. Lemesle G, Delhaye C, Sudre A, et al. Impact of high loading and maintenance dose of clopidogrel within the first 15 days after percutaneous coronary intervention on patient outcome. Am Heart J 2009;157:375–82.
203. Angiolillo DJ, Bernardo E, Palazuelos J, et al. Functional impact of high clopidogrel maintenance dosing in patients undergoing elective percutaneous coronary interventions. Results of a randomized study. Thromb Haemost 2008;99:161–8.
204. Teirstein P. Updates from ongoing DAPT studies: United States: GRAVITAS randomized trial. Paper presented a: Transcatheter Cardiovascular Therapeutics; September 21, 2009; San Francisco, CA. Available at: http://www.tctmd.com/txshow.aspx?tid=939078&id=83972&trid=938634. Accessed October 27, 2009.
205. Mehta SR. A randomized comparison of a clopidogrel high loading and maintenance dose regimen versus standard dose and high versus low dose aspirin in 25,000 patients with acute coronary syndromes: results of the CURRENT OASIS 7 trial. Paper presented at: European Society of Cardiology; August 30, 2009; Barcelona, Spain.
206. Mehta SR. CURRENT-STEMI PCI: double-dose vs. standard-dose clopidogrel in ACS patients undergoing PCI for STEMI. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 24, 2009; San Francisco, CA. Available at: http://www.tctmd.com/txshow.aspx?tid=938642&id=81330&trid=938634. Accessed October 27, 2009.
207. Cuisset T, Frere C, Quilici J, et al. Glycoprotein IIb/IIIa inhibitors improve outcome after coronary stenting in clopidogrel nonresponders: a prospective, randomized study. J Am Coll Cardiol Intv 2008;1:649–53.
208. Valgimigli M, Campo G, de Cesare N, et al. Intensifying platelet inhibition with tirofiban in poor responders to aspirin, clopidogrel, or both agents undergoing elective coronary intervention: results from the double-blind, prospective, randomized Tailoring Treatment with Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel study. Circulation 2009;119:3215–22.
209. Angiolillo DJ, Capranzano P, Goto S, et al. A randomized study assessing the impact of cilostazol on platelet function profiles in patients with diabetes mellitus and coronary artery disease on dual antiplatelet therapy: results of the OPTIMUS-2 study. Eur Heart J 2008;29:2202–11.
210. de Jaegere P, Mudra H, Figulla H, et al. Intravascular ultrasound-guided optimized stent deployment. Immediate and 6 months clinical and angiographic results from the Multicenter Ultrasound Stenting in Coronaries Study (MUSIC Study). Eur Heart J 1998;19:1214–23.
211. Fujii K, Carlier SG, Mintz GS, et al. Stent underexpansion and residual reference segment stenosis are related to stent thrombosis

after sirolimus-eluting stent implantation: an intravascular ultrasound study. J Am Coll Cardiol 2005;45:995–8.
212. Alfonso F, Suarez A, Perez-Vizcayno MJ, et al. Intravascular ultrasound findings during episodes of drug-eluting stent thrombosis. J Am Coll Cardiol 2007;50:2095–7.
213. Briguori C, Tobis J, Nishida T, et al. Discrepancy between angiography and intravascular ultrasound when analysing small coronary arteries. Eur Heart J 2002;23:247–54.
214. de Feyter PJ, Kay P, Disco C, Serruys PW. Reference chart derived from post-stent-implantation intravascular ultrasound predictors of 6-month expected restenosis on quantitative coronary angiography. Circulation 1999;100:1777–83.
215. Hoffmann R, Mintz GS, Mehran R, et al. Intravascular ultrasound predictors of angiographic restenosis in lesions treated with Palmaz-Schatz stents. J Am Coll Cardiol 1998;31:43–9.
216. Hong MK, Mintz GS, Lee CW, et al. Intravascular ultrasound predictors of angiographic restenosis after sirolimus-eluting stent implantation. Eur Heart J 2006;27:1305–10.
217. Takebayashi H, Kobayashi Y, Mintz GS, et al. Intravascular ultrasound assessment of lesions with target vessel failure after sirolimus-eluting stent implantation. Am J Cardiol 2005;95:498–502.
218. de Ribamar Costa J Jr., Mintz GS, Carlier SG, et al. Intravascular ultrasound assessment of drug-eluting stent expansion. Am Heart J 2007;153:297–303.
219. Cook S, Wenaweser P, Togni M, et al. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. Circulation 2007;115:2426–34.
220. Uren NG, Schwarzacher SP, Metz JA, et al. Predictors and outcomes of stent thrombosis: an intravascular ultrasound registry. Eur Heart J 2002;23:124–32.
221. Cheneau E, Leborgne L, Mintz GS, et al. Predictors of subacute stent thrombosis: results of a systematic intravascular ultrasound study. Circulation 2003;108:43–7.
222. Okamura T, Serruys PW, Regar E. Three-dimensional visualization of intracoronary thrombus during stent implantation using the second generation, Fourier domain optical coherence tomography. Eur Heart J 2010;31:625.
223. Mintz GS. What to do about late incomplete stent apposition? Circulation 2007;115:2379–81.
224. Hoffmann R, Morice MC, Moses JW, et al. Impact of late incomplete stent apposition after sirolimus-eluting stent implantation on 4-year clinical events: intravascular ultrasound analysis from the multicentre, randomised, RAVEL, E-SIRIUS and SIRIUS trials. Heart 2008;94:322–8.
225. Hong MK, Mintz GS, Lee CW, et al. Late stent malapposition after drug-eluting stent implantation: an intravascular ultrasound analysis with long-term follow-up. Circulation 2006;113:414–9.
226. Hassan AK, Bergheanu SC, Stijnen T, et al. Late stent malapposition risk is higher after drug-eluting stent compared with bare-metal stent implantation and associates with late stent thrombosis. Eur Heart J 2009;31:1172–80.
227. van der Hoeven BL, Liem SS, Dijkstra J, et al. Stent malapposition after sirolimus-eluting and bare-metal stent implantation in patients with ST-segment elevation myocardial infarction: acute and 9-month intravascular ultrasound results of the MISSION! intervention study. J Am Coll Cardiol Intv 2008;1:192–201.
228. Kubo T, Imanishi T, Kitabata H, et al. Comparison of vascular response after sirolimus-eluting stent implantation between patients with unstable and stable angina pectoris: a serial optical coherence tomography study. J Am Coll Cardiol Img 2008;1:475–84.
229. Waksman R. Late thrombosis after radiation. Sitting on a time bomb. Circulation 1999;100:780–2.
230. Sianos G, Hofma S, Ligthart JM, et al. Stent fracture and restenosis in the drug-eluting stent era. Catheter Cardiovasc Interv 2004;61: 111–6.
231. Surmely JF, Kinoshita Y, Dash D, et al. Stent strut fracture-induced restenosis in a bifurcation lesion treated with the crush stenting technique. Circ J 2006;70:936–8.
232. Lee MS, Jurewitz D, Aragon J, Forrester J, Makkar RR, Kar S. Stent fracture associated with drug-eluting stents: clinical characteristics and implications. Catheter Cardiovasc Interv 2007;69:387–94.
233. Aoki J, Nakazawa G, Tanabe K, et al. Incidence and clinical impact of coronary stent fracture after sirolimus-eluting stent implantation. Catheter Cardiovasc Interv 2007;69:380–6.
234. Lee SH, Park JS, Shin DG, et al. Frequency of stent fracture as a cause of coronary restenosis after sirolimus-eluting stent implantation. Am J Cardiol 2007;100:627–30.
235. Nakazawa G, Finn AV, Vorpahl M, et al. Incidence and predictors of drug-eluting stent fracture in human coronary artery a pathologic analysis. J Am Coll Cardiol 2009;54:1924–31.
236. Popma JJ, Tiroch K, Almonacid A, Cohen S, Kandzari DE, Leon MB. A qualitative and quantitative angiographic analysis of stent fracture late following sirolimus-eluting stent implantation. Am J Cardiol 2009;103:923–9.
237. Doi H, Maehara A, Mintz GS, et al. Classification and potential mechanisms of intravascular ultrasound patterns of stent fracture. Am J Cardiol 2009;103:818–23.
238. Brilakis ES, Maniu C, Wahl M, Barsness G. Unstable angina due to stent fracture. J Invasive Cardiol 2004;16:545.
239. Carter AJ. Drug-eluting stent fracture promise and performance. J Am Coll Cardiol 2009;54:1932–4.
240. Aoki J, Kirtane A, Leon MB, Dangas G. Coronary artery aneurysms after drug-eluting stent implantation. J Am Coll Cardiol Intv 2008;1:14–21.
241. Slota PA, Fischman DL, Savage MP, Rake R, Goldberg S. Frequency and outcome of development of coronary artery aneurysm after intracoronary stent placement and angioplasty. STRESS Trial Investigators. Am J Cardiol 1997;79:1104–6.
242. Baumbach A, Bittl JA, Fleck E, et al. Acute complications of excimer laser coronary angioplasty: a detailed analysis of multicenter results. Coinvestigators of the U.S. and European Percutaneous Excimer Laser Coronary Angioplasty (PELCA) Registries. J Am Coll Cardiol 1994;23:1305–13.
243. Bell MR, Garratt KN, Bresnahan JF, Edwards WD, Holmes DR Jr. Relation of deep arterial resection and coronary artery aneurysms after directional coronary atherectomy. J Am Coll Cardiol 1992;20:1474–81.
244. Gupta RK, Sapra R, Kaul U. Early aneurysm formation after drug-eluting stent implantation: an unusual life-threatening complication. J Invasive Cardiol 2006;18:E140–2.
245. Porto I, MacDonald S, Banning AP. Intravascular ultrasound as a significant tool for diagnosis and management of coronary aneurysms. Cardiovasc Intervent Radiol 2004;27:666–8.
246. Alfonso F, Perez-Vizcayno MJ, Ruiz M, et al. Coronary aneurysms after drug-eluting stent implantation: clinical, angiographic, and intravascular ultrasound findings. J Am Coll Cardiol 2009; 53:2053–60.
247. Feres F, Costa JR Jr., Abizaid A. Very late thrombosis after drug-eluting stents. Catheter Cardiovasc Interv 2006;68:83–8.
248. Aziz S, Morris JL, Perry RA. Late stent thrombosis associated with coronary aneurysm formation after sirolimus-eluting stent implantation. J Invasive Cardiol 2007;19:E96–8.
249. Sano K, Mintz GS, Carlier SG, et al. Volumetric intravascular ultrasound assessment of neointimal hyperplasia and nonuniform stent strut distribution in sirolimus-eluting stent restenosis. Am J Cardiol 2006;98:1559–62.
250. Kastrati A, Mehilli J, Dirschinger J, et al. Intracoronary Stenting and Angiographic Results: Strut Thickness Effect on Restenosis Outcome (ISAR-STEREO) trial. Circulation 2001;103:2816–21.
251. Pache J, Kastrati A, Mehilli J, et al. Intracoronary Stenting and Angiographic Results: Strut Thickness Effect on Restenosis Outcome (ISAR-STEREO-2) trial. J Am Coll Cardiol 2003;41:1283–8.
252. Kereiakes DJ, Cox DA, Hermiller JB, et al. Usefulness of a cobalt chromium coronary stent alloy. Am J Cardiol 2003;92:463–6.
253. Awata M, Nanto S, Uematsu M, et al. Angioscopic comparison of neointimal coverage between zotarolimus- and sirolimus-eluting stents. J Am Coll Cardiol 2008;52:789–90.
254. Kim J-S, Jang I-K, Fan C, et al. Evaluation in 3 months duration of neointimal coverage after zotarolimus-eluting stent implantation by optical coherence tomography: the ENDEAVOR OCT trial. J Am Coll Cardiol Intv 2009;2:1240–7.
255. Kim JW, Seo HS, Park JH, et al. A prospective, randomized, 6-month comparison of the coronary vasomotor response associated with a zotarolimus- versus a sirolimus-eluting stent: differential recovery of coronary endothelial dysfunction. J Am Coll Cardiol 2009;53:1653–9.
256. Meredith IT, Ormiston J, Whitbourn R, et al. First-in-human study of the Endeavor ABT-578-eluting phosphorylcholine-encapsulated

stent system in de novo native coronary artery lesions: Endeavor I trial. EuroIntervention 2005;1:157–64.
257. Meredith IT, Ormiston J, Whitbourn R, Kay IP, Muller D, Cutlip DE. Five-year clinical follow-up after implantation of the endeavor zotarolimus-eluting stent: ENDEAVOR I, first-in-human study. Catheter Cardiovasc Interv 2009;74:989–95.
258. Fajadet J, Wijns W, Laarman GJ, et al. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. Circulation 2006;114:798–806.
259. van Leeuwen F. Randomised trial comparing the ENDEAVOR zotarolimus-eluting stent and the Driver bare metal stent in single de novo native coronary artery lesions: five-year clinical follow-up of ENDEAVOR II. Paper presented at: EuroPCR; May 19–22, 2009; Barcelona, Spain.
260. Kandzari DE, Leon MB, Popma JJ, et al. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease: a randomized controlled trial. J Am Coll Cardiol 2006;48:2440–7.
261. Eisenstein EL, Leon MB, Kandzari DE, et al. Long-term clinical and economic analysis of the Endeavor zotarolimus-eluting stent versus the Cypher sirolimus-eluting stent: 3-year results from the ENDEAVOR III trial (randomized controlled trial of the Medtronic Endeavor drug [ABT-578] eluting coronary stent system versus the Cypher sirolimus-eluting coronary stent system in de novo native coronary artery lesions). J Am Coll Cardiol Intv 2009;2:1199–207.
262. Kandzari D, Mauri L, Popma J, et al. ENDEAVOR III: 5 year final outcomes. Paper presented at: The American College of Cardiology Scientific Sessions; March 14–16, 2010; Atlanta, GA.
263. Hamm C. 5 Years later and more than 20,000 patients studied: the ENDEAVOR clinical program. Paper presented at: EuroPCR; May 19–22, 2009; Barcelona, Spain. Available at: http://www.pcronline.com/Lectures/2009/5-years-later-and-more-than-20-000-patients-studied-the-ENDEAVOR-clinical-programme. Accessed June 20, 2009.
264. Leon MB, Mauri L, Popma JJ, et al. A randomised comparison of the Endeavor zotarolimus-eluting stent versus the TAXUS paclitaxel-eluting stent in de novo native coronary lesions: 12-month outcomes from the ENDEAVOR IV trial. J Am Coll Cardiol 2010;55:543–54.
265. Leon M. The ENDEAVOR and ENDEAVOR Resolute zotarolimus-eluting stent: comprehensive update of the clinical trial program (featuring the first presentation of the ENDEAVOR IV 3-year results). Paper presented at: Transcatheter Cardiovascular Therapeutics; September 21, 2009; San Francisco, CA. Available at: http://www.tctmd.com/txshow.aspx?tid=939082&id=84004&trid=938634. Accessed October 28, 2009.
266. Park SJ. Comparison of sirolimus- and paclitaxel-eluting stents vs zotarolimus-eluting stents in real world practice: the ZEST randomized controlled trial. Paper presented at: i2 Summit at the American College of Cardiology Scientific Sessions; March 29–31, 2009; Orlando, FL.
267. Rasmussen K, Maeng M, Kaltoft A, et al. Efficacy and safety of zotarolimus-eluting and sirolimus-eluting coronary stents in routine clinical care (SORT OUT III): a randomised controlled superiority trial. Lancet 2010;375:1090–99.
268. Lotan C, Meredith IT, Mauri L, Liu M, Rothman MT, for the EFI. Safety and effectiveness of the Endeavor zotarolimus-eluting stent in real-world clinical practice: 12-month data from the E-Five Registry. J Am Coll Cardiol Intv 2009;2:1227–35.
269. Meredith I. Real world outcomes in patients with coronary artery disease treated with the endeavor ZES: 2-year results from the E-Five Registry. Paper presented at: EuroPCR; May 2009; Barcelona, Spain.
270. Rivero F, Moreno R, Barreales L, et al. Lower levels of in-stent late loss are not associated with the risk of stent thrombosis in patients receiving drug-eluting stents. EuroIntervention 2008;4:124–32.
271. Camenzind E, Wijns W, Mauri L, et al. Rationale and design of the Patient Related OuTcomes with Endeavor versus Cypher stenting Trial (PROTECT): randomized controlled trial comparing the incidence of stent thrombosis and clinical events after sirolimus or zotarolimus drug-eluting stent implantation. Am Heart J 2009;158:902–9.e5.
272. Serruys PW, Ong ATL, Piek JJ, et al. A randomised comparison of a durable polymer everolimus-eluting stent with a bare metal coronary stent: the SPIRIT FIRST trial. EuroIntervention 2005;1:58–65.
273. Wiemer M, Serruys PW, Miquel-Hebert K, et al. Five-year long-term clinical follow-up of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo coronary artery lesions: the SPIRIT FIRST trial. Catheter Cardiovasc Interv 2010;75:997–1003.
274. Serruys PW, Ruygrok P, Neuzner J, et al. A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent: the SPIRIT II trial. EuroIntervention 2006;2:286–94.
275. Garg S, Serruys PW, Onuma Y, et al. Three-year clinical follow-up of the XIENCE V everolimus-eluting coronary stent system in the treatment of patients with de novo coronary artery lesions. The SPIRIT II trial. J Am Coll Cardiol Intv 2009;2:1190–8.
276. Garg S, Serruys PW, Miquel-Hebert K. Four year clinical follow up of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo coronary artery lesions: the SPIRIT II trial. Catheter Cardiovasc Interv 2010. In press.
277. Stone GW, Midei M, Newman W, et al. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. JAMA 2008;299:1903–13.
278. Stone GW. The XIENCE V-PROMUS everolimus-eluting stent: comprehensive update of the clinical trial program. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 21, 2009; San Francisco, CA. Available at: http://www.tctmd.com/txshow.aspx?tid=939082&id=84006&trid=938634. Accessed October 28, 2009.
279. Stone GW, Rizvi A, Newman W, et al. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med 2010;362:1663–74.
280. Chevalier B. SPIRIT V single arm study: 2 year follow-up. Paper presented at: EuroPCR; May 25–28, 2010; Paris, France.
281. Kedhi E, Joesoef KS, McFadden E, et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet 2010;375:201–9.
282. Onuma Y, Kukreja N, Piazza N, et al. The everolimus-eluting stent in real-world patients: 6-month follow-up of the X-SEARCH (Xience V Stent Evaluated at Rotterdam Cardiac Hospital) registry. J Am Coll Cardiol 2009;54:269–76.
283. Aoki J, Abizaid AC, Ong AT, Tsuchida K, Serruys PW. Serial assessment of tissue growth inside and outside the stent after implantation of drug-eluting stent in clinical trials. Does delayed neointimal growth exist? EuroIntervention 2005;1:235–55.
284. Claessen BE, Beijk MA, Legrand V, et al. Two-year clinical, angiographic, and intravascular ultrasound follow-up of the XIENCE V everolimus-eluting stent in the treatment of patients with de novo native coronary artery lesions: the SPIRIT II trial. Circ Cardiovasc Interv 2009;2:339–47.
285. Park KW, Yoon JH, Kim JS, et al. Efficacy of Xience/Promus versus Cypher in rEducing Late Loss after stENTing (EXCELLENT) trial: study design and rationale of a Korean multicenter prospective randomized trial. Am Heart J 2009;157:811–7 e1.
286. Reuters. Drug-Eluting Stent Penetration Lowest in Arkansas, Outnumbered by Bare-Metal Stents. September 21, 2009. Available at: http://www.reuters.com/article/pressRelease/idUS75669+21-Sep-2009+PRN20090921?sp = true. Accessed October 24, 2009.
287. Stone GW, Ellis SG, Colombo A, et al. Offsetting impact of thrombosis and restenosis on the occurrence of death and myocardial infarction after paclitaxel-eluting and bare metal stent implantation. Circulation 2007;115:2842–7.
288. Pfisterer M, Brunner-La Rocca HP, Rickenbacher P, et al. Long-term benefit-risk balance of drug-eluting vs. bare-metal stents in daily practice: does stent diameter matter? Three-year follow-up of BASKET. Eur Heart J 2009;30:16–24.
289. Tu JV, Bowen J, Chiu M, et al. Effectiveness and safety of drug-eluting stents in Ontario. N Engl J Med 2007;357:1393–402.
290. Brunner-La Rocca HP, Kaiser C, Bernheim A, et al. Cost-effectiveness of drug-eluting stents in patients at high or low risk of major cardiac events in the Basel Stent KostenEffektivitats Trial (BASKET): an 18-month analysis. Lancet 2007;370:1552–9.

291. Neyt M, Van Brabandt H, Devriese S, De Laet C. Cost-effectiveness analyses of drug eluting stents versus bare metal stents: a systematic review of the literature. Health Policy 2009;91:107–20.
292. Canoui-Poitrine F, Jeanblanc G, Alberti C, et al. Cost effectiveness of sirolimus-eluting stents compared with bare metal stents in acute myocardial infarction: insights from the TYPHOON trial. Appl Health Econ Health Policy 2009;7:19–29.
293. Bischof M, Briel M, Bucher HC, Nordmann A. Cost-effectiveness of drug-eluting stents in a US Medicare setting: a cost-utility analysis with 3-year clinical follow-up data. Value in Health 2009;12:649–56.
294. National Institute for Health and Clinical Excellence. Final appraisal determination: drug-eluting stents for the treatment of coronary artery disease. Available at: http://guidance.nice.org.uk/TA/WaveR/4. Accessed July 2010.
295. Lemos PA, Hoye A, Goedhart D, et al. Clinical, angiographic, and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation in complex patients: an evaluation from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) study. Circulation 2004;109:1366–70.
296. Abizaid A, Kornowski R, Mintz GS, et al. The influence of diabetes mellitus on acute and late clinical outcomes following coronary stent implantation. J Am Coll Cardiol 1998;32:584–9.
297. Kereiakes DJ, Young JJ. Percutaneous coronary revascularization of diabetic patients in the era of drug-eluting stents. Rev Cardiovasc Med 2005;6 Suppl 1:48–58.
298. Aronson D, Bloomgarden Z, Rayfield EJ. Potential mechanisms promoting restenosis in diabetic patients. J Am Coll Cardiol 1996; 27:528–35.
299. Corpus RA, George PB, House JA, et al. Optimal glycemic control is associated with a lower rate of target vessel revascularization in treated type II diabetic patients undergoing elective percutaneous coronary intervention. J Am Coll Cardiol 2004;43:8–14.
300. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. JAMA 2002;287: 2570–81.
301. Garg P, Normand SL, Silbaugh TS, et al. Drug-eluting or bare-metal stenting in patients with diabetes mellitus: results from the Massachusetts Data Analysis Center Registry. Circulation 2008;118:2277–85.
302. Frobert O, Lagerqvist B, Carlsson J, Lindback J, Stenestrand U, James SK. Differences in restenosis rate with different drug-eluting stents in patients with and without diabetes mellitus: a report from the SCAAR (Swedish Angiography and Angioplasty Registry). J Am Coll Cardiol 2009;53:1660–7.
303. Kim MH, Hong SJ, Cha KS, et al. Effect of paclitaxel-eluting versus sirolimus-eluting stents on coronary restenosis in Korean diabetic patients. J Interv Cardiol 2008;21:225–31.
304. Chan C, Zambahari R, Kaul U, et al. A randomized comparison of sirolimus-eluting versus bare metal stents in the treatment of diabetic patients with native coronary artery lesions: the DECODE study. Catheter Cardiovasc Interv 2008;72:591–600.
305. Jensen LO, Maeng M, Thayssen P, et al. Neointimal hyperplasia after sirolimus-eluting and paclitaxel-eluting stent implantation in diabetic patients: the Randomized Diabetes and Drug-Eluting Stent (DiabeDES) intravascular ultrasound trial. Eur Heart J 2008;29: 2733–41.
306. Maeng M, Jensen LO, Galloe AM, et al. Comparison of the sirolimus-eluting versus paclitaxel-eluting coronary stent in patients with diabetes mellitus: the diabetes and drug-eluting stent (DiabeDES) randomized angiography trial. Am J Cardiol 2009;103:345–9.
307. Tomai F, Reimers B, De Luca L, et al. Head-to-head comparison of sirolimus- and paclitaxel-eluting stent in the same diabetic patient with multiple coronary artery lesions: a prospective, randomized, multicenter study. Diabetes Care 2008;31:15–9.
308. Jensen LO. DiabeDES III Trial: hyperplasia and angiographic late lumen loss after sirolimus eluting and zotarolimus eluting stent implantation in diabetic patients. Paper presented at: European Society of Cardiology; September 2009; Barcelona, Spain.
309. Grube E. SPIRIT V diabetic randomised control trial 1 year results. Paper presented at: EuroPCR; May 25–28, 2010. Available at: http://www.pcronline.com/Lectures/2010/SPIRIT-V-diabetic-randomised-control-trial-1-year-results. Accessed May 29, 2010.
310. Kirtane AJ, Patel R, O'Shaughnessy C, et al. Clinical and angiographic outcomes in diabetics from the ENDEAVOR IV trial: randomized comparison of zotarolimus- and paclitaxel-eluting stents in patients with coronary artery disease. J Am Coll Cardiol Intv 2009;2:967–76.
311. Kirtane AJ, Ellis SG, Dawkins KD, et al. Paclitaxel-eluting coronary stents in patients with diabetes mellitus: pooled analysis from 5 randomized trials. J Am Coll Cardiol 2008;51:708–15.
312. Stettler C, Allemann S, Wandel S, et al. Drug eluting and bare metal stents in people with and without diabetes: collaborative network meta-analysis. BMJ 2008;337:a1331.
313. Kastrati A. Sirolimus-eluting stents versus paclitaxel eluting stents in patients with coronary artery disease and diabetes mellitus: meta-analysis of randomised trials. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 2009; San Francisco, CA.
314. Kapur A, Hall RJ, Malik IS, et al. Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients: 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial. J Am Coll Cardiol 2010;55:432–40.
315. Banning A, Westaby S, Morice MC, et al. Comparison of cardiac surgery and paclitaxel-eluting stents in nondiabetic and diabetic patients with left main and/or 3-vessel coronary artery disease. J Am Coll Cardiol 2010;55:1067–75.
316. Farkouh ME, Dangas G, Leon MB, et al. Design of the Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease (FREEDOM) trial. Am Heart J 2008;155:215–23.
317. Fox KA, Poole-Wilson P, Clayton TC, et al. 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial. Lancet 2005;366:914–20.
318. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13–20.
319. Kushner FG, Hand M, Smith SC Jr., et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2009;54:2205–41.
320. Ong AT, Hoye A, Aoki J, et al. Thirty-day incidence and six-month clinical outcome of thrombotic stent occlusion after bare-metal, sirolimus, or paclitaxel stent implantation. J Am Coll Cardiol 2005;45:947–53.
321. Tolleson TR, Newby LK, Harrington RA, et al. Frequency of stent thrombosis after acute coronary syndromes (from the SYMPHONY and 2nd SYMPHONY trials). Am J Cardiol 2003;92:330–3.
322. Finn AV, Nakazawa G, Kolodgie F, Virmani R. Drug eluting or bare metal stent for acute myocardial infarction: an issue of safety? Eur Heart J 2009;30:1828–30.
323. Kastrati A, Dibra A, Spaulding C, et al. Meta-analysis of randomized trials on drug-eluting stents vs. bare-metal stents in patients with acute myocardial infarction. Eur Heart J 2007;28:2706–13.
324. Brar SS, Leon MB, Stone GW, et al. Use of drug-eluting stents in acute myocardial infarction: a systematic review and meta-analysis. J Am Coll Cardiol 2009;53:1677–89.
325. Kukreja N, Onuma Y, Garcia-Garcia HM, Daemen J, Van Domburg R, Serruys PW. Primary percutaneous coronary intervention for acute myocardial infarction: long-term outcome after bare metal and drug-eluting stent implantation. Circ Cardiovasc Interv 2008;1:103–10.
326. Singh M, Rihal CS, Gersh BJ, et al. Twenty-five-year trends in in-hospital and long-term outcome after percutaneous coronary intervention: a single-institution experience. Circulation 2007;115: 2835–41.
327. Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 2001;344:1117–24.
328. Serruys PW. ARTS I—the rapamycin eluting stent; ARTS II— the rosy prophecy. Eur Heart J 2002;23:757–9.
329. Kappetein AP, Dawkins KD, Mohr FW, et al. Current percutaneous coronary intervention and coronary artery bypass grafting practices for three-vessel and left main coronary artery disease.

Insights from the SYNTAX run-in phase. Eur J Cardiothorac Surg 2006;29:486–91.
330. Daemen J, Boersma E, Flather M, et al. Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. Circulation 2008;118: 1146–54.
331. Bravata DM, Gienger AL, McDonald KM, et al. Systematic review: the comparative effectiveness of percutaneous coronary interventions and coronary artery bypass graft surgery. Ann Intern Med 2007;147: 703–16.
332. Hlatky MA, Boothroyd DB, Bravata DM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. Lancet 2009;373:1190–7.
333. Hannan EL, Racz MJ, Walford G, et al. Long-term outcomes of coronary-artery bypass grafting versus stent implantation. N Engl J Med 2005;352:2174–83.
334. Rodriguez AE, Maree AO, Mieres J, et al. Late loss of early benefit from drug-eluting stents when compared with bare-metal stents and coronary artery bypass surgery: 3 years follow-up of the ERACI III registry. Eur Heart J 2007;28:2118–25.
335. Hannan EL, Wu C, Walford G, et al. Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. N Engl J Med 2008;358:331–41.
336. Daemen J, Kukreja N, Serruys PW. Drug-eluting stents vs. coronary-artery bypass grafting. N Engl J Med 2008;358:2641–2; author reply 2643–4.
337. Morice MC. Multivessel disease lessons from SYNTAX (early results and 2 year follow-up): interventional perspectives. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 21, 2009; San Francisco, CA.
338. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 appropriateness criteria for coronary revascularization: a report by the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology. J Am Coll Cardiol 2009;53:530–53.
339. Smith SC Jr., Feldman TE, Hirshfeld JW Jr., et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). J Am Coll Cardiol 2006;47:1–121.
340. Kandzari DE, Colombo A, Park SJ, et al. Revascularization for unprotected left main disease: evolution of the evidence basis to redefine treatment standards. J Am Coll Cardiol 2009;54:1576–88.
341. Meliga E, Garcia-Garcia HM, Valgimigli M, et al. Impact of drug-eluting stent selection on long-term clinical outcomes in patients treated for unprotected left main coronary artery disease: the Sirolimus Vs Paclitaxel Drug-Eluting Stent for Left Main Registry (SP-DELFT). Int J Cardiol 2009;137:16–21.
342. Lee JY, Park DW, Yun SC, et al. Long-term clinical outcomes of sirolimus- versus paclitaxel-eluting stents for patients with unprotected left main coronary artery disease: analysis of the MAIN-COMPARE (revascularization for unprotected left main coronary artery stenosis: comparison of percutaneous coronary angioplasty versus surgical revascularization) registry. J Am Coll Cardiol 2009; 54:853–9.
343. Park D-W, Seung KB, Kim Y-H, et al. Long-term safety and efficacy of stenting versus coronary artery bypass grafting for unprotected left main coronary artery disease: 5-year results from the MAIN-COMPARE (revascularization for unprotected left main coronary artery stenosis: comparison of percutaneous coronary angioplasty versus surgical revascularization) registry. J Am Coll Cardiol 2010;56:117–24.
344. Naik H, White AJ, Chakravarty T, et al. A meta-analysis of 3,773 patients treated with percutaneous coronary intervention or surgery for unprotected left main coronary artery stenosis. J Am Coll Cardiol Intv 2009;2:739–47.
345. Serruys PW. Left main lessons from SYNTAX (early results and 2 year follow-up): interventional perspectives. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 21, 2009; San Francisco, CA. Available at: http://www.tctmd.com/txshow.aspx?tid=9390768&id=83938&trid=938634. Accessed September 21, 2009.
346. Kappetein AP, Sabik JF III, Serruys PW, Stone GW. Evaluation of Xience Prime versus coronary artery bypass surgery for effectiveness of left main revascularisation. The EXCEL trial. 2009. Available at: http://www.sbhci.org.br/pdf/EXCELSitequalificationquestionnaire.pdf. Accessed November 1, 2009.
347. Stone GW, Reifart NJ, Moussa I, et al. Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part II. Circulation 2005;112:2530–7.
348. Olivari Z, Rubartelli P, Piscione F, et al. Immediate results and one-year clinical outcome after percutaneous coronary interventions in chronic total occlusions: data from a multicenter, prospective, observational study (TOAST-GISE). J Am Coll Cardiol 2003;41: 1672–8.
349. Kirschbaum SW, Baks T, van den Ent M, et al. Evaluation of left ventricular function three years after percutaneous recanalization of chronic total coronary occlusions. Am J Cardiol 2008;101:179–85.
350. Suero JA, Marso SP, Jones PG, et al. Procedural outcomes and long-term survival among patients undergoing percutaneous coronary intervention of a chronic total occlusion in native coronary arteries: a 20-year experience. J Am Coll Cardiol 2001;38:409–14.
351. Hoye A, van Domburg RT, Sonnenschein K, Serruys PW. Percutaneous coronary intervention for chronic total occlusions: the Thoraxcenter experience 1992–2002. Eur Heart J 2005;26:2630–6.
352. Prasad A, Rihal CS, Lennon RJ, Wiste HJ, Singh M, Holmes DR Jr. Trends in outcomes after percutaneous coronary intervention for chronic total occlusions: a 25-year experience from the Mayo Clinic. J Am Coll Cardiol 2007;49:1611–8.
353. de Labriolle A, Bonello L, Roy P, et al. Comparison of safety, efficacy, and outcome of successful versus unsuccessful percutaneous coronary intervention in "true" chronic total occlusions. Am J Cardiol 2008;102:1175–81.
354. Ge L, Iakovou I, Cosgrave J, et al. Immediate and mid-term outcomes of sirolimus-eluting stent implantation for chronic total occlusions. Eur Heart J 2005;26:1056–62.
355. Hoye A, Tanabe K, Lemos PA, et al. Significant reduction in restenosis after the use of sirolimus-eluting stents in the treatment of chronic total occlusions. J Am Coll Cardiol 2004;43:1954–8.
356. Agostoni P, Valgimigli M, Biondi-Zoccai GG, et al. Clinical effectiveness of bare-metal stenting compared with balloon angioplasty in total coronary occlusions: insights from a systematic overview of randomized trials in light of the drug-eluting stent era. Am Heart J 2006;151:682–9.
357. Werner GS, Krack A, Schwarz G, Prochnau D, Betge S, Figulla HR. Prevention of lesion recurrence in chronic total coronary occlusions by paclitaxel-eluting stents. J Am Coll Cardiol 2004;44:2301–6.
358. Nakamura S, Muthusamy TS, Bae JH, Cahyadi YH, Udayachalerm W, Tresukosol D. Impact of sirolimus-eluting stent on the outcome of patients with chronic total occlusions. Am J Cardiol 2005;95: 161–6.
359. Hoye A, Ong ATL, Aoki J, et al. Drug-eluting stent implantation for chronic total occlusions: comparison between the sirolimus- and paclitaxel-eluting stent. EuroIntervention 2005;1:193–7.
360. De Felice F, Fiorilli R, Parma A, et al. Clinical outcome of patients with chronic total occlusion treated with drug-eluting stents. Int J Cardiol 2009;132:337–41.
361. Garcia-Garcia HM, Daemen J, Kukreja N, et al. Three-year clinical outcomes after coronary stenting of chronic total occlusion using sirolimus-eluting stents: insights from the rapamycin-eluting stent evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. Catheter Cardiovasc Interv 2007;70:635–9.
362. Shen ZJ, Garcia-Garcia HM, Garg S, et al. Five-year clinical outcomes after coronary stenting of chronic total occlusion using sirolimus-eluting stents: insights from the rapamycin-eluting stent evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. Catheter Cardiovasc Interv 2009;74:979–86.
363. Colmenarez HJ, Escaned J, Fernandez C, et al. Efficacy and safety of drug-eluting stents in chronic total coronary occlusion recanalization:

a systematic review and meta-analysis. J Am Coll Cardiol 2010;55: 1854–66.
364. Taggart DP. Arterial or venous conduits for redo coronary artery bypass grafting? Heart 1998;80:1–2.
365. Yap CH, Sposato L, Akowuah E, et al. Contemporary results show repeat coronary artery bypass grafting remains a risk factor for operative mortality. Ann Thorac Surg 2009;87:1386–91.
366. Savage MP, Douglas JS Jr., Fischman DL, et al. Stent placement compared with balloon angioplasty for obstructed coronary bypass grafts. Saphenous Vein De Novo Trial Investigators. N Engl J Med 1997;337:740–7.
367. Ratliff NB, Myles JL. Rapidly progressive atherosclerosis in aorto-coronary saphenous vein grafts. Possible immune-mediated disease. Arch Pathol Lab Med 1989;113:772–6.
368. Mauri L, Cox D, Hermiller J, et al. The PROXIMAL trial: proximal protection during saphenous vein graft intervention using the Proxis embolic protection system: a randomized, prospective, multicenter clinical trial. J Am Coll Cardiol 2007;50:1442–9.
369. Baim DS, Wahr D, George B, et al. Randomized trial of a distal embolic protection device during percutaneous intervention of saphenous vein aorto-coronary bypass grafts. Circulation 2002; 105:1285–90.
370. Stone GW, Rogers C, Ramee S, et al. Distal filter protection during saphenous vein graft stenting: technical and clinical correlates of efficacy. J Am Coll Cardiol 2002;40:1882–8.
371. Mehta SK, Frutkin AD, Milford-Beland S, et al. Utilization of distal embolic protection in saphenous vein graft interventions (an analysis of 19,546 patients in the American College of Cardiology-National Cardiovascular Data Registry). Am J Cardiol 2007;100:1114–8.
372. Brilakis ES, Saeed B, Banerjee S. Drug eluting stents in saphenous vein graft intervention: a systematic review. EuroIntervention 2010; 5:722–30.
373. Brilakis ES, Lichtenwalter C, de Lemos JA, et al. A randomized controlled trial of a paclitaxel-eluting stent versus a similar bare-metal stent in saphenous vein graft lesions: the SOS (Stenting of Saphenous Vein Grafts) trial. J Am Coll Cardiol 2009;53:919–28.
374. Ge L, Iakovou I, Sangiorgi GM, et al. Treatment of saphenous vein graft lesions with drug-eluting stents: immediate and midterm outcome. J Am Coll Cardiol 2005;45:989–94.
375. Lee MS, Shah AP, Aragon J, et al. Drug-eluting stenting is superior to bare metal stenting in saphenous vein grafts. Catheter Cardiovasc Interv 2005;66:507–11.
376. Hoffmann R, Pohl T, Koster R, Blindt R, Boeckstegers P, Heitzer T. Implantation of paclitaxel-eluting stents in saphenous vein grafts: clinical and angiographic follow-up results from a multicentre study. Heart 2007;93:331–4.
377. Minutello RM, Bhagan S, Sharma A, et al. Long-term clinical benefit of sirolimus-eluting stents compared with bare metal stents in the treatment of saphenous vein graft disease. J Interv Cardiol 2007;20:458–65.
378. Applegate RJ, Sacrinty M, Kutcher M, Santos R, Gandhi S, Little W. Late outcomes of drug-eluting versus bare metal stents in saphenous vein grafts: propensity score analysis. Catheter Cardiovasc Interv 2008;72:7–12.
379. Chu WW, Rha SW, Kuchulakanti PK, et al. Efficacy of sirolimus-eluting stents compared with bare metal stents for saphenous vein graft intervention. Am J Cardiol 2006;97:34–7.
380. Ellis SG, Kandzari D, Kereiakes DJ, et al. Utility of sirolimus-eluting Cypher stents to reduce 12-month target vessel revascularization in saphenous vein graft stenoses: results of a multicenter 350-patient case-control study. J Invasive Cardiol 2007;19:404–9.
381. Wohrle J, Nusser T, Kestler HA, Kochs M, Hombach V. Comparison of the slow-release polymer-based paclitaxel-eluting Taxus-Express stent with the bare-metal Express stent for saphenous vein graft interventions. Clin Res Cardiol 2007;96:70–6.
382. Bansal D, Muppidi R, Singla S, et al. Percutaneous intervention on the saphenous vein bypass grafts—long-term outcomes. Catheter Cardiovasc Interv 2008;71:58–61.
383. Brodie BR, Wilson H, Stuckey T, et al. Outcomes with drug-eluting versus bare-metal stents in saphenous vein graft intervention: results from the STENT (Strategic Transcatheter Evaluation of New Therapies) Group. J Am Coll Cardiol Intv 2009;2:1105–12.
384. De Labriolle A, Bonello L, Lemesle G, et al. Clinical presentation and outcome of patients hospitalized for symptomatic in-stent restenosis treated by percutaneous coronary intervention: comparison between drug-eluting stents and bare-metal stents. Arch Cardiovasc Dis 2009;102:209–17.
385. Bainey KR, Norris CM, Graham MM, Ghali WA, Knudtson ML, Welsh RC. Clinical in-stent restenosis with bare metal stents: is it truly a benign phenomenon? Int J Cardiol 2008;128:378–82.
386. Waksman R, Raizner AE, Yeung AC, Lansky AJ, Vandertie L. Use of localised intracoronary beta radiation in treatment of in-stent restenosis: the INHIBIT randomised controlled trial. Lancet 2002; 359:551–7.
387. Leon MB, Teirstein PS, Moses JW, et al. Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. N Engl J Med 2001;344:250–6.
388. Waksman R, Ajani AE, White RL, et al. Five-year follow-up after intracoronary gamma radiation therapy for in-stent restenosis. Circulation 2004;109:340–4.
389. Saia F, Lemos PA, Sianos G, et al. Effectiveness of sirolimus-eluting stent implantation for recurrent in-stent restenosis after brachytherapy. Am J Cardiol 2003;92:200–3.
390. Feres F, Munoz JS, Abizaid A, et al. Comparison between sirolimus-eluting stents and intracoronary catheter-based beta radiation for the treatment of in-stent restenosis. Am J Cardiol 2005;96:1656–62.
391. Stone GW, Ellis SG, O;Shaughnessy CD, et al. Paclitaxel-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: the TAXUS V ISR randomized trial. JAMA 2006;295: 1253–63.
392. Ellis SG, O'Shaughnessy CD, Martin SL, et al. Two-year clinical outcomes after paclitaxel-eluting stent or brachytherapy treatment for bare metal stent restenosis: the TAXUS V ISR trial. Eur Heart J 2008;29:1625–34.
393. Holmes DR Jr., Teirstein P, Satler L, et al. Sirolimus-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: the SISR randomized trial. JAMA 2006;295:1264–73.
394. Holmes DR Jr., Teirstein PS, Satler L, et al. 3-Year follow-up of the SISR (Sirolimus-Eluting Stents Versus Vascular Brachytherapy for In-Stent Restenosis) trial. J Am Coll Cardiol Intv 2008;1:439–48.
395. Lee SW, Park SW, Park DW, et al. Comparison of six-month angiographic and three-year outcomes after sirolimus-eluting stent implantation versus brachytherapy for bare metal in-stent restenosis. Am J Cardiol 2007;100:425–30.
396. Alfonso F, Perez-Vizcayno MJ, Hernandez R, et al. A randomized comparison of sirolimus-eluting stent with balloon angioplasty in patients with in-stent restenosis: results of the Restenosis Intrastent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting (RIBS-II) trial. J Am Coll Cardiol 2006;47:2152–60.
397. Alfonso F, Perez-Vizcayno MJ, Hernandez R, et al. Long-term clinical benefit of sirolimus-eluting stents in patients with in-stent restenosis: results of the RIBS-II (Restenosis Intrastent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting) study. J Am Coll Cardiol 2008;52:1621–7.
398. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009;119:480–6.
399. Cosgrave J, Melzi G, Biondi-Zoccai GG, et al. Drug-eluting stent restenosis the pattern predicts the outcome. J Am Coll Cardiol 2006;47:2399–404.

Key Words: bare-metal stents ■ drug-eluting stents ■ sirolimus-eluting stents ■ paclitaxel-eluting stents ■ zotarolimus-eluting stents ■ everolimus-eluting stents ■ stent thrombosis ■ restenosis ■ diabetes ■ cost-effectiveness ■ stent fracture ■ left main disease ■ myocardial infarction ■ saphenous vein grafts ■ clopidogrel.

APPENDIX

For a complete list of all study acronyms and their definitions, please see the online version of this article.

Appendix I Trial Acronyms

Trial Acronym	Trial	Reference
ARRIVE	The TAXUS Peri-Approval Registry: A Multi-Centre Safety Surveillance	130
ARTS- II	Arterial Revascularization Therapies Study Part II	77, 80-81
BASKET-LATE	Basel Stent Kosten Effektivitats Trial	124, 288
BENESTENT	Belgian Netherlands Stent	11
CARDiA	Coronary Artery Revascularization in Diabetes Trial	314
COMPARE	Second-Generation Everolimus-Eluting and Paclitaxel-Eluting Stents in Real-Life Practice	281
C-SIRIUS	Canadian-Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions	47
CURRENT OASIS-7	Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/ Optimal Anti-Platelet Strategy for Interventions	205, 206
DAPT	Dual Anti-Platelet Therapy Trial	185
DECODE	A Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent in the Treatment of Diabetic Patients With Native Coronary Artery Lesions	304
DELFT	Drug-Eluting Stent for Left Main	341
DES-DIABETES	Drug-Eluting Stents in Patients With Diabetes Mellitus	102, 103
DESSERT	Diabetes Drug-Eluting Sirolimus Stent Experience in Restenosis Trial	52
DiabeDES	Diabetes and Drug-Eluting Stent	306
DIABETES	Diabetes and Sirolimus-Eluting Stent	49–51
E-FIVE	Endeavor Stent Registry	268, 269
ENDEAVOR I-IV	Endeavor Stent Evaluation Studies	256-265
E-SIRIUS	European-Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions	48
ERACI	Argentine Randomized Study: Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Multi-Vessel Disease	334
EXCEL	Evaluation of Xience Prime Versus Coronary Artery Bypass Surgery	346
EXCELLENT	Efficacy of Xience/Promus Versus Cypher in Reducing Late Loss After Stenting for Effectiveness of Left Main Revascularization	285
FREEDOM	Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease	316
GISSOC II-GISE	Gruppo Italiano di Studio sullo Stent nelle Occlusioni Coronariche II–Società Italiana di Cardiologia Invasiva	69
GRAVITAS	Gauging Responsiveness With A VerifyNow assay - Impact on Thrombosis And Safety	204
HORIZONS-AMI	Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction	91, 92
ISAR-DESIRE	Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for In-stent Restenosis	116, 117
ISAR-DIABETES	Intracoronary Stenting and Angiographic Results: Do Diabetic Patients Derive Similar Benefit From Paclitaxel-Eluting and Sirolimus-Eluting Stents?	104
ISAR-LEFT MAIN	Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions	113
ISAR-SAFE	Intracoronary Stenting and Angiographic Results: Safety and Efficacy of 6 Months Dual Anti-Platelet Therapy After Drug-Eluting Stenting	184
ISAR-SMART 3	Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents to Abrogate Restenosis in Small Arteries Trial	115
LONG DES II	Comparison of Sirolimus-Eluting Stent, Paclitaxel-Eluting Stent and Bare Metal Stent in the Treatment of Long Coronary Lesions	114

Trial Acronym	Trial	Reference
MAIN COMPARE	Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization	27, 342, 343
MDACR	Massachusetts Data Analysis Center Registry	301
MISSION!	A Prospective Randomized Controlled Trial to Evaluate the Efficacy of Drug-Eluting Stents Versus Bare-Metal Stents for the Treatment of Acute Myocardial Infarction	55, 56
OPTIMIZE	Optimized Duration of Clopidogrel Therapy Following Treatment With the Endeavor Zotarolimus-Eluting Stent (ZES) in the "Real-World"	183
PASEO	Paclitaxel or Sirolimus-Eluting Stent Versus Bare Metal Stent in Primary Angioplasty	57,58
PASSION	Paclitaxel-Eluting Stent Versus Conventional Stent in Myocardial Infarction With ST-Segment Elevation	93-95
PLATO	A Study of Platelet Inhibition and Patient Outcomes	189
PREMIER	Prospective Registry Evaluating Myocardial Infarction: Events and Recovery	172
PRISON II	Primary Stenting of Totally Occluded Native Coronary Arteries II	66-68
PROSIT	Prospective Randomized Trial of Sirolimus Versus Paclitaxel-Eluting Stent System Trial	111, 112
PROTECT	Patient Related Outcomes With Endeavor Versus Cypher Stenting Trial	271
RAVEL	Randomized Study With the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions	42, 46
REALITY	Comparison of the Cypher Sirolimus-Eluting and the Taxus Paclitaxel-Eluting Stent Systems Trial	105
RESEARCH	Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital	78, 79
RIBS-II	Restenosis Intra-Stent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting	396, 397
RRISC	Reduction of Restenosis in Saphenous Vein Grafts With Cypher Sirolimus-Eluting Stent	74, 75
SCAAR	Swedish Angiography and Angioplasty Registry	33, 126, 302
SCANDSTENT	The Stenting Coronary Arteries in Non-Stress/Benestent Disease	72, 73
SCORPIUS	German Multicenter Randomized Single Blind Study of the CYPHER Sirolimus-Eluting Stent in the Treatment of Diabetic Patients With De Novo Native Coronary Artery Lesions	53
SESAMI	Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction	59, 60
SES-SMART	Sirolimus-Eluting Versus Uncoated Stents for Prevention of Restenosis in Small Coronary Arteries	70, 71
SIRIUS	Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions	43-45
SIRTAX	Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization	106,107
SORT-OUT II	Danish Organization on Randomized Trials With Clinical Outcome II Paclitaxel Versus Sirolimus in Everyday Clinical Practice	108
SORT-OUT III	Prospective Randomized Comparison of Zotarolimus-Eluting and Sirolimus-Eluting Stents in Patients With Coronary Artery Disease	267
SOS	Stent or Surgery	373
SPIRIT trials	Clinical Evaluation of the Xience V Everolimus-Eluting Coronary Stent System	272-280

Trial Acronym	Trial	Reference
SISR	Sirolimus-Eluting Stent With Vascular Brachytherapy for the Treatment of In-Stent Restenosis From Bare Metal Stents	393, 394
STENT	Strategic Transcatheter Evaluation of New Therapies	131, 383
STRATEGY	Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent Versus Abciximab and Bare-Metal Stent in Myocardial Infarction	61, 62
STRESS	Stent Restenosis Study	12
SYNTAX	Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery	28
TAXI	Comparison Between Paclitaxel and Sirolimus Stents in the Real World of Interventional Cardiology	109,110
TAXUS I, II, IV, V, VI	TAXUS evaluation studies	82-90
TAXUS ATLAS	TAXUS Liberté-SR Stent for the Treatment of De Novo Coronary Artery Lesions	99-101
TRITON TIMI 38	Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction	187, 188
T-SEARCH	Taxus-Stent Evaluated at Rotterdam Cardiology Hospital	97, 98
TYCOON	Two-Year Clopidogrel Need Study	182
TYPHOON	Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated With Balloon Angioplasty	63, 64
ZEST	Comparison of Sirolimus- and Paclitaxel-Eluting Stents Versus Zotarolimus-Eluting Stents in Real World Practice	266

Chapter 2.2

Coronary Stents –Looking Forward

J Am Coll Cardiol 2010; 56(10):S43-S78

Scot Garg, Patrick W. Serruys

Coronary Stents

Looking Forward

Scot Garg, MB, ChB, Patrick W. Serruys, MD, PhD

Rotterdam, the Netherlands

Despite all the benefits of drug-eluting stents (DES), concerns have been raised over their long-term safety, with particular reference to stent thrombosis. In an effort to address these concerns, newer stents have been developed that include: DES with biodegradable polymers, DES that are polymer free, stents with novel coatings, and completely biodegradable stents. Many of these stents are currently undergoing pre-clinical and clinical trials; however, early results seem promising. This paper reviews the current status of this new technology, together with other new coronary devices such as bifurcation stents and drug-eluting balloons, as efforts continue to design the ideal coronary stent. (J Am Coll Cardiol 2010;56:S43–78) © 2010 by the American College of Cardiology Foundation

Part 1 has highlighted the impressive clinical benefits seen following the introduction of drug-eluting stents (DES); however, in parallel, it also serves to highlight the safety concerns associated with their use, which have predominantly centered around stent thrombosis (ST) (1–3). The cause of ST is clearly multifactorial, and in addition to patient and lesion factors, a portion of blame has been attributed to the stent polymer (4), which has subsequently become a focal area for new research and stent development.

The second-generation DES have more biocompatible polymers, and although they have already demonstrated impressive safety results at medium-term follow-up (5–7), additional improvements are anticipated from the newer metallic durable polymer DES that have been developed. Despite this, however, concerns persist over the presence of a nonerodable polymer, which remains exposed to the coronary artery environment long after its useful function has been served. These concerns appear justified in light of evidence from animal and human studies, which suggest that these nonerodable polymers can cause persistent arterial wall inflammation and delayed vascular healing, both of which may subsequently have a role in precipitating ST and delayed restenosis (8–11).

The findings from these studies accelerated the development of DES coated with biodegradable polymers. These stents offer the attractive combination of controlled drug elution in parallel with biodegradation of the polymer into inert monomers. Therefore, after biodegradation is complete, only a bare-metal stent (BMS) remains, thereby reducing the long-term risks associated with the presence of a permanent polymer (12).

In recent times, an extension of this concept has been the development of DES that are completely free of polymer, and of BMS coated in novel coatings. Finally, completely biodegradable magnesium and polymeric stents have been developed, which completely disappear once vascular healing has taken place.

In Part 2, this new stent technology, together with other coronary devices such as bifurcation stents and drug-eluting balloons that are all currently undergoing investigation in pre-clinical and clinical trials, is reviewed. This new stent technology encompasses a wide range of devices, and although not a definitive classification, devices in the following discussion have been grouped together along similar types of polymer. It must be acknowledged, however, that this classification does not cater for all possibilities.

Metallic DES With Durable Polymers

Numerous new durable polymer metallic DES are under development. These stents build on the knowledge and experiences gained from the first- and second-generation DES described in Part 1, while utilizing new polymer technology, antiproliferative agents, and metal stent platforms in a bid to improve clinical outcomes and safety (Table 1) (13–17).

New polymer technology: Endeavor Resolute. The Endeavor Resolute zotarolimus-eluting stent (ZES) (Medtronic, Santa Rosa, California) is the next version of the Endeavor ZES and is currently undergoing clinical evaluation. This ZES consists of the Driver cobalt chromium stent platform and a Biolinx polymer—a blend of 3 different polymers: the hydrophobic C10 polymer to control drug release; the biocompatible and hydrophilic C19 polymer; and polyvinyl pyrrolidone to

From the Department of Interventional Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands. Drs. Garg and Serruys report that they have no relationships to disclose.

Manuscript received December 9, 2009; revised manuscript received June 1, 2010, accepted June 15, 2010.

Abbreviations and Acronyms

BDS = biodegradable stent

BE = balloon-expandable

BMS = bare-metal stent(s)

BVS = bioresorbable vascular scaffold

C.E. = Conformité Européene

DAPT = dual antiplatelet therapy

DEB = drug-eluting balloon

DES = drug-eluting stent(s)

EES = everolimus-eluting stent(s)

EPC = endothelial progenitor cell

FDA = Food and Drug Administration

FIM = first in man

ISR = in-stent restenosis

IVUS = intravascular ultrasound

IVUS-VH = intravascular ultrasound-virtual histology

MACE = major adverse cardiovascular events

MI = myocardial infarction

NES = novolimus-eluting stent(s)

OCT = optical coherence tomography

PCI = percutaneous coronary intervention

PES = paclitaxel-eluting stent(s)

PF = polymer-free

PLA = poly-L-lactide

PLGA = 50:50 poly DL-lactide-co-glycolide

PLLA = poly-L-lactic acid

SES = sirolimus-eluting stent(s)

SE = self-expanding

ST = stent thrombosis

TLR = target lesion revascularization

TVR = target vessel revascularization

ZES = zotarolimus-eluting stent(s)

allow an early burst of drug release (18). The polymer allows delayed drug release, such that at least 85% of the zotarolimus is released within 60 days, with the remainder being released within 180 days (Fig. 1) (18,19). Ultimately, this delayed release is intended to match the delayed healing times seen in complex lesions. Evaluation of the stent in the 139-patient multicenter, nonrandomized, first-in-man (FIM) RESOLUTE (Evaluation of the new generation zotarolimus-eluting coronary stent system) study demonstrated an angiographic in-stent late loss of 0.22 mm at 9-months follow-up and respective rates of major adverse cardiovascular events (MACE), target lesion revascularization (TLR), and any definite/probable ST of 8.6%, 0.7%, and 0.0% at 12-month follow-up, and 11.6%, 1.6%, and 0.0% at 3-year follow-up (13,20,21).

Further evaluation of the Resolute stent has taken place in the RESOLUTE All-Comers trial, which enrolled 2,300 patients who were randomized in a 1:1 ratio to treatment with either the Resolute ZES or the Xience V (Abbott Vascular, Santa Clara, California) everolimus-eluting stent (EES). At 12-months clinical follow-up in a predominantly off-label population, the Resolute ZES was found to be noninferior to EES with respect to the primary clinical end point of target lesion failure, a composite of cardiac death, target vessel myocardial infarction (MI), and clinically indicated TLR (ZES 8.2% vs. EES 8.3%, $p_{noninferiority} < 0.001$). In addition, in a subgroup of patients who were randomized to 13-month angiographic follow-up, ZES was again found to be noninferior to EES with respect to the powered angiographic secondary end point of in-stent diameter stenosis (ZES 21.65 ± 14.42% vs. EES 19.76 ± 14.64%, $p_{noninferiority} = 0.04$). Considering the complex patient population, the

Table 1 New Metallic Stents With Durable Polymers That Are Either Currently Available Outside the U.S. or Undergoing Clinical Evaluation

Stent (Manufacturer) (Ref. #)	Drug (Dosage)	Drug Release (%), Time	Stent Platform	Strut/Polymer Coating Thickness, μm	Study (No. of Patients)	Angiographic Follow-Up, Months	In-Stent Late Loss, mm (vs. Control)	Binary Restenosis, % (vs. Control)	Current Status
Endeavor RESOLUTE (Medtronic) (13)	Zotarolimus (10 μg/mm)	85%, 60 days	Cobalt chromium	91/4.1	FIM (n = 139)	9	0.22	1.0	C.E.
Elixir DESyne (Elixir Medical) (14,15)	Novolimus (5 μg/mm)	80%, 12 weeks	Cobalt chromium	80/<3	FIM (n = 15)	8	0.31	0.0	Ongoing trials
TAXUS Element (Boston Scientific) (16,17)	Paclitaxel (1 μg/mm^2)	<10%, 90 days	Platinum chromium	81/15	RCT (Element PES = 942) vs. (Express PES = 320)	9	0.34 vs. 0.26*	—	C.E.
PROMUS Element (Boston Scientific)	Everolimus (1 μg/mm^2)	87%, 90 days	Platinum chromium	81/6	—	—	—	—	C.E.

All differences are not significant unless stated. *Reached pre-specified noninferiority criteria.
C.E. = Conformité Européene; FIM = first in man; PES = paclitaxel-eluting stent(s); RCT = randomized controlled trial.

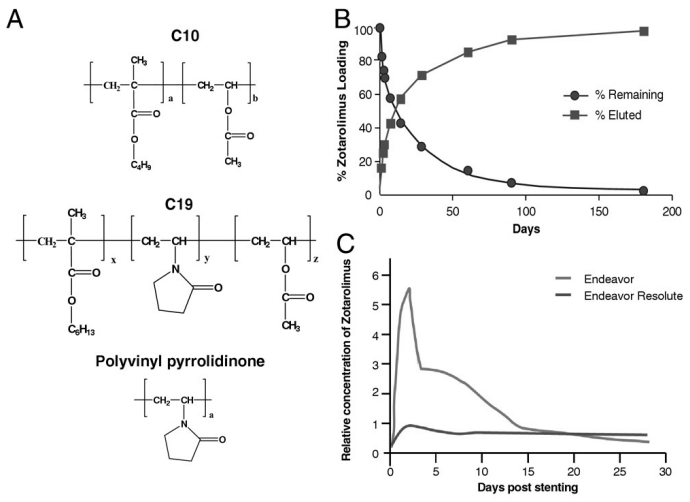


Figure 1 The Endeavor Resolute Stent

(A) The chemical structure of the 3 components of the BioLinx polymer system. The hydrophobic C10 polymer is based on hydrophobic butyl methacrylate to provide adequate hydrophobicity for zotarolimus. The hydrophilic C19 polymer is manufactured from a mixture of hydrophobic hexyl methacrylate, and hydrophilic vinyl pyrrolidinone and vinyl acetate monomers, to provide enhanced biocompatibility. The hydrophilic polyvinyl pyrrolidinone increases the initial drug burst and enhances biocompatibility. **(B)** The drug release pattern of zotarolimus; >85% is released within the first 60 days, with drug elution complete by 180 days. **(C)** A comparison of the relative arterial concentrations of zotarolimus in the porcine coronary artery model at various times post-implantation of the Endeavor and Endeavor Resolute stents. The Endeavor stent maintains effective drug levels through the initial loading of arterial tissue with zotarolimus during the first 2 weeks of elution. Conversely, the Endeavor Resolute stent sustains an effective drug level in the tissue through continued, sustained elution. **B and C** are reproduced with permission from Meredith et al. (18) and Udipi et al. (19), respectively.

overall rate of ST was low at 2.3% and 1.5% for ZES and EES, respectively (p = 0.17) (22).

New antiproliferative agents: Elixir DESyne novolimus-eluting stent (NES). The Elixir DESyne NES (Elixir Medical, Sunnyvale, California) consists of: 1) a cobalt chromium stent platform (Figs. 2A and 2B); 2) a durable poly(n-butyl methacrylate) polymer, which is similar to that found on the Cypher sirolimus-eluting stent (SES) (Cordis, Warren, New Jersey); and 3) a drug coating of novolimus, which represents a new antiproliferative mammalian target of rapamycin (mTOR) inhibitor, which is a metabolite of sirolimus, that has been specifically developed for the stent. This modified mTOR inhibitor has a similar efficacy to currently available agents; however, it has both a lower drug dose (NES 5 μg/mm of stent length vs. ZES 10 μg/mm) and polymer load (polymer thickness <3 μm vs. 4.1 μm on ZES) compared with other first- and second-generation DES, and therefore is conceivably safer.

The feasibility of using novolimus on a DES has been assessed in the 15-patient FIM EXCELLA (Elixir Medical Clinical Evaluation of the Novolimus-Eluting Coronary Stent System) study, which reported an angiographic in-stent late loss of 0.31 ± 0.25 mm, and a percentage volume obstruction on intravascular ultrasound (IVUS) of 6.0 ± 4.4% at 8-month follow-up, together with no MACE through 12 months (14) and 1 MACE event at 24 months (15).

Further assessment of the NES has been performed in the single-blind, prospective EXCELLA-II study, which randomized 210 patients to treatment with either NES (n = 139) or ZES (n = 71) (23). At 9-month follow-up, the primary end point of angiographic in-stent late loss was measured at 0.11 ± 0.32 mm and 0.63 ± 0.42 mm in patients treated with NES and ZES, respectively ($p_{noninferiority}$ <0.0001, $p_{superiority}$ <0.0001). During clinical follow-up, there were no significant differences between stent groups in the device-orientated composite end point (NES 2.9% vs. ZES 5.6%, p = 0.45) or its individual components of cardiac death, target vessel MI, and clinically indicated TLR. The rate of ST was comparable between both groups (23).

New metal stent platforms: platinum chromium Element stent platform. A platinum chromium alloy forms the basis of the new Element stent platform (Boston Scientific, Natick, Massachusetts), which has been combined with

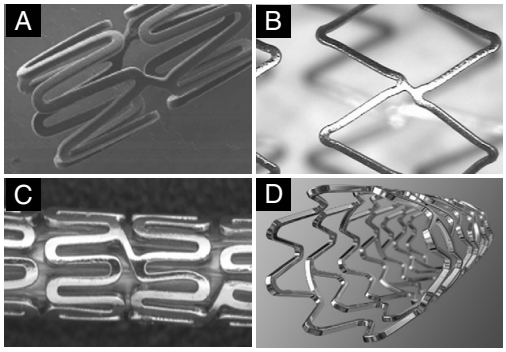


Figure 2 **Examples of New Durable Polymer Metallic Stents**

(A, B) The cobalt chromium Elixir DESyne novolimus-eluting stent crimped **(A)** and expanded **(B)**. **A** is reproduced with permission from Costa et al. (14). **(C, D)** The platinum chromium everolimus-eluting Element stent crimped **(C)** and expanded **(D)**. Images **C and D** are courtesy of Boston Scientific.

everolimus on the Promus Element (Boston Scientific) EES, and gained the Conformité Européene (C.E.) mark in November 2009 (Figs. 2C and 2D). The Element platform is also available combined with paclitaxel on the TAXUS Element (Boston Scientific) paclitaxel-eluting stent (PES), which received C.E. mark in May 2010. Platinum chromium offers distinct advantages over stainless steel and cobalt chromium; the alloy is twice as dense as iron or cobalt chromium, and therefore has much greater radio-opacity. In addition, its increased radial strength enables thinner stent struts, which has been shown to reduce clinical and angiographic restenosis (24,25).

The Promus Element, which has a strut thickness of 81 μm compared with 96 μm for the TAXUS Liberté, has been compared with the cobalt chromium Promus EES (Boston Scientific) in 1,532 patients in the randomized multicenter PLATINUM (A Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of up to Two De Novo Coronary Artery Lesions) clinical trial. Two parallel subtrials will also evaluate the Promus Element stent in small vessels and in long lesions. The trial completed enrolment in September 2009, and results will be used to support U.S. Food and Drug Administration (FDA) approval.

The TAXUS Element stent is currently undergoing evaluation in the ongoing PERSEUS (A Prospective Evaluation in a Randomized Trial of the Safety and Efficacy of the Use of the TAXUS Element Paclitaxel-Eluting Coronary Stent System for the Treatment of De Novo Coronary Artery Lesions) clinical trial program, which has so far reported results from 2 parallel studies in patients with single, de novo lesions (16,17). These 2 studies are:

1. The noninferiority PERSEUS Workhorse trial, which randomized, in a 3:1 ratio, 1,262 patients with lesions less than 28 mm long, in vessels between 2.75 and 4.00 mm in diameter, to treatment with the TAXUS Element (n = 942) or the TAXUS Express PES (n = 320) (16). At 9-month angiographic follow-up, there was no significant difference in late loss between the Element and Express stents (Element 0.34 $\pm$ 0.55 mm vs. Express 0.26 $\pm$ 0.52 mm, p = 0.33). The rate of the primary end point of target lesion failure at 12 months was 5.6%, and 6.1% for Element and Express stents, respectively (p = 0.78), which reached the pre-specified criteria for noninferiority. In addition, there were no significant differences in the clinical end points of MACE, mortality, MI, and ST.
2. The superiority PERSEUS Small Vessel trial, which compared the TAXUS Element stent to historical BMS controls in patients with lesions <20 mm in length, in vessels between 2.25 and 2.75 mm in diameter (17). Overall, the study enrolled 224 patients treated with the Element stent, who were compared with 125 lesion-matched historical controls treated with a BMS from the TAXUS IV study. Results at 9 months follow-up demonstrated a significantly lower primary end point of in-stent late loss with the Element stent compared with the BMS stent (0.38 $\pm$ 0.51 mm vs. 0.80 $\pm$ 0.53 mm, p < 0.001). At 12-month follow-up, the rates of target lesion failure and MACE were both significantly lower with the Element stent, whereas safety end points and ST were comparable between both stents.

Overall, these initial, promising studies of the Element stent demonstrate its superiority to the BMS Express stent,

and noninferiority to the PES Express stent with respect to efficacy, with no apparent safety concerns. Further evaluation continues.

DES With Biodegradable Polymers

At present, numerous DES with biodegradable polymers are available commercially in Europe, with several others undergoing concurrent clinical trials. The physical properties of these stents, together with angiographic follow-up results from FIM studies or randomized trials, are summarized in Table 2 (26–41). Interest has focused on these stents because initially after implantation, they theoretically may offer the antirestenotic benefits of a standard DES, whereas once the polymer has biodegraded, they speculatively may offer the safety benefits of a BMS.

There are many challenges remaining for this new polymer technology, which include, among others, establishing the optimal biocompatibility, composition, formulation, and degradation time of the polymer. In addition, attention must be paid to the pharmacokinetics of the antiproliferative agent released by the degradation of the polymer, and the variation in polymer degradation time, which can be affected by production factors such as the use of long polymer chains, decreased polymer hydrophobicity, and greater polymer crystalinity, together with physical and biological environmental factors (42).

The most important remaining question, however, is whether this new technology will lead to improved clinical outcomes. It must be stressed that the clinical advantage of stents with biodegradable polymers is currently hypothetical. Unfortunately, present studies of these stents are limited by short-term follow-up, and although results have been promising, definitive data on the long-term benefits are currently lacking. Importantly, evidence indicates that polymer breakdown can be associated with a significant inflammatory reaction, which at times can create an acidic environment. Moreover, complications may also occur as a result of a persistent immune response to monomer breakdown products (43). These sequelae of polymer breakdown reiterate the need for large-scale clinical trials with long-term follow-up to determine whether stents with biodegradable polymers are as safe as, let alone safer than, stents with durable polymers.

Despite the aforementioned uncertainties, numerous biodegradable polymer stents have been developed.

Sirolimus based. SUPRALIMUS STENT. The Supralimus stent (Sahajanand Medical Technologies, Gujrat, India) is a stainless steel sirolimus-eluting stent (SES) with a biodegradable polymer mix of poly-L-lactide (PLA), poly vinyl pyrrolidone, poly lactide-*co*-caprolactone, and poly lactide-*co*-glycolide (PLGA). Approximately one-half of the sirolimus has eluted by day 9, with elution being complete within 48 days; the polymer, on the other hand, completely biodegrades within 7 months. The stents' clinical effectiveness and safety was initially demonstrated in the 100-patient SERIES I (Study of the Supralimus Sirolimus Eluting Stent in the Treatment of Patients With Real World Coronary Artery Lesions) FIM study, which reported a rate of in-stent angiographic restenosis of 0.0% and a late loss of 0.09 ± 0.37 mm at 6-month follow-up. At 30 months, the rate of target vessel revascularization (TVR) was 4%, with no reported definite ST (26). Similar clinical effectiveness and safety have been reported at 6-month follow-up in the larger eSERIES multicenter registry, which included over 1,100 patients (44).

Recently, the Supralimus stent has been compared to the Infinnium PES (Sahajanand Medical Technologies), which also has a biodegradable polymer, and a BMS in the randomized, multicenter PAINT (Percutaneous Intervention With Biodegradable-Polymer Based Paclitaxel-Eluting, Sirolimus-Eluting, or Bare Stents for the Treatment Of De Novo Coronary Lesions) study of 274 low-risk patients. Results demonstrated that compared with BMS controls, the 2 DES stents had significantly lower late loss and significantly lower rates of TVR and MACE at 9- and 12-month follow-up, respectively. In addition, the Supralimus SES stent was shown to have a significantly lower late loss compared with the Infinnium PES; however, this did not translate into any difference in clinical outcomes (39).

Further evaluation of the stent is continuing in the ongoing SERIES III noninferiority trial that aims to randomize 400 patients to treatment with either the Xience V EES (Abbott Vascular) stent or the Supralimus SES stent, with the primary end point of 9-month in-stent late loss.

EXCEL STENT. The stainless steel Excel stent (JW Medical Systems, Weihai, China) is coated with sirolimus and a poly-L-lactic acid (PLLA) biodegradable polymer, which completes degradation in 6 to 9 months. Recent data from the CREATE (Multi-Center Registry Trial of EXCEL Biodegradable Polymer Drug-Eluting Stent) registry in over 2,000 patients has reported a rate of MACE of 3.1% at 18 months follow-up, and most encouragingly, a rate of ST of 0.87%, despite 80.5% of patients discontinuing clopidogrel at 6 months (27).

NEVO STENT. The NEVO stent (Cordis) is an open-cell, cobalt chromium stent, with a PLGA biodegradable polymer that elutes sirolimus. Uniquely, the polymer and sirolimus are contained within reservoirs, which eliminates the need for a surface polymer coating, thereby reducing tissue–polymer contact by over 75% (Fig. 3). This principle of using reservoirs for drug elution in combination with a PLGA biodegradable polymer is not new, and has previously been utilized on the similarly designed paclitaxel-eluting CoStar stent (Conor MedSystems, Palo Alto, California).

The CoStar stent was initially assessed in the PISCES (Paclitaxel In-Stent Controlled Elution Study), FIM Costar I (Cobalt Chromium Stent With Antiproliferative for Restenosis), and EuroStar (European cobalt STent with Antiproliferative for Restenosis) studies, which not only established the

Table 2 Metallic Stents With a Biodegradable Polymer That Are Either Currently Available Outside the U.S., or Undergoing Clinical Evaluation

Stent (Manufacturer) (Ref. #)	Drug (Dosage)	Drug Release (%), Time (days)	Stent Platform	Strut/Max Coating Thickness, μm	Polymer Type (Duration of Biodegradation, Months)	Study (No. of Patients)	Angiographic Follow-Up, Months	In-Stent Late Loss, mm (vs. Control)	Binary Restenosis, % (vs. Control)	Current Status
Supralimus (Sahajanand Medical) (26)	Sirolimus (125 μg/19 mm)	50%, 9–11	SS	80/4–5	PLLA PLGA, PLC, PVP (7)	FIM (n = 100)	6	0.09	0.0	Ongoing trials
Excel stent (JW Medical System) (27)	Sirolimus (195–376 μg)	NA	SS	119/15	PLA (6–9)	Registry (n = 2,077)	6–12	0.21	3.8	Ongoing trials
NEVO (Cordis) (28)	Sirolimus (166 μg/17 mm)	80%, 30	CoCr	99	Reservoirs of PLGA (3)	RCT (Nevo n =202 vs. PES n = 192)	6	0.13 vs. 0.36†	1.1 vs. 8.0*	Ongoing trials
BioMatrix (Biosensors) (29,30)	Biolimus A9 (15.6 μg/mm)	45%, 30	SS	112/10‡	Abluminal PLA (6–9)	RCT (BES n = 857 vs. SES n = 850)	9	0.13 vs. 0.19	20.9 vs. 23.3†§	C.E
NOBORI (Terumo) (31)	Biolimus A9 (15.6 μg/mm)	45%, 30	SS	112/10‡	Abluminal PLA (6–9)	RCT (BES n = 153 vs. PES n = 90)	9	0.11 vs. 0.32*	0.7 vs. 6.2*	C.E.
Axxess (Devax Inc) (32)	Biolimus A9 (22 μg/mm)	45%, 30	Nitinol	152/15‡	Abluminal PLA (6–9)	Registry (n = 302)	9	0.29 MB 0.29 SB	2.3 MB 4.8 SB	C.E.
XTENT (Xtent) (33,34)	Biolimus A9 (15.6 μg/mm)	45%, 30	CoCr	NA	Abluminal PLA (6–9)	Registry (n = 100)	6	0.22	7.5	C.E.
SYNERGY (Boston Scientific) (35)	Everolimus (LD 56 μg/20 mm) (SD 113 μg/20 mm)	50%, 60	PtCr	71/3 (LD) 4 (SD)	PLGA Rollcoat Abluminal (3)	RCT (SD vs. LD vs. PROMUS Element n = 291)	6	NA	NA	Ongoing trials—to start 2010
Combo (OrbusNeich) (37)	EPC + sirolimus (5 μg/mm)	NA	SS	NA	Abluminal	NA	NA	NA	NA	FIM—started Dec 2009
Elixir Myolimus (Elixir Medical) (38)	Myolimus (3 μg/mm)	90%, 90	CoCr	80/<3	Abluminal PLA (6–9)	FIM (n = 15)	6	0.15	0	Trials—ongoing
Infinnium (Sahajanand) (39,40)	Paclitaxel (122 μg/19 mm)	50%, 9–11	SS	80/4–5	PLLA PLGA, PLC PVP (7)	RCT (Infinn n = 111 vs. BMS n = 57)	9	0.54 vs. 0.90†	8.3 vs. 25.5*	C.E.
JACTAX Liberté (Boston Scientific) (41)	Paclitaxel (9.2 μg/16 mm)	100%, 60	SS	97/<1‡	JAC polymer Abluminal (4)	FIM (n = 103)	9	0.33	5.2	Trials—ongoing

All differences are not significant unless stated. *$p < 0.05$; †$p < 0.001$; ‡abluminal polymer; §noninferiority.

BES = biolimus-eluting stent(s); BMS = bare-metal stent(s); CoCr = cobalt chromium; EPC = endothelial progenitor capture; JAC = Juxtaposed Abluminal Coating; LD = low dose; NA = not available; PLC = 75/25 poly L-lactide-co-caprolactone; PLGA = 50:50 poly DL-lactide-co-glycolide; PLLA = poly-L-lactic acid; PtCr = platinum chromium; PVP = polyvinyl pyrrolidone; SD = standard dose; SES = sirolimus-eluting stent(s); SS = stainless steel; tbc = to be confirmed; other abbreviations as in Table 1.

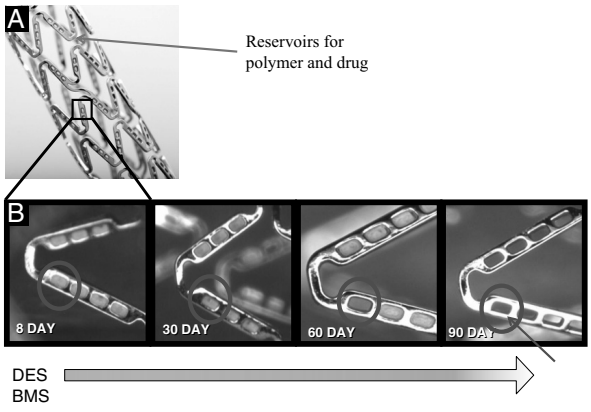


Figure 3 **The NEVO Stent Design**

(A) The NEVO cobalt chromium stent, which has an open-cell design and unique reservoirs that contain a biodegradable polymer and sirolimus mix that **(B)** completely biodegrades within 90 days.

optimal release kinetics for paclitaxel (10 μg/30 days; abluminal direction), but also demonstrated satisfactory binary in-stent restenosis (ISR) rates and in-stent late loss (45–47). Unfortunately, disappointing results were subsequently reported in the first randomized assessment of the CoStar stent, which was ultimately shown not to be noninferior to PES. Specifically, the CoStar II study enrolled 1,700 patients who were randomized to percutaneous coronary intervention (PCI) with the CoStar stent (n = 989) or the TAXUS PES (Boston Scientific) (n = 686) (48). (Twenty-five patients were deregistered prior to randomization due to a failure to confirm angiographic inclusion criteria at the time of the index PCI.) At 8 months, the rate of MACE was CoStar 11.0% versus PES 6.9% ($p = 0.005$), which was driven by the significantly higher rate of TVR with the CoStar stent (8.1% vs. 4.3%, $p = 0.002$). Moreover, angiographic follow-up at 9 months reported respective late losses for the CoStar and PES of 0.49 mm and 0.18 mm, respectively ($p < 0.0001$). Explanations for these results, which are in contrast to the previous CoStar studies, include among others, the learning curve for new device implantation by the investigators; changes in the manufacturing process during the trial that may have affected the paclitaxel release kinetics; and the small number of patients in the earlier studies. Of great importance and relevance to the NEVO stent is that in an attempt to maximize long-term safety, the dose of paclitaxel, which has a narrow therapeutic window, on the CoStar stent may have been too small to inhibit neointimal proliferation. Conversely, in the NEVO stent, the sirolimus dose and release kinetics are similar to those found on the Cypher (Cordis) SES, thus ensuring that drug elution is complete within 90 days. In addition, the highly hemo- and biocompatible polymer is also fully bioabsorbed within the same period, leaving a BMS.

The stent has so far only been evaluated in the NEVO-RES I (NEVO RES-ELUTION) study, which was a randomized, multicenter, noninferiority study comparing the NEVO stent to the TAXUS Liberté PES stent in 394 patients with single de novo coronary artery lesions. At 6-month angiographic follow-up, the primary end point of in-stent late lumen loss was significantly lower in patients treated with the NEVO stent (0.13 mm vs. 0.36 mm, $p < 0.0001$); a superiority that was preserved irrespective of diabetes status, lesion length, or vessel diameter (28). Clinical end points at both 6 months and 12 months were numerically lower in the NEVO-treated group, although these differences did not reach significance. The rate of ST was 0.0% and 1.1% ($p = 0.24$) in patients treated with the NEVO and PES stent, respectively.

Future trials of this promising stent technology are planned for 2010. In particular, the NEVO II study has commenced and will randomize 2,500 "all-comers" to treatment with either the NEVO stent or the Xience V EES stent, with clinical follow-up planned annually out to 5 years. Similar long-term follow-up is also planned for 1,300 U.S. patients enrolled in the nonrandomized NEVO III study.

Biolimus A9 based. Biolimus A9 is a highly lipophilic sirolimus analogue that has been combined with an abluminal PLA biodegradable polymer on a number of different stent platforms. The polymer biodegrades within 6 to 9

months, and its abluminal location ensures more targeted tissue release and reduced systemic exposure. The different stent platforms utilizing this combination have all had encouraging clinical results, as described later.

BIOMATRIX STENT. The Biomatrix stent (Biosensors, Morges, Switzerland) was shown to be noninferior for MACE, a composite of cardiac death, MI, and ischemia-driven TVR at 12-month follow-up when compared with the Cypher SES among the 1,707 patients enrolled in the randomized, all-comers LEADERS (Limus Eluted from A Durable versus Erodable Stent coating) trial (Biomatrix 10.6% vs. Cypher 12.0%, p = 0.37) (29). More recently, the preservation of this noninferiority has been confirmed at 2-year follow-up (49). Of note, the stent's PLA polymer is expected to have completely biodegraded by 9 months (Fig. 4), and therefore, even though the study is not adequately powered to detect differences in ST events, it is promising to observe the occurrence of fewer very late ST events (>1 year) with the Biomatrix stent (0.2% vs. 0.5%) (49). Further promising data in support of a biodegradable polymer were obtained in an optical coherence tomography (OCT) substudy, which demonstrated a higher rate of near complete (>95%) strut coverage with the Biomatrix stent when compared with the Cypher SES at 9-months follow-up (89.3% vs. 63.3%, p = 0.03) (50).

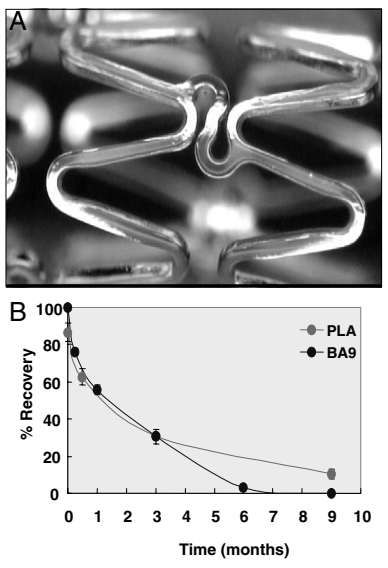


Figure 4 The BioMatrix Flex Stent

(A) The stainless steel BioMatrix Flex stent. **(B)** The elution pattern of Biolimus A9 (BA9) and the corresponding biodegradation pattern of the poly-lactic acid (PLA) polymer.

NOBORI STENT. The Nobori stent (Terumo, Leuven, Belgium) utilizes the same PLA polymer and the same antiproliferative agent as the aforementioned BioMatrix Flex stent. Physically, both stent platforms are identical, the only differences being the delivery system, delivery balloon, and the stent coating process. The BioMatrix stent is coated by an automated autopipette proprietary technology, whereas the Nobori stent is not coated using an automated process. The Nobori stent has so far been compared with the Cypher SES and TAXUS PES with promising results. In the NOBORI CORE study, the reported late loss at 9-month follow-up between the 99 patients randomized to treatment with either the Nobori stent or the Cypher SES was 0.10 mm, and 0.12 mm, respectively (p = 0.66) (51). Moreover, treatment with the Nobori stent also appeared to result in a significantly better recovery of endothelial function (52). This finding has subsequently been reconfirmed by Hamilos et al. (53) who demonstrated normal vasodilation after implantation of the Nobori stent, in line with other second-generation DES and BMS, compared with the paradoxical vasoconstriction observed following implantation of first-generation DES.

Following on from this, the Nobori I study randomized 243 patients to treatment with either the Nobori stent (n = 153) or the TAXUS PES stent (n = 90). Results at 9 months among the 86% of patients returning for follow-up demonstrated noninferiority, and subsequent superiority, of the Nobori stent with respect to late loss when compared with the TAXUS PES stent (0.11 mm vs. 0.32 mm, $p_{noninferiority} < 0.001$, $p_{superiority} = 0.001$). Similarly, the rate of Academic Research Consortium (ARC)-defined ST at 9-month follow-up was also lower with the Nobori stent (0.0% vs. 2.2%) (31). Overall, the evaluation of the Nobori stent has so far been performed in over 3,000 patients, and encouragingly, no episodes of very late ST have been reported. Further assessment of the stent is underway, including randomized comparisons in "real-life" populations with the Xience V EES in the COMPARE 2 (n = 2,700) and BASKET PROVE 2 (n = 2,400) studies; and the Cypher Select SES in SORT-OUT IV study (n = 2,400) (54).

AXXESS STENT. The structural properties of the self-expanding, conical-shaped nitinol Axxess (Devax, Lake Forest, California) bifurcation stent are summarized in Table 2. The stent, which is deployed by withdrawing a covering sheath, is ideally placed at the level of the carina, thereby allowing continued easy access to both distal branches, which can be provisionally treated with PCI if required. The stent was first assessed in the 139 patient Axxess Plus registry, which reported successful implantation of the device in the main branch in 93.5% of cases; however, 80% and 42% of patients, respectively, required 2 or 3 additional stents to cover the lesion. Two-thirds of the 9

device failures occurred due to improper positioning of the stent, either proximal or distal to the carina. At 6-month follow-up, in-stent late loss was 0.09 mm, whereas ISR and TLR were 4.8% and 7.5%, respectively (55). Further evaluation of the device has been performed in the prospective DIVERGE (Drug Eluting Stent Intervention for Treating Side Branches Effectively) study, which recruited 302 patients, of whom 21.7% and 64.7% required additional stenting of 1 or both branches, respectively. At 9-month follow-up, the rate of MACE was 7.7%, TLR 6.4%, and ST 1% (32).

XTENT CUSTOM NX STENT. The XTENT Custom NX stent (Xtent, Menlo Park, California) was a unique customizable DES that had a modular design made up of multiple 6-mm segments that were interdigitated, allowing for separation at each 6-mm segment (Fig. 5). These features enabled the length of the stent to be customized to the lesion length at the treatment site. The stent was available with either 6 or 10 segments, allowing the placement of up to 36 mm or 60 mm of stent, respectively. The potential benefits of this customization were the ability to treat long lesions without overlapping stents, and improving stent apposition and lesion coverage, while maintaining vessel conformability. The stent's safety and efficacy were confirmed both clinically and angiographically in the CUSTOM I, II, and III studies (33,34). Despite its C.E. mark, the lack of randomized data, coupled with the firm's financial difficulties unfortunately lead to Xtent going into liquidation in August 2009.

Myolimus. MYOLIMUS-ELUTING STENT. The myolimus-eluting Elixir stent (Elixir Medical, Sunnyvale, California) is a thin strut cobalt chromium stent coated with a PLA polymer without any underlying primer coating. The polymer facilitates elution of the new macrocylic lactone, myolimus, which is produced by replacement of the oxygen on C32 of the macrocylic ring, and has a comparable potency, in terms of inhibition of smooth muscle cells, to sirolimus. The FIM study enrolled 15 patients, and at 6 months angiographic follow-up, in-stent late lumen loss, binary restenosis, and percentage neointimal volume obstruction were 0.15 mm, 0.0%, and 1.4%, respectively. Clinical events out to 9 months consisted of 1 MI; there was no death, TLR, or ST (38). A second, single-arm multicenter registry that recruited 30 patients has also been completed. Half of the patients had angiographic follow-up at 6 months, whereas the remaining returned at 12 months. Late lumen loss and percentage neointimal volume obstruction were 0.08 mm and 3.2%, and 0.13 mm and 5.4% at 6 and 12 months, respectively; there was no binary restenosis. Clinical events, assessed at 12 months, demonstrated no mortality or ST; there were, however, 2 MIs and 2 TLRs (56).

Paclitaxel. INFINNIUM STENT. The Infinnium stent (Sahajanand Medical Technologies) is a stainless steel stent coated with paclitaxel, and a heparinized polymer blend of PLA, PLGA, and polyvinyl pyrrolidine. The stent's efficacy and safety were confirmed in 103 low-risk patients enrolled in the SIMPLE II (Safety and Efficacy of the Infinnium Paclitaxel-Eluting Stent) multicenter registry (40). A more extensive evaluation of the stent compared with the Supralimus stent and a BMS control was performed in the previously described PAINT study (39).

JACTAX STENT. The JACTAX Liberté PES stent (Boston Scientific) is a stainless steel PES stent, which has a novel abluminal PLA polymer, known as the Juxtaposed Abluminal Coating technology (JAC). This polymer has a microdrop structure, such that the 16-mm JACTAX stent has 2,700 microdots, each containing 3.4 ng of polymer (total

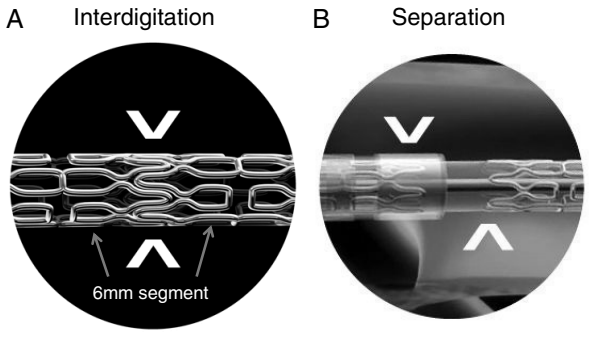


Figure 5 The Xtent

(A) The XTENT Custom NX DES System, which is composed on 6-mm separate segments that are interdigitated, and can be separated **(B)** in vivo using a specialized delivery stent to enable the stent length to be customized once the lesion has been crossed. Image courtesy of Xtent Inc.

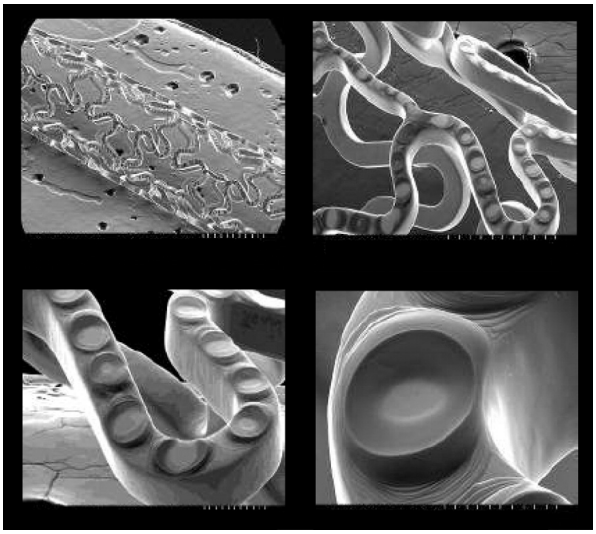


Figure 6 **The JacTAX Stent Polymer**

Scanning electron microscopy showing the microdrop structure of the Juxtaposed Abluminal Coating (JAC) coating technology in use on the JACTAX Liberté stent (Boston Scientific).

9.2 μg) (Fig. 6). The polymer is only applied to the outer surface of the stent, thereby ensuring that there is minimal polymer, with little, if any, strut-to-strut or balloon-to-strut polymer interaction. The thickness of the polymer ($\leq$1 μm) is approximately 18 times less than that found on the TAXUS Liberté stent, whereas the corresponding polymer mass is 100 times less. Paclitaxel is combined with the polymer in a 1:1 ratio and subsequently released in a controlled manner over 90 days, whereas the polymer is fully resorbed within 6 to 9 months. The JACTAX stent is currently being evaluated with a coating of either low-dose (LD) or high-dose (HD) paclitaxel; nevertheless, the high-dose preparation still only contains 1/10 of the dose of paclitaxel as found on the TAXUS Liberté stent. Preliminary analysis of OCT data from the OCTDESI study suggests that the use of a lower dose of paclitaxel has no significant adverse effect on the stent's overall performance. In the OCTDESI (Optical Coherence Tomography Drug Eluting Stent Investigation) study, Guagliumi randomized 60 patients to treatment with the JACTAX LD, JACTAX HD, and TAXUS Liberté stents, and reported a comparative proportion of uncovered stent struts, and neointimal volume among all 3 stents at 6 month follow-up (57).

Individually, the high-dose stent has been assessed in the JACTAX (Juxtaposed Abluminal Coating TAXUS) HD FIM study, which enrolled 103 patients who received a JACTAX HD stent, and angiographic results were then compared with 217 historical matched controls treated with the TAXUS Liberté stent from the ATLAS study (58). The study demonstrated lower rates of in-stent late loss (0.33 mm vs. 0.39 mm, $p = 0.36$) and binary restenosis (5.2% vs. 9.2%, $p = 0.22$) with the JACTAX HD stent compared with the TAXUS Liberté stent at 9 months follow-up. In addition, the rate of the primary end point of MACE (a composite of cardiac death, MI, and ischemia-driven TVR) was 7.8%, meeting the prespecified criteria for noninferiority; there were no deaths, Q-wave MIs, or ST during follow-up (41). Clinical evaluation of the JACTAX LD stent is currently being performed in the ongoing JACTAX LD DES trial, which is randomizing 130 patients to treatment with either the JACTAX LD stent or the TAXUS Liberté stent. The primary end point of MACE at 9 months is expected to be reported in 2010.

SYNERGY STENT. The SYNERGY stent (Boston Scientific) is currently being investigated in the 291 patient multicenter EVOLVE trial. Two doses of everolimus (PROMUS-like, 113 μg/20 mm stent; and half-PROMUS, 56 μg/20 mm stent) delivered on an Element stent using an ultrathin rollcoat abluminal bioerodable polymer (PLGA) are being compared to the PROMUS Element stent. The primary clinical end

point is target lesion failure at 30 days, while the primary angiographic end point is 6-month in-stent late loss (35).

Nonpolymeric DES

One step further from DES with biodegradable polymers are DES that are completely polymer free. The perceived advantages of these stents include: 1) avoiding the adverse effects of a polymer's presence long term; 2) improved healing; 3) improvement to the integrity of the stent's surface, as no polymer is present that can be peeled off (59,60); and 4) offering the possibility of a shorter duration of dual antiplatelet therapy (DAPT).

Despite the absence of a polymer, these stents are still able to elute antiproliferative drugs in a controlled manner. This is achieved by either:

1. Dissolving the antiproliferative agent into a nonpolymeric biodegradable carrier on the stent's surface.
2. Impregnating the antiproliferative agent in pure form onto the porous surface of the stent. There were initial concerns that a porous surface would have an adverse effect on long-term outcomes; however, this has not been substantiated by the results of specific clinical studies (61).
3. Attaching the antiproliferative agent directly to the stent surface using either covalent bonding or crystallization/chemical precipitation.

Current clinical studies of polymer-free stents are limited, and at present, only the YUKON DES (Translumina, Hechingen, Germany) is available commercially in Europe, whereas several others are undergoing FIM clinical studies. The physical properties of these stents, together with angiographic follow-up results from FIM studies or randomized trials, are summarized in Table 3 (62–65). The polymer-free DES currently undergoing investigation include:

YUKON DES. The polymer-free, stainless steel YUKON DES (Translumina) offers the unique ability to customize the dose of rapamycin in the catheter lab. The stent has a microporous surface, which functions as a drug reservoir, removing the requirement of a polymer (66). The stent consists of 2 components, the pre-mounted stent in a disposable coating cartridge, and a coating device (Fig. 7). For stent coating, the cartridge holding the stent system is placed into a specific coating device, and a 1-ml drug reservoir containing dissolved rapamycin in a pre-defined volume is connected to the cartridge. Initial studies have established that the optimal concentration of rapamycin to prevent restenosis and TLR is 2% (67). The coating process, which takes approximately 8 min, is initialized by the advancement of the drug into a mobile, positionable ring containing 3 jet units, which allow for uniform delivery of the drug into 2-μm-deep pores on the stent's surface. After the coating has been sprayed, the stent surface is dried by removing the solvent with pressured air, leaving a uniform layer and a sirolimus-coated stent that is available for immediate use.

Table 3 Polymer-Free Metallic Stents That Are Either Currently Available Outside the U.S., or Undergoing Clinical Evaluation

Stent (Manufacturer) (Ref. #)	Drug (Dosage)	Drug Release (%), Time	Stent Platform	Coating Thickness, μm	Surface Modification	Study (No. of Patients)	Angiographic Follow-Up, Months	In-Stent Late Loss, mm (vs. Control)	Binary Restenosis, % (vs. Control)	Current Status
AmazoniaPax (Minvasys) (62)	Paclitaxel (2.5 μg/mm^2)	98%, 30 days	CoCr	73/5*	Abluminal microdrop spray crystallization process	FIM (Pax n = 16 vs. PES n = 15)	4	0.77 vs. 0.42	NA	C.E.
BioFREEDOM (Biosensors) (63)	Biolimus A9 (SD† 15.6 μg/mm) (LD‡ 7.8 μg/mm)	90%, 50 h	SS	112	Microporous surface	FIM (SD† n = 25 vs. LD‡ n = 25 vs. PES n = 25)	4	0.08 vs. 0.37†§ 0.12 vs. 0.37‡§	NA	Ongoing trials
VESTAsync (MV Therapeutics) (64)	Sirolimus (total = 55 μg)	100%, 3 months	SS	65/0.6	Nanoporous hydroxyapitate	FIM (n = 15)	9	0.36	0	Ongoing trials
Yukon (Translumina) (65)	Sirolimus (11.7–21.9 μg)	67%, 7 days	SS	87	Microporous surface	RCT (Yukon n = 225 vs. PES n = 225)	9	0.48 vs. 0.48	12.6 vs. 11.6	C.E.

All differences are not significant unless stated. *abluminal; †standard dose (SD) = 15.6 μg/mm; ‡low dose (LD) = 7.8 μg/mm; §$p < 0.001$.
Abbreviations as in Tables 1 and 2.

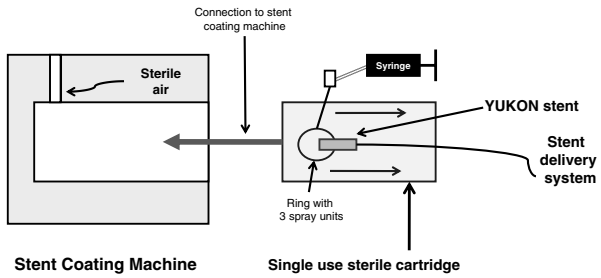


Figure 7 **Schematic Diagram of the YUKON Stent Coating Machine**

The stent is inserted into a sterile single-use cartridge, which is then placed in the stent coating machine. The syringe, which contains the desired antiproliferative drug at the appropriate dose, is used to inject the drug, which is then sprayed uniformly over the stent using the ring of 3 spray units. Finally, the stent is dried using sterile pressurized air.

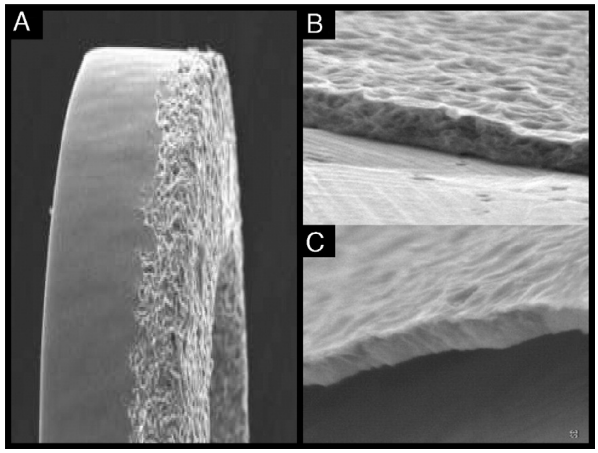
After complete drug release, the remaining microporous surface appears to favor the adhesion of endothelial cells. This was initially suggested by angiographic follow-up data, (61) and more recently confirmed by OCT, which have demonstrated significantly greater neointimal thickening and stent strut coverage with the YUKON stent compared with SES at 3-month follow-up (68).

Clinical data comes from the randomized ISAR–TEST (Intracoronary Stenting and Angiographic Restenosis–Test Equivalence Between 2 Drug-Eluting Stents) study and a "real-world" registry, which collectively have included over 400 patients treated with this 2% rapamycin concentration. Results indicate noninferiority of the YUKON stent when compared with PES at 9- to 12-month follow-up (65,69). Notably, long-term data from an angiographic observational study of 1,331 patients have recently reported a significantly lower change in late loss between 6 to 8 months and 2 years for the YUKON stent, when compared with SES and PES (YUKON 0.01 $\pm$ 0.42 mm, SES 0.17 $\pm$ 0.50 mm, and PES 0.13 $\pm$ 0.50 mm, $p < 0.001$) (70). This important observation suggests that these polymer-free stents may not be subject to the "late-catch up" phenomena that has been reported with permanent polymer DES, and appears to be worse in those stents using "limus"-based antiproliferative coatings (71–73). It is interesting to note that between the 2 stents eluting sirolimus, the lower absolute late loss at both 6 months and 2 years was seen with the conventional SES. This is consistent with the aforementioned OCT data, indicating greater neointimal hyperplasia with the YUKON stent, and is likely to be related to the rapid release of sirolimus. This, together with the late loss observed with the YUKON stent, is similar to the performance of the ENDEAVOR ZES, which also has a rapid drug release pattern, high late loss at short-term follow-up, and has been less susceptible to delayed restenosis compared with other limus DES (7,74). Clinically, use of the YUKON stent, as with ZES, may lead to less very late ST; however, definitive data are lacking.

BioFreedom. The BioFreedom stent (Biosensors) is a 316L stainless steel, polymer-free stent, coated with Biolimus A9 (Fig. 8A). Pre-clinical studies in the porcine model have reported lower injury scores; lower numbers of struts with fibrin, granulomas, and giant cells; significantly lower percentage diameter stenosis, and greater endothelialization with the BioFreedom stent when compared with SES at 180-day follow-up (75). In addition, pharmacokinetic studies have demonstrated the complete absence of Biolimus A9 in the surrounding myocardium, neointima, and on the stent itself by 180 days. Similarly, blood concentrations of Biolimus A9 have been reported to peak 120 min after implantation, before rapidly declining such that they are barely detectable at 90 days, and undetectable at 180 days (76).

The first cohort of the FIM study of the BioFreedom stent recruited 75 relatively low-risk patients with de novo lesions that were less than 14 mm in length, and in coronary vessels that were between 2.25 and 3.00 mm in diameter. Patients were randomized to treatment with either a standard-dose BioFreedom stent (15.6 μg/mm), a low-dose BioFreedom stent (7.8 μg/mm), or a TAXUS PES. At 4-month follow-up, there were no MACE or ST events with either the standard-dose BioFreedom stent or the TAXUS PES. The MACE rate for the low-dose stent was 8.0%. Angiographic follow-up at 4 months revealed a significantly lower in-stent late loss with both BioFreedom stents compared with PES (BioFreedom standard dose vs. low dose vs. TAXUS; 0.08 mm vs. 0.12 mm vs. 0.37 mm, $p < 0.0001$ and $p = 0.002$, respectively). A second cohort of 105 patients randomized to the same 3 arms has completed recruitment, with 12-month follow-up results available in late 2010 (63).

VESTAsyn sirolimus-eluting stent. This stainless steel stent (VESTAsyn, MIV Therapeutics, Atlanta, Georgia) has a nano-thin microporous hydroxyapatite surface coating



Figures 8 **Scanning Electron Microscopy of the Surface of the BioFreedom Stent and of the VESTAsync Stent**

(A) BioFreedom stent and **(B and C)** the VESTAsync stent. The rough surface **(B)** of the hydroxyapatite coating of the VESTAsyn stent is smoothed over **(C)** following the addition of 0.6 μm coating of sirolimus.

impregnated with a low dose (55 μg) of polymer-free sirolimus (Figs. 8B and 8C). Pre-clinical studies indicate that this low dose of sirolimus, which is made possible by the hydroxyapatite platform, results in reduced signs of delayed vascular healing, thus indicating less local toxicity and a faster healing response (77). The elution of sirolimus is complete within 3 months, whereas the hydroxyapatite is stable over 4 months, and has a total lifetime of 9 to 12 months, after which it is expected to completely dissolve.

The stent has so far been assessed in the VESTASYNC I (Hydroxyapatite Polymer-Free Sirolimus-Eluting Stent for the Treatment of Single De Novo Coronary Lesions) FIM clinical trial in 15 patients, with encouraging results (64). Angiographic follow-up at 4 and 9 months demonstrated effective reductions in late loss and intimal hyperplasia, and no evidence of any late-catch up using either quantitative coronary angiography (QCA) or IVUS. At 1-year follow-up, there were no reported clinical events (64), whereas at 3 years follow-up, 1 patient had undergone a TLR (78).

Further evaluation is planned in more complex patient groups in the VESTAsyncII study, which will enroll 75 patients randomized 3:1 to either the VESTAsyn SES or a control BMS, with a primary end point of late loss at 8 months follow-up (78).

Amazonia Pax. The Amazonia Pax stent (Minvasys, Genevilliers, France) is the only polymer-free stent that is made of cobalt chromium, and elutes paclitaxel. The stent has an open-cell design, with 73-μm-thick struts, which are coated with a 5-μm-thick abluminal coating of polymer-free paclitaxel at a dose of 2.5 μg/mm^2. The pure paclitaxel is applied using a microdrop spray crystallization process. This consistent coating ensures that 98% of the drug is eluted within 30 days, and ensures that by 45 days all that remains is a bare-metal cobalt chromium stent.

Clinical evaluation is ongoing. The multicenter Pax A study randomized 30 patients to treatment with either the Amazonia stent or the TAXUS PES (62). At 4 months, the respective in-stent late lumen loss and percentage neointimal volume obstruction for the Amazonia and PES were 0.77 mm versus 0.42 mm ($p = 0.20$), and 19% versus 6% ($p = 0.08$). There were no deaths or ST events; however, 2 patients treated with PES had a TLR, whereas 1 patient in the Amazonia arm had a post-procedural MI, and another had a TLR.

The ongoing Pax B study is a prospective multicenter registry that will enroll 100 patients. The primary end point is angiographic in-stent late lumen loss at 9-month follow-up, with results anticipated in late 2010 (79).

DES With Durable Polymers Versus Biodegradable Polymer Versus Polymer Free

Presently, the ISAR-TEST 3 (Intracoronary Stenting and Angiographic Restenosis Investigators–Test Efficacy of Rapamycin-Eluting Stents With Different Polymer Coating Strategies) represents the only comparison of 3 stents with different types of polymer and the same antiproliferative drug (80,81). This noninferiority study randomized 605

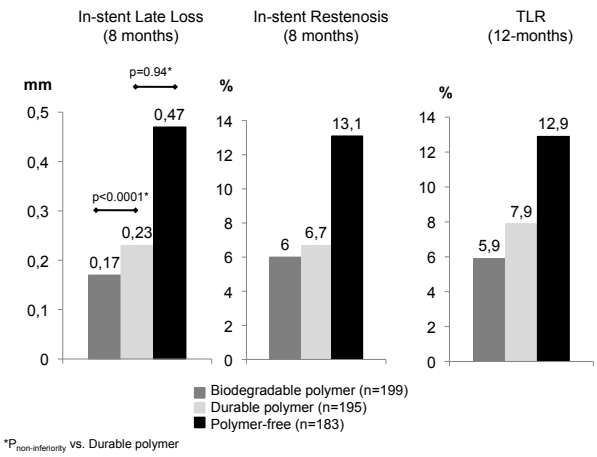


Figure 9 **Results From the ISAR–TEST-3 study**

In the ISAR–TEST-3 study, patients were treated with sirolimus-eluting stents that either had a durable polymer, a biodegradable polymer, or were polymer free. TLR = target lesion revascularization.

patients to rapamycin-eluting stents with either a durable polymer (n = 202), a biodegradable polymer (n = 202), or a stent that was polymer free (n = 201). At 6- to 8-month angiographic follow-up, the biodegradable polymer stent met its pre-specified criterion for noninferiority in terms of in-stent late lumen loss (0.23 mm vs. durable polymer 0.17 mm, $p_{noninferiority}$ <0.001); whereas the polymer-free stent failed to achieve noninferiority (0.47 mm vs. 0.17 mm, $p_{noninferiority}$ = 0.94) (Fig. 9). Despite these results, clinical outcomes at 1 year demonstrated a similar safety profile for the 3 stents; however, efficacy appeared numerically inferior with the polymer-free stent, and comparable between the biodegradable and durable polymer stents. At 2 years follow-up, clinical outcomes remained comparable in terms of rates of mortality, MI, and stent thrombosis. The rate of TLR was also comparable between all 3 stents; however, the absolute increase in TLR between 1- and 2-year follow-up was notably higher with the biodegradable polymer and durable polymer stents, when compared with the polymer-free stent (Δ2.5% vs. Δ2.5% vs. Δ0.5%). Paired angiographic follow-up was available in 69% of patients, and demonstrated a delayed in-stent late lumen loss of 0.17, 0.16, and −0.01 mm for biodegradable polymer, durable polymer, and polymer-free stents, respectively ($p < 0.001$). Importantly, these results indicate that not only are biodegradable polymer stents still susceptible to the delayed restenosis observed previously with durable polymer stents (71–73), but they also indicate that polymer free stents are less prone to this unwanted long-term phenomenon. This observation is consistent with that previously reported by Byrne et al. (70), and warrants additional investigation.

Dual Polymer-Free (PF) DES Versus Durable Polymer SES Versus Durable Polymer ZES

The failure of polymer-free stents to demonstrate noninferiority compared with durable polymer stents in the ISAR-TEST 3 prompted interest in dual PF DES. This approach, which was aimed at improving the antirestenotic performance of polymer-free stents through the use of a second antiproliferative agent that targeted a different part of the cell cycle, was evaluated in the ISAR–TEST-2 (Intracoronary Stenting and Angiographic Restenosis–Test Efficacy of Three Limus Eluting Stents-2) study (82,83). This study randomized 1,007 patients to treatment with SES (n = 335), ZES (n = 339), or a dual PF DES (n = 333) that eluted sirolimus and the antioxidant probucol, which has previously been shown to reduce neointimal hyperplasia (84). The rate of the primary end point of binary restenosis at 6- to 8-month follow-up was dual PF DES 11.0%, ZES 19.3% ($p < 0.001$ vs. dual PF DES), and SES 12.0% ($p = 0.68$ vs. dual PF DES). Clinical outcomes at 1-year follow-up demonstrated comparable safety in terms of mortality, MI, and ST between the 3 stents; however, rates of TLR were significantly lower with the dual PF DES stent compared with ZES (dual PF DES 6.8% vs. ZES 13.6%, $p = 0.001$), and comparable with SES (dual PF DES 6.8% vs. SES 7.2%, $p = 0.83$).

Table 4 Metallic Stents With Novel Coatings That Are Either Currently Available Outside the U.S., or Undergoing Clinical Evaluation

Stent (Manufacturer) (Ref. #)	Coating	Stent Platform	Strut Thickness, μm	Study	No. of Patients (Study/Control)	Angiographic Follow-Up, Months	Late Loss, mm (vs. Control)	Binary Restenosis,% (vs. Control)	Current Status
Catania stent (CeloNova Biosciences) (85)	Polyzene F	CoCr	65–74	FIM	n = 55	6	0.60	6.8	C.E.
TiNOX stent (Hexacath) (86)	Titanium Nitride-oxide	SS	90	RCT (vs. BMS)	n = 92 (45/47)	6	0.55 vs. 0.90*	15 vs. 33	C.E.
Genous stent (OrbusNiech) (87)	CD34+ antibody	SS	100	RCT (vs. PES)	n = 193 (98/95)	6–12	1.14 vs. 0.55†	NA	C.E

All differences are not significant unless stated. *$p < 0.05$; †$p < 0.001$.
Abbreviations as in Tables 1 and 2.

At 2-year follow-up, safety clinical outcomes remained comparable among the 3 groups (83). Similar to the 1-year results, rates of TLR were significantly lower with dual PF DES compared with ZES ($p = 0.006$), and comparable between dual PF and SES. Moreover, as seen in the ISAR–TEST-3, the absolute increase in TLR between 1- and 2-year follow-up was notably higher with the durable polymer SES compared with the dual PF SES (Δ3.5% vs. Δ0.9%, $p = 0.009$). Likewise, paired angiographic follow-up demonstrated a significantly greater increase in in-stent binary restenosis with the durable SES compared with the dual PF SES (Δ6.6% vs. Δ2.9%, $p = 0.002$). Overall, this study demonstrated that dual PF DES offer a reduction in delayed restenosis compared with first-generation DES, while maintaining a comparable safety profile. Importantly, this reduction in delayed restenosis with the polymer-free stent is consistent with other studies such as ISAR–TEST and ISAR–TEST-3 (70,80,81), suggesting these stents may hold promise for the future.

Stents With Novel Coatings

The physical properties of these stents with novel coatings, together with angiographic follow-up results from FIM studies or randomized trials, are summarized in Table 4 (85–87).

Catania stent. This cobalt chromium, modified open-cell stent (CeloNova BioSciences, Newnan, Georgia) is unique because its surface is modified by a 40-nm-thick coating of the NanoThin Polyzene-F polymer (standard DES polymer thicknesses are 5.3–16 μm). Polyzene F is a biocompatible, biostatic, proprietary formulation of poly[bis(trifluoroethoxy)-phosphazene], which has anti-inflammatory, bacteria-resistant, and pro-healing qualities. Furthermore, the coating ensures that the stent has a very low surface thrombogenicity, which can potentially reduce ST. The FIM ATLANTA (Assessment of The LAtest Non-Thrombogenic Angioplasty stent) study reported a 6-month late lumen loss of 0.6 mm, whereas at 12-month follow-up, there were no reported deaths or MI, and a clinically driven TLR rate of 3.6% in the 55 patients treated with the Catania stent (85). No ST was observed, despite DAPT being given for only 30 days. In addition, OCT, which was performed in 15 patients, showed that 99.5% of struts were fully covered at 6 months (88). Recent registry data have also demonstrated the absence of ST events at 6 months follow-up among 94 patients with acute coronary syndrome who were treated with the Catania stent and received only 30 days of DAPT (89). Ongoing evaluation is taking place in the ATLANTA-II prospective registry, which has enrolled 300 patients, 14% of whom presented with ST-elevation MI. At 1-year follow-up, the cumulative rate of MACE was 8.8%, with individual rates of cardiac death, MI, and TLR of 2.5%, 0.7%, and 6.5%, respectively. DAPT was again given for only 30 days, and the rate of ST was 0.7% due to 2 cases of subacute ST (90).

Titan-2 stent. The Titan-2 stent (Hexacath, Rueil-Malmaison, France) is a stainless steel stent coated in titanium-nitride oxide (Fig. 10), which has been shown to inhibit platelet aggregation, minimize fibrin deposition, reduce inflammation, and promote healing. The TiNOX (Randomized Comparison of a Titanium-Nitride-Oxide–Coated Stent With a Stainless Steel Stent for Coronary Revascularization) study randomized 92 patients to treatment with either a BMS or a BMS coated with titanium-nitride oxide, and reported a significant reduction in late loss (0.55 vs. 0.90, $p = 0.03$) at 6-month follow-up. Clinical evaluation demonstrated significantly reduced MACE, which was driven primarily by a reduction in TLR, with the titanium-coated stent at 6-month follow-up (86), with more recent results indicating preservation of this out to 5-year follow-up (91). Additional studies include the

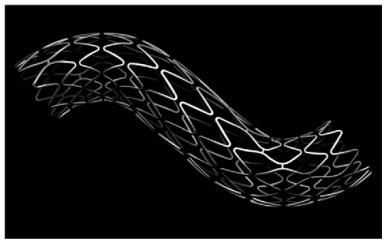


Figure 10 The Stainless Steel Titan-2-Stent

Image courtesy of Hexacath, France.

TITAX-AMI (A Prospective, Randomized Trial Comparing TITAN-2 Stent and TAXUS-Liberte Stent in Acute Myocardial Infarction) trial, which randomized 425 patients with ST-elevation MI to treatment with either the Titan-2 stent or the TAXUS PES stent. At 2-year follow-up, there were significant reductions in MACE, cardiac death, MI, and ST with the use of the Titan-2 stent. In addition, despite the absence of an antiproliferative drug, the rate of TLR was still numerically lower with the Titan-2 stent (9.3% vs. 10.4%, p = 0.9) (92). Three-year outcomes from registry data have also demonstrated favorable results for the Titan-2 stent compared with the TAXUS PES with respect to significantly lower MACE and the absence of ST (93).

In contrast to these encouraging results, the Titan-2 stent failed to demonstrate noninferiority when compared with the ZES Endeavor stent in the randomized 300-patient TIDE (Randomized Trial Comparing Titan- vs. Endeavor-stents) study (94). At 6-month angiographic follow-up, in-stent late lumen loss was 0.64 mm and 0.47 mm for the Titan-2 stent and ZES, respectively ($p_{noninferiority} = 0.54$). Of note, differences in late lumen loss were more pronounced in patients with diabetes, small vessel disease, and over age 65 years. Nevertheless, clinical outcomes assessed at 1 year were comparable.

Genous Bio-engineered R-stent. This bare-metal stainless steel stent (OrbusNeich, Fort Lauderdale, Florida) is unique in containing on its luminal surface immobile CD34 antibodies (Fig. 11). In pre-clinical studies, these antibodies were able bind to endothelial progenitor cells (EPCs), resulting in a rapidly formed, functional endothelial covering of the stent's struts, which ultimately has the potential to reduce ST and restenosis. Unfortunately, the CD34+ markers that are used to phenotype EPCs are nonspecific, and are shared by other hematopoietic stem cells. Therefore, it is possible for the EPC capture stent to sequester other bone marrow cell lines such as smooth muscle progenitor cells, which in turn can lead to neointimal proliferation (95,96). This is reflected in published clinical studies that have shown low rates of ST despite only 1 month of DAPT; however, late loss at 6-month follow-up has repeatedly been above 0.6 mm (97–99). Recent data from the TRIAS (TRI-stent Adjudication Study) HR study, which is the only randomized trial published so far, reported a late loss as high as 1.14 ± 0.64 mm, and an overall higher target vessel failure with the Genous stent compared with the TAXUS PES (87). Encouragingly, preliminary data at 2-year follow-up demonstrated a lower absolute increase in TLR between 1 and 2 years in those treated with EPC stent compared to PES (100). This may reflect regression of late loss with the EPC stent, as was previously observed in the HEALING II (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth) study in which late loss fell by 16.9% between 6 and 18 months, and/or it may reflect late catch-up with PES (73,98). Additional promising data come from the 5,000 patients enrolled in e-HEALING registry, which reported rates of MACE, MI, and ST at 1-year follow-up of 7.7%, 1.7%, and 1.0%, respectively (101).

A new application of the EPC capture technology has been to use it to enhance vessel healing in association with DES technology in a Combo Stent (OrbusNeich), which incorporates EPC capture technology together with abluminal low-dose sirolimus and a biodegradable polymer. Data from histology and OCT at 28-day follow-up in the porcine model indicate that this combination stent promotes endothelialization while also reducing neointimal formation and inflammation, when compared with the standard SES and Genous EPC stent (102). Overall, the Combo Stent offers the potential to improve vascular healing while still maintaining effective control over neointimal proliferation. The REMEDEE (Randomized Evaluation of an Abluminal sirolimus coated Bio-Engineered Stent) FIM study has been initiated, and aims to randomize 180 patients to treatment with either the Combo Stent or

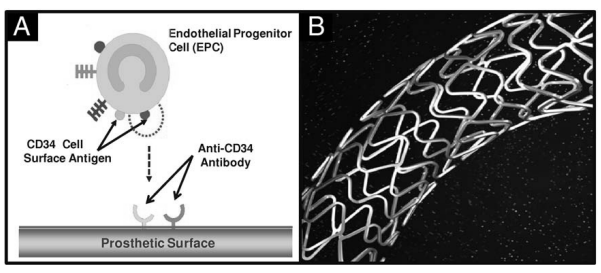


Figure 11 **The Genous Stent**

(A) Schematic representation of the endothelial progenitor cell (EPC) capture technology. The CD-34 antigens on the surface of the EPCs attach to the anti-CD-34 antibodies on the stent's surface, promoting endothelialization. **(B)** The stainless steel Genous stent. **B** courtesy of OrbusNeich.

the TAXUS Liberté PES, with a primary end point of late loss at 9-month follow-up (37).

The late loss of the 3 novel coated stents described in the previous text ranges from 0.55 to 1.14 mm. Although the results for the Catania and Titan-2 stents are superior to conventional BMS, they are, none the less, inferior to the majority of the currently available DES. A late loss of approximately 0.50 to 0.60 mm has been reported as the threshold above which a TLR is triggered (103), and this may explain the superior results at short-term follow-up of the Titan-2 stent compared with BMS, and its comparable TLR with PES (86,93). The current studies of these "novel-coated" stents are limited by their small sample size, and it is too early to comment as to whether the absence of an antiproliferative coating will hamper their long-term development.

Biodegradable Stents (BDS)

Fully BDS offer several potential advantages over conventional bare or drug-coated metallic stents. These include potential reductions in adverse events such as ST, because drug elution and vessel scaffolding are only provided by the stent until the vessel has healed, and as such, no triggers for ST, such as nonendothelialized stent struts, or drug polymers are present long term. The absence of these foreign materials may also reduce the requirements for long-term DAPT, reducing the risk of associated bleeding complications. Physiologically, the absence of a rigid metallic casing can facilitate the return of vessel vasomotion, adaptive shear stress, late luminal enlargement, and late expansive remodeling.

Additional long-term advantages of using BDS include an improvement in future treatment options, as PCI or surgical revascularization can be performed in areas of previous stenting without restriction. Furthermore, BDS can negate some of the other problems associated with use of permanent metallic stents such as the covering of side branches, overhang at ostial lesions, and the "blooming effect" seen when using noninvasive imaging techniques such as computed tomography angiography or MRI (104). Finally, BDS can help eliminate the concerns that a minority of patients have at the thought of having "an implant in their bodies for the rest of their lives" (105).

The current BDS are composed of either a polymer or a metal alloy. Numerous different polymers are available, each with a different chemical composition and subsequent bioabsorption time. The most frequently used polymer in the current generation of BDS is PLLA, which is already used in numerous clinical items, such as resorbable sutures, soft-tissue implants, orthopedic implants, and dialysis media. The PLLA is metabolized via the Krebs cycle over a period of approximately 12 to 18 months, into small, inert particles of carbon dioxide and water, which are then phagocytosed by macrophages (Fig. 12) (106).

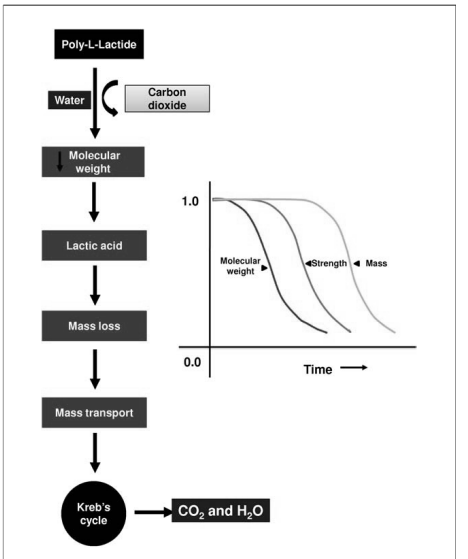


Figure 12 The Metabolism of PLLA

(A) The metabolism of poly-L-lactic acid (PLLA) biodegradable stents. Hydrolysis of PLLA results in the loss of molecular weight, and reduction in strength and mass; ultimately the PLLA is metabolized into lactic acid, carbon dioxide (CO_2) and water (H_2O). **(B)** Bioabsorption curves for a bioabsorbable material: molecular weight is lost first, followed by strength and then mass. Therefore, the stent loses its biomedical importance long before significant mass loss has occurred.

Despite the advantages, there are 3 major hurdles to using a polymer as the backbone to a coronary stent, namely, the lack of radio-opacity, which necessitates radio-opaque stent markers; the reduced radial force as compared with stainless steel, necessitating thicker stent struts; and the reduced ability of the stents to be deformed.

BDS were first implanted in animals as early as 1980; however, despite the impressive results of these early stents, namely, minimal thrombosis, moderate intimal hyperplasia, and a limited inflammatory response, the technology failed to develop (107). This was primarily due to an inability to manufacture an ideal polymer that could limit inflammation and restenosis (108). As described earlier, the inherent limitations of DES have been the major driving force behind the current development of BDS. At present, no BDS has either the C.E. mark or U.S. FDA approval; however, the numerous stents that are currently undergoing pre-clinical and clinical trials are summarized in Table 5 (36,109–116), and a selection of stents are described in detail in the following text.

PLLA stents. THE IGAKI-TAMAI STENT. The bare Igaki-Tamai PLLA coronary stent (Kyoto Medical Planning Co.

Table 5 A Comparison of the Properties of Biodegradable Stents

Stent	Strut Material	Drug Elution	Stent Radio-Opacity	Total Strut Thickness (μm)	Crossing Profile (mm)	Duration of Radial Support (Months)	Absorption Time (Months)	Development Stage (Ref. #)
Igaki-Tamai	Poly-L-lactic acid	Nil	Gold markers	170	Covered sheath ≥8-F	6	24	Clinical trials (109–111)
BVS								
Revision 1.0	Poly-L-lactide	Everolimus	Platinum markers	156	1.4	Weeks	24	Clinical trial: ABSORB cohort A (112,113)
Revision 1.1	Poly-L-lactide	Everolimus	Platinum markers	156	1.4	3	24	Clinical trial: ABSORB cohort B (114)
OrbusNeich	3 × lactide polymers	Yes	Tantalum markers	—	1.1	6	—	No pre-clinical data
REVA Generation I	Tyrosine-derived polycarbonate	Nil	Covalently bound iodine	100	1.7	3–6	36	RESORB study FIM complete (36)
ReZolve	Tyrosine-derived polycarbonate	Sirolimus	Covalently bound iodine	114–228	1.5	3–6	36	FIM planned 2010
IDEAL								
Generation I	Polymer + salicylate	Sirolimus salicylate	Nil	200	2.0	3	6	Whisper FIM (115)
Generation II	Polymer + salicylate	Sirolimus salicylate	Nil	175	1.5	—	—	Pre-clinical studies planned in 2010
AMS								
AMS-1	Magnesium alloy	Nil	Nil	165	1.2	Days/weeks	<4	PROGRESS AMS FIM study (116)
AMS-2	Magnesium alloy	Nil	Nil	120	—	Weeks	>4	Pre-clinical stage
AMS-3	Magnesium alloy	Yes	Nil	120	—	Weeks	>4	Pre-clinical stage

AMS = absorbable metallic stent; BTI = Bioabsorbable Therapeutics Inc; BVS = bioabsorbable vascular solutions; FIM = first in man.

Figure 13 The Igaki-Tamai Stent With Gold Markers

A marker is shown in the **insert**.
Photograph courtesy of Kyoto Medical Group, Japan.

Ltd., Kyoto, Japan) degraded over 18 to 24 months and was the first fully BDS to undergo evaluation in humans. The stent was mounted on a standard angioplasty balloon and, uniquely, was both thermal self-expanding and balloon expandable. The initial self-expansion occurred following the use of heated contrast (up to 70°C) in the delivery balloon, whereas the final self-expansion of the stent occurred at 37°C in the 20 to 30 min after stent deployment (Fig. 13).

The FIM study of the Igaki-Tamai stent (15 patients, 19 lesions, 25 stents) demonstrated no MACE or ST events within 30 days, and 1 repeat PCI at 6-month follow-up. Encouragingly, the loss index (late loss/acute gain) was 0.48, which was comparable to BMS, and demonstrated for the first time that BDS did not induce excess intimal hyperplasia. Furthermore, IVUS imaging demonstrated no significant stent recoil at day 1, and as expected from the properties of PLLA, continued stent expansion was observed in the first 3 months of follow-up. The mean stent cross-sectional area increased from 7.42 ± 1.51 mm^2 at baseline to 8.18 ± 2.42 mm^2 ($p = 0.086$) at 3 months, and 8.13 ± 2.52 mm^2 at 6 months (109).

A second larger study in 50 elective patients (63 lesions, 84 stents) reported favorable long-term clinical results at 3- and 10-year follow-up, which currently represents the longest available evaluation of a BDS. The study demonstrated the complete absence of stent struts on IVUS at 3-years follow-up, together with a mean angiographic diameter stenosis of 25%. At 10-year clinical follow-up, survival rates free from death, cardiac death, MACE, and TLR were 89%, 98%, 60%, and 76%, respectively (110). In total, there were 3 ST events: 1 subacute event occurring at day 5, possibly due to inadequate heparinization at the time of PCI

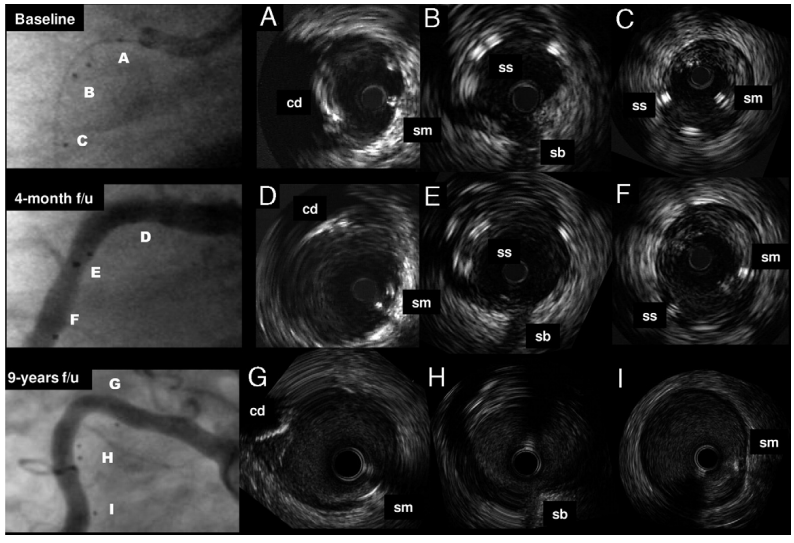


Figure 14 **Coronary Angiograms and IVUS Images From a Right Coronary Artery Stented With an Igaki-Tamai Stent**

The right coronary artery was stented with an Igaki-Tamai stent in August 2000 and followed-up for 10 years. **(A to C)** Baseline intravascular ultrasound (IVUS) images taken using a Boston Scientific Ultracross 30 MHz IVUS catheter, and the corresponding angiogram. The stent struts (ss), which were 0.17 mm thick at baseline, are seen in **A and C,** together with the gold stent markers (sm), and a calcium deposit (cd) (9 o'clock, **A**). In **B**, 4 struts located at the 2, 9, 10, and 11 o'clock positions are visible, at a side branch (sb). The mean luminal area and mean vessel area in the stented segment were measured to be 13.06 mm^2 and 27.59 mm^2, respectively. **(D to F)** IVUS images at 4-month follow-up (f/u). The stent markers (sm), stent struts (ss), and a calcium deposit (cd) are all seen. Mean luminal area and mean vessel area were 14.00 mm^2 and 31.68 mm^2, respectively. **(G to I)** IVUS images at 9-year follow-up. The stent markers (sm) and calcium deposit (cd) are still visible 9 years after the procedure. Struts are not visible, although some highly echogenic signals may represent the remnants of some struts (10 to 11 o'clock, **H**). The mean luminal area, and vessel area on IVUS analysis are similar to the results at 4-month follow-up (13.7 and 26.7 mm^2, respectively). Reproduced with permission from Onuma et al. (117).

(111), and 1 subsequent late and very late ST event. The angiographic and IVUS appearances of the stent struts out to 10-year follow-up are shown in Figure 14 (117).

Despite the impressive results, the failure of the stent to progress was primarily centered on the use of heat to induce self-expansion. There were concerns that this could cause necrosis of the arterial wall leading to excessive intimal hyperplasia (118), or increased platelet adhesion leading to ST (119). None of these concerns were substantiated in the initial studies; however, only low-risk patients were enrolled. Currently, the stent is only available in Europe for peripheral use; however, there are plans to review its use in coronary arteries. At present, the stent has no drug coating, and although early studies of the stent coated in the tyrosine kinase antagonist ST 638 or paclitaxel showed promising results, they have been confined to non-human studies (120,121).

ABBOTT VASCULAR BIORESORBABLE VASCULAR SCAFFOLD (BVS). The Abbot Vascular everolimus-eluting BVS (Abbott Vascular) is the only PLA BDS that is currently undergoing clinical trials. The device, which is fully absorbed over 2 years, has a backbone of PLLA, which is subsequently coated in a thin layer of a 1:1 mixture of an amorphous matrix of poly-D,L-lactide (PDLLA) and 8.2 μg/mm of the antiproliferative drug everolimus. The PDLLA enables controlled release of everolimus, such that 80% has been eluded by 30 days, which is similar to that seen on the Xience V EES. Encouragingly, studies also indicated that the BVS has comparable acute vessel recoil to the EES, inferring similar initial radial strength (122). The natural loss of polymer mass through bioabsorption, however, which approximates to 30% after 1 year and to 60% after 18 months, ensures that this radial strength is not maintained long term (Fig. 15). Although the stent is radiolucent, 2 platinum markers at each end allow easy visualization on angiography and other imaging modalities.

The first BVS device (Revision 1.0) had a strut thickness of 150 μm and a crossing profile of 1.4 mm, and consisted of circumferential out-of-phase zigzag hoops, with struts linked together directly or by thin and straight bridges

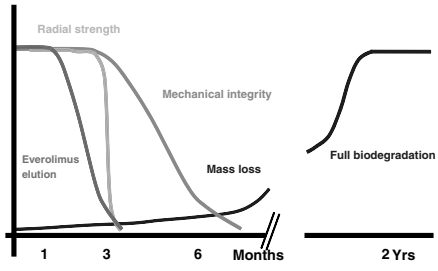


Figure 15 **The Bioabsorption and Drug Release Pattern of the BVS Device**

The early loss of radial strength has been addressed with the new Revision 1.1 BVS stent (data on file at ABBOTT Vascular).

(Fig. 16A). The stent had to be kept stored below −20°C to prevent physical aging of the polymer and to ensure device stability, which was both inconvenient and limited shelf life to 8 weeks.

Following encouraging pre-clinical studies (123), the safety and feasibility of the first-generation BVS implant was assessed in 30 low-risk patients with de novo coronary lesions who were enrolled in the prospective, open-label, multicenter FIM ABSORB (A Bioresorbable Everolimus-Eluting Coronary Stent System for Patients With Single De-Novo Coronary Artery Lesion) study (112,113,124,125). The study plans to assess clinical outcomes on an annual basis out to 5 years, and so far, results are available out to 3 years follow-up. In addition, at 6 months and 2 years, to gain a greater understanding of in vivo changes to the implanted device and local vasculature, multimodality intravascular imaging was performed using IVUS, intravascular ultrasound-virtual histology (IVUS-VH), palpography, and OCT.

The study demonstrated clinical safety of the BVS as there was only 1 ischemia-driven major adverse event (non–Q-wave MI) at 6 months, whereas no MACE events were reported in the following 30 months. Of note, no ST has been observed out to 3 years follow-up (125). Angiographic follow-up at 6 months demonstrated a late loss of 0.44 mm, which although comparable to values from the early DES studies (126), and somewhat lower than historical values for BMS (>0.8 mm) (127), is still notably higher than that observed with the Xience V EES (0.11 mm) (128). Reassuringly, there was no significant increase in delayed late loss from 6 months to 2 years among the 19 patients who returned for angiographic follow-up ($p = 0.23$). The 6-month late loss represented a combination of neointimal hyperplasia, which was comparable to that observed with the Xience V EES (127), and a reduction in scaffold area, which occurred through a combination of acute and chronic scaffold recoil, and nonuniform vessel support (Fig. 17). Chronic scaffold recoil, which occurred as a consequence of the loss of radial strength with bioresorption, represents a new phenomenon that is not observed with nonabsorbable metallic stents.

The results from multimodality imaging during follow-up helped confirm bioresorption of the implant. Direct confirmation was made by observing the absence of stent struts using IVUS and OCT at baseline and follow-up (Fig. 18). Indirect confirmation involved documenting between baseline and follow-up: 1) the reduction in hyperechogenicity; 2) the significant increase in strain pattern on palpography; 3) the change in plaque composition on IVUS-VH, and 4) the return of vasoactivity following administration of methyl-ergometrine maleate or acetylcholine (113,129,130).

Importantly, the ABSORB study not only demonstrated the feasibility and safety of using a biodegradable scaffold, but it also provided vital data that have lead to important design modifications to the device. This second-generation device, Revision 1.1, utilizes the same polymer, and has the same total absorption time of approximately 2 years; however, a change in the processing procedure has ensured that it is able to provide radial support for longer. Of note, the new design has in-phase zigzag hoops linked by bridges, which allows for a more consistent drug application

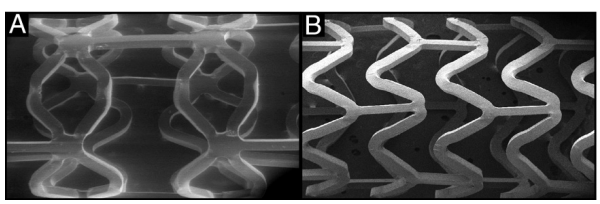


Figure 16 **The BVS Device**

(A) The first-generation BVS device, Revision 1.0. **(B)** The second-generation device, Revision 1.1. There is a clear change in the device design with the out-of-phase zigzag pattern connected directly or by straight bridges (**A,** Revision 1.0) being replaced by the in-phase hoops linked by straight bridges (**B,** Revision 1.1).

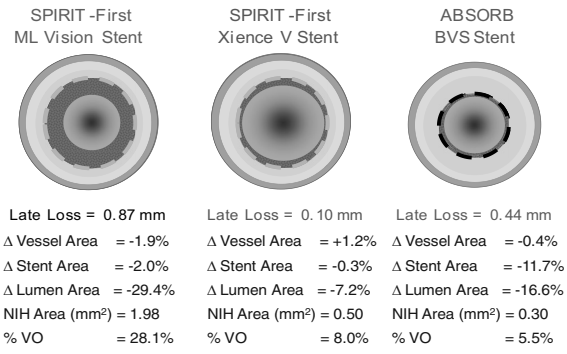


Figure 17 **A Comparison of the Temporal Changes in Quantitative Coronary Angiographic and Intravascular Ultrasound Parameters Seen in the SPIRIT First and ABSORB Studies**

A comparison of the late loss, and the changes in vessel area, stent area, lumen area, neointimal hyperplasia area (NIH) and percentage volume obstruction (%VO) between baseline and follow-up between the bare-metal Multi-Link Vision Stent, the everolimus-eluting Xience V stent, and the biodegradable BVS device.

(Fig. 16B) (113) and, as recently confirmed by OCT, more uniform strut distribution and vessel wall support (131). Stent security has been improved, reducing the likelihood of stent dislodgement, which occurred in 2 patients in Cohort A of the ABSORB study; 1 stent was successfully retrieved, whereas 1 was deployed in a non–target vessel. Finally, from a practical aspect, the stent can now be stored at room temperature. The device is currently being assessed in the recently enrolled 101-patient Cohort B ABSORB trial. Preliminary results of the first 45 patients who returned for angiographic follow-up at 6 months are very encouraging, and suggest that the medium-term performance of the device has been improved following changes in the manufacturing process and geometry of the Revision 1.1 (114). Specifically, at 6 months, late lumen loss was 0.19 mm, which was notably lower than that seen with the Revision 1.0, and on a par with that commonly seen with DES. Further to that, intravascular imaging in the form of IVUS-VH and OCT both demonstrated minimal device shrinkage with follow-up, which previously had been implicated in the disappointing late loss seen in Cohort A. In addition, the absence of any significant change in IVUS-VH signal or strut core area on OCT during follow-up reaffirmed the improved mechanical integrity of the device. Finally, clinical event rates were low, with only 1 patient experiencing an MI and 1 patient experiencing a TLR; of note, there were no ST events according to protocol or ARC. Longer follow-up is ongoing.

Currently recruiting is the ABSORB EXTEND multicenter single-arm registry, which aims to eventually recruit 1,000 patients, while in the pipeline for the future is a pivotal noninferiority trial of the BVS versus a DES.

THE REVA STENT: POLY (IODINATED DESAMINOTYROSYL-TYROSINE ETHYL ESTER) CARBONATE STENT. The REVA stent (REVA Medical, San Diego, California) is a poly(iodinated desaminotyrosyl-tyrosine ethyl ester) carbonate stent that degrades into water, carbon dioxide, and ethanol, leaving iodinated desaminotyrosyl-tyrosine, which is absorbed and excreted from the body (Fig. 19). The stent, which is radio-opaque because of the iodination of the desaminotyrosine ring (Fig. 20), has a resorption time of approximately 36 months. The first version lacked an antiproliferative coating and had a slide and locking design that provided both flexibility and strength. This design eliminated hinge points and therefore minimized polymer strain by over 75%, thereby preventing deformation and weakening of the polymer during stent deployment. Following stent deployment, the locking mechanism maintained the acute lumen gain and functioned to provide additional support to the stent during vessel remodeling. Data indicate minimal acute stent recoil, and radial force that is comparable to a BMS (132).

Following successful preclinical trials, 27 patients with de novo lesions were enrolled in the RESORB (REVA Endovascular Study of a Bioresorbable Coronary Stent) FIM study. The study demonstrated good acute reductions in diameter stenosis following stent deployment, together with minimal vessel shrinkage at follow-up. However, focal mechanical failures driven by polymer embrittlement led to a higher than anticipated rate of TLR (66.7%) between 4- and 6-month follow-up. Interestingly, the degree of neointimal hyperplasia was similar to a BMS (36).

A redesign of the stent has ensued, resulting in the second-generation ReZolve stent (REVA Medical) (Fig. 20C).

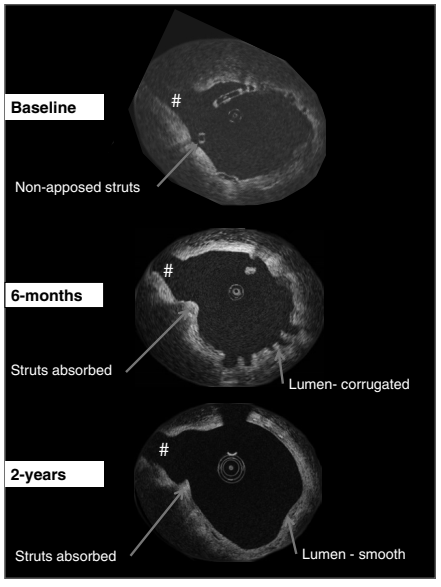


Figure 18 **The Serial Changes Seen on OCT in the ABSORB study**

At baseline, several unapposed struts can be seen crossing the side branch **(#)**. At 6-month follow-up, the unapposed stent struts have been absorbed, and the lumen has a corrugated appearance, whereas at 2-years follow-up, the lumen is smooth, and there is little evidence to suggest that there has been a stent implanted in this location in the past. Reprinted with permission from Serruys et al. (113).

This stent has a more robust polymer, a spiral slide and lock mechanism to improve clinical performance, and a coating of sirolimus. The sirolimus elution is such that 80% is eluted by 30 days, and 95% is eluted by 90 days. Successful pre-clinical trials have been performed, and clinical trials are anticipated to commence in late 2010 (133).

IDEAL POLY(ANHYDRIDE ESTER) SALICYLIC ACID STENT. The 8-F compatible, balloon expandable radio-opaque IDEAL BDS (Bioabsorbable Therapeutics, Menlo Park, California) is unique in that its backbone consists of poly-anhydride ester together with salicylic acid, and an 8.3 μg/mm coating of sirolimus (Fig. 21). This combination ensures that the stent is able to provide both antiproliferative and anti-inflammatory properties. On release, salicylic acid is absorbed into the vessel wall, and this is likely to account for the reduction in inflammation seen with this polymer, when compared with a BMS or Cypher SES (134). Sirolimus, which is present in a surface area dose that is approximately 25% of that found on the Cypher stent, is eluted over 30 days, whereas complete stent degradation occurs over 12 months. The stent's radial strength at implant is significantly greater than both a BMS and Cypher stent; however, this decreases with bioabsorption, such that by approximately 60 days, it is equal to the Cypher stent.

The 12-month follow-up of 11 patients enrolled in the FIM Whisper study was completed in July 2009. Preliminary results confirmed the stent's safety and radial strength, with no evidence of acute or chronic recoil, however, insufficient neointimal suppression was noted (115). This is likely to be the consequence of the rapid elution of sirolimus, coupled with an inadequate initial dose.

A second-generation stent has been developed with a higher dose of sirolimus and a slower drug release pattern. Furthermore, the stent design has been optimized, which has resulted in a reduced crossing profile (6.0-F compatible), and thinner struts (175 μm). Pre-clinical porcine coronary implants and a FIM study are anticipated in 2010 (115).

OTHER PLLA BDS. Arterial Remodeling Technologies (A.R.T) (Noisy le Roi, France), Tissue Gen (Dallas, Texas), Elixir Medical, and OrbusNeich are all developing PLLA BDS; however, these stents have yet to progress beyond pre-clinical trials to date (135–137).

Biodegradable metallic stent technology. ABSORBABLE METALLIC STENT. The balloon-expandable AMS-1 BDS (AMS-1, Biotronik, Berlin, Germany) is composed of 93% magnesium (approximate weight of 3.0 × 10 mm is 3 mg) and 7% rare earth metals (Fig. 22). The stent has a high mechanical strength; and has notable other properties that are comparable to stainless steel stents, such as low elastic

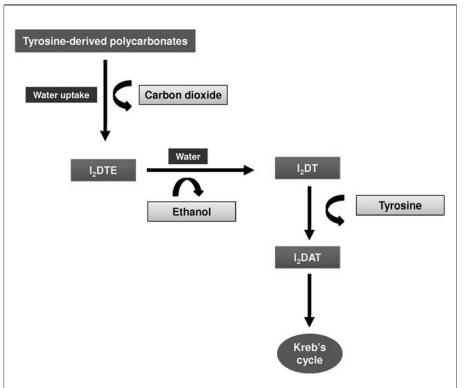


Figure 19 **The Metabolism of Tyrosine-Polycarbonate Stents**

Initially, hydrolysis of the tyrosine-polycarbonate produces iodinated desaminotyrosyl-tyrosine ethyl esters (I_2DTE), and releases carbon dioxide. I_2DTE is hydrolyzed into iodinated desaminotyrosyl-tyrosine (I_2DT) and ethanol. Cleavage of I_2DT produces tyrosine and iodinated desaminotyrosine (I_2DAT), which enters the Krebs cycle.

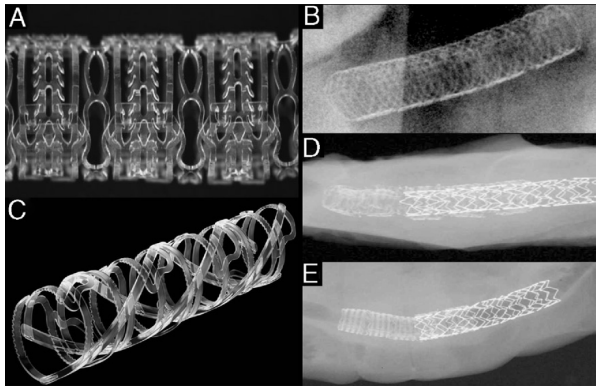


Figure 20 **The REVA Stent**

(A) The first-generation REVA stent with the slide and lock design. **(B)** A demonstration of the stent's radio-opacity due to the iodination of the tyrosine molecules. (**C)** The second-generation ReZolve REVA stent with the spiral slide and lock design. **(D, E)** X-ray appearance 1 month after deployment of the first-generation stent **(D)** and second-generation stent **(E)** demonstrating a greater number of stent struts with the second-generation stent following modifications to the stent polymer. Images provided courtesy of REVA Medical Inc.

recoil (<8%), a high collapse pressure (0.8 bar), and minimal shortening after inflation (<5%) (116). Pre-clinical assessment indicates the AMS-1 is rapidly endothelialized, with magnesium degrading within 60 days into inorganic salts with little associated inflammatory response (138). Furthermore, the negative charge that the degradation produces ensures that the stent is hypothrombogenic (139).

The PROGRESS AMS (Clinical Performance and Angiographic Results in Absorbable Metal Stents) study was a multicenter, nonrandomized, prospective study assessing the efficacy and safety of the AMS-1 stent in 63 patients (71 stents) with single de novo lesions. At 12-month follow-up, there were no deaths, MIs, or ST, thus confirming the stent's safety; in addition, there was also return of vessel vasoreactivity. The rate of MACE (a composite of cardiac death, nonfatal MI, and clinically driven TLR) was 23.8% and 26.7% at 4 and 12 months follow-up, respectively, and therefore, the study achieved its primary end point; however, the rate of TLR (clinically and nonclinically driven) was a disappointing 39.7% at 4-month and 45.0% at 12-month follow-up (116). Additional data from both IVUS and QCA indicate that the in-stent late loss of 1.08 mm at 4 months was the result of the stent having a lower initial radial force compared with a conventional metallic stent, and the rapid loss of this radial force as a consequence of early, rapid AMS-1 stent degradation. Other factors contributing to the luminal loss seen at follow-up were thickening of extra stent tissue (13.5%) and neointimal formation (41%) (140).

Reassuringly, angiography and IVUS at long-term follow-up in 8 patients who did not experience an event at 4 months has shown that no evidence of either later recoil or the late development of neointima. In fact, in some patients, evidence was seen of neointimal regression and/or an increase in vessel and lumen volume (140).

Importantly, the results from this initial study have been utilized to improve the stent's design. Modifications have centered on prolonging stent degradation time and enabling drug elution, thereby reducing restenosis that was partly due to negative remodeling, and partly due to an excessive healing response. The new-generation stents consist of the AMS-2 and -3.

The AMS-2 stent use a different magnesium alloy, resulting in the stent having a higher collapse pressure and also a slower degradation time. Furthermore, there has been a reduction in the strut thickness from 165 μm to 120 μm; an alteration to the stent's surface; and to improve radial strength, a change in the cross-sectional shape of the strut, from a rectangle to a square. These changes have had the desired effect in pre-clinical trials (141).

The AMS-3 stent (DREAMS = Drug Eluting AMS) is a modification of the AMS-2 stent, and is designed with the aim of reducing neointimal hyperplasia by incorporating a bioresorbable matrix for controlled release of an antiproliferative drug. The drug and its release kinetics are under investigation; however, the stent will be assessed in the BIOSOLVE-I FIM study planned for late 2010 (141).

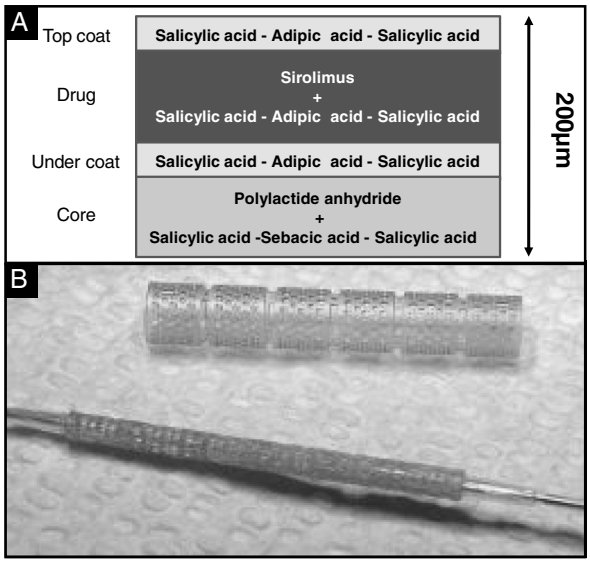


Figure 21 The Poly (Anhydride Ester) Salicylic Acid IDEAL Stent

(A) The stent strut in cross section indicating the location of the anti-proliferative drug sirolimus, and the 2 salicylate polymers. **(B)** The gross appearance of the stent.

Self-Expanding (SE) Stents

SE stents were the first stents to be implanted in coronary arteries (142), being quickly followed by balloon-expandable (BE) stents, such that both technologies were used with similar frequency in the early days of coronary stenting. SE stents are made from nitinol, an alloy of nickel and titanium, which is uniquely suited for this purpose given its shape memory; biocompatibility; fatigue resistance; and superelastic qualities that allow it to withstand large amounts of recoverable strain.

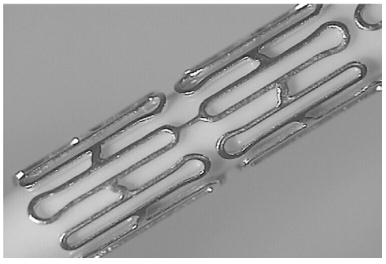


Figure 22 The Absorbable Metallic Stent

In addition to comparable outcomes, SE stents offer distinct advantages over BE stents, such as a lower incidence of edge dissections (143,144), reduced rates of side-branch occlusion and no-reflow (144), and positive remodeling (144). Furthermore, animal data suggest that SE stents offer the ability to prevent immediate vessel wall injury, which may eventually translate into a reduction in neointimal hyperplasia and a larger lumen area (145). Some of the drawbacks associated with the use of SE stents are related to their mechanical properties; for example, precisely matching stent size to vessel size is hindered by the continued outward radial force that SE stents exert after deployment, leading to negative chronic recoil, and a subsequently larger vessel at follow-up. In addition, SE stents are housed within a delivery catheter that ensures stent security; however, these catheters can be cumbersome to use, and have an associated learning curve. Importantly, the delivery profile of these stents is dictated by strut dimensions, as opposed to the balloon profile in BE stents. Finally, placement accuracy of SE stents is complicated by stent foreshortening on expansion, and/or

forward spring movements of the stent from the delivery system once deployment commences.

Unfortunately, the arrival of DES led to a loss of interest among stent companies in pursuing the development of SE-stents, and they were largely abandoned for coronary use. Recently, however, there appears to have been a resurgence of interest in this technology for niche coronary settings following new stent designs that have incorporated thinner struts, a drug coating, and improved delivery systems.

At present SE stents are being investigated for use in patients with the following.

Bifurcation lesions. There is optimism that nitinol SE-dedicated bifurcation stents, which include the Axxess (Devax), Stentys (Stentys SAS, Clichy, France), and Cappella Sideguard (Cappella, Auburndale, Massachusetts), will lead to improved outcomes in the treatment of bifurcation lesions, because of their ability to conform more optimally than a conventional BE-stent to the angulated anatomy (Table 6, Fig. 23) (32,55,146–162).

Vulnerable plaque. MIs commonly result from disruption of thin-cap fibroatheromas (163). It follows that preemptive treatment of these lesions involves preventing cap rupture and promoting endothelialization. Understandably, BE-stents are not well suited to these delicate lesions owing to the high radial forces required for their deployment. Conversely, SE stents offer the advantage of not inducing vessel injury during implantation, thereby minimizing the risk of embolizing necrotic material and thrombus distally. In the long term, the lack of strut penetration into necrotic core may reduce the risk of ST, which may occur through the substantially delayed arterial healing that occurs when struts penetrate the necrotic core (164,165). The vProtect Luminal Shield (Prescient Medical, Doylestown, Pennsylvania) SE stent (Fig. 24A) has been shown in animal studies to promote vascular healing, and importantly, to achieve complete endothelialization of the stented vessel segment within 7 days (166). Furthermore, data from the FIM study have demonstrated that the "shield" can induce plaque remodeling and has a positive vascular healing profile as demonstrated on IVUS. Currently, the stent is being assessed in the prospective, randomized SECRITT I (Santorini Criteria for Investigating and Treating Thin Capped Fibroatheroma Trial) pilot study, which is evaluating the safety and feasibility of stenting a vulnerable plaque with the vProtect Luminal Shield compared with a medically treated, nonstented (control) group (167).

Lesions in small-diameter vessels. The use of BE stents in vessels with small diameters is inherently associated with a risk of edge dissection, owing to the high pressures required for optimal stent implantation. Both inadequate stent strut apposition and stent expansion are subsequent risks for ST and restenosis. For lesions located in small-sized vessels, the use of an SE stent, which can minimize barotrauma and the risk of edge dissections, therefore offers distinct advantages. The Cardiomind Sparrow (Cardiomind, Sunnyvale, California) is a small-profile nitinol SE-stent that is designed specifically for lesions in small-diameter vessels (2.00 to 2.75 mm) (Figs. 24B and 24C) (168). The stent, which has a strut thickness of 61 μm, is pre-loaded on an 0.014-inch guidewire, with 2 to 3 cm of radio-opaque guidewire at the distal end enabling positioning within the vessel. The stent is deployed through a dedicated Sparrow delivery system that facilitates electrolysis of mechanical latches holding down each end of the stent. The electric current required for release of each latch is $<$0.2 mA, and release occurs within 20 s. The CARE I (Cardiomind Sparrow DES Trial) feasibility study was performed in 21 patients with de novo lesions in vessels of 2.0 to 2.5 mm diameter. At 6-month follow-up, a 13% rise in stent volume index was observed together with a binary restenosis rate of 20%. There was no ST at 30 days, and 2 MACE events through to 24-months follow-up (169).

The next-generation Sparrow stent has a strut thickness of 67 μm, and is coated in a 4-μm-thick layer of sirolimus at a dose of 6 μg/mm, and an 8-μm-thick biodegradable PLA/PLGA polymer. It is currently being assessed in the CARE-II study that will randomize 220 patients with lesions $\leq$20 mm in length, in vessels between 2.00 and 2.75 mm in diameter to treatment with the bare-metal Cardiomind Sparrow, the drug-coated Cardiomind Sparrow, or a BMS. Interim results at 8-months follow-up are expected in 2010 (170).

Dedicated Bifurcation Stents

Bifurcation lesions continue to pose a challenge to today's interventional cardiologist. In spite of the frequent occurrence of bifurcation lesions, the optimal procedural strategy, which maintains both main- and side-branch patency, remains to be established. Historically, a 2-stent strategy was considered the ideal method of dealing with a bifurcation lesion as this produced the best angiographic result; however, data from multiple randomized studies (171–176) and 3 recent meta-analyses indicate that a provisional main-branch stenting strategy is as efficacious as a 2-stent strategy (177–179). A caveat to this, however, is the wide anatomical variation of bifurcation lesions, such that those with a large side branch supplying an extensive myocardial territory, or a side branch with extensive disease may not be suited for a provisional T-stenting technique. Moreover, in those situations where a 2-stent strategy is required, debate continues over which stenting technique to use (176,180,181). Besides requiring operator skill and experience, these conventional stenting techniques for bifurcation lesions have a number of other limitations, including: 1) the inability to completely scaffold the side-branch ostium; 2) distortion of the main-branch stent following side-branch dilation; 3) the difficulty of maintaining access to the side branch throughout the procedure; 4) failure to wire the side branch through the main-branch stent; and

Table 6 Summary of the Main Characteristics and Trial Results of Currently Available Dedicated Bifurcation Stents

Stent Type (Company) (Ref. #)	Device Profile	Stent Material	Drug Coating	SB Protection	Ostial SB Coverage	Study Name*	No. of Patients (Follow-Up, Months)	Additional Stenting, % MB/SB	Binary In-Stent Restenosis % MB/SB	LLL, mm MB/SB	MACE, %	Death, %	MI, %	TLR, %
Balloon-expandable stents														
Antares† (TriReme Medical) (148)	6-F	SS	—	+	+	FIM (TOP study)	39 (1)	NA	NA	NA	5.9	0.0	5.1	2.9
Invatec Twin-Rail (Invatec) (149)	6-F	SS	—	+	+/−	FIM (DESIRE)	15 (7)	17/23	NA	NA	14.3	0.0	0.0	14.3
Multi-Link Frontier† (Abbott Vascular) (150)	7-F	SS	—	+	+/−	Registry	105 (6)	40/43	25.3/—	0.84/0.34	17.1	0.0	3.8	13.3
Nile Croco† (Minvasys) (151)	6-F	CoCr	—	+	+/−	Registry	93 (6)	NA	NA	NA	12.0	2.0	0.0	9.4
Nile Pax† (Minvasys) (152)	6-F	CoCr	Abluminal Paclitaxel	+	+/−	FIM	102 (30)	—/27	NA	NA	1.0	1.0	1.0	0.0
Petal (Boston Scientific) (153,154)	7-F	PtCr	Paclitaxel	+	+	FIM (Petal Trial)	28 (12)	28/25	10/10	0.41/0.18	14.8	0.0	3.7	7.4
SideKick (Y-Med) (155)	5-F	CoCr	—	+	+/−	FIM	17 (2–3)	40‡	NA	NA	5.8	0.0	5.8	0.0
SLK-View† (Advanced Stent Tech) (156)	8-F	SS	—	+	−	Registry	81 (4)	14/25	28.7/37.7	1.1/0.81	31.0	1.3	2.5	21.3
Tryton† (Tryton Medical) (157)	6-F	CoCr	—	NA	++	FIM (Tryton I)	30 (6)	39/—	0/0	0.25§/0.17	9.9	3.3‖	6.6	6.6
Self-expanding stents														
Axxess (Devax) (32,55)	7-F	Nitinol	Abluminal Biolimus A9	+	−	Registry (DIVERGE)	302 (9)	64.7‡	2.3/4.8	0.29/0.29	7.7	0.7	4.3	4.3
Sideguard† (Cappella) (158,159)	6-F	Nitinol	—	NA	++	FIM (Sideguard I & II)	93 (12)	NA	12/25	0.21/0.58	12.0	1.2‖	3.6	7.2
Stentys† (Stentys) (160,161)	7-F	Nitinol	Paclitaxel	−	+/−	FIM (OPEN I)	40 (3¶, 6#)	9/13	25/14	0.83§	5.1	0.0	2.5	2.5

*All multicenter studies; †C.E. mark; ‡not specified how many in main branch (MB) or side branch (SB); §proximal main branch; ‖cardiac death; ¶clinical follow-up; #angiographic follow-up. Adapted from Abizaid et al. (162).
LLL = late lumen loss; MI = myocardial infarction; TLR = target lesion revascularization; other abbreviations as in Tables 1 and 2.

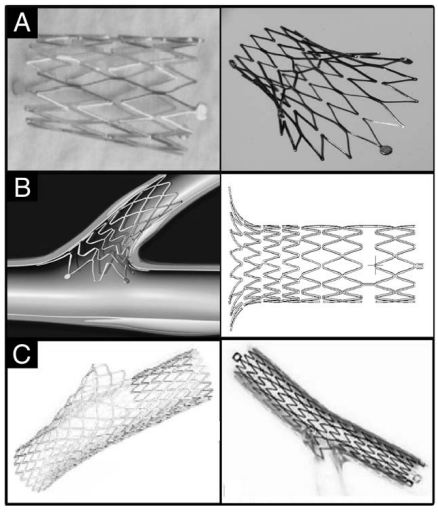


Figure 23 **Self-Expanding Dedicated Bifurcation Stents**

(A) Axxess, **(B)** Sideguard, and **(C)** Stentys.

5) side-branch jailing. A consequence of these limitations has been the development of numerous dedicated bifurcation stents, which are summarized in Table 6.

These bifurcation stents can be broadly divided into 3 groups (Figs. 23 and 25):

1. Stents that facilitate provisional side-branch stenting and maintain direct access to the side branch after main-branch stenting. These stents consist of a pre-formed main-branch stent with side ports to facilitate access to the side branch. Examples include: Antares (TriReme Medical Inc., Pleasanton, California), Invatec Twin-rail (Invatec, Brescia, Italy), Multi-Link Frontier (Abbott Vascular), Nile Croco (Minvasys), Petal (Boston Scientific), SLK-view (Advance Stent Technologies, Pleasanton, California), StenTys (StenTys), and Y-Med Side-Kick (Y-Med, San Diego, California).
2. Stents designed to treat the side branch first. These stents are designed for those bifurcation lesions with significant side-branch disease; a second stent is required for the main branch. Examples include: Sideguard (Cappella, Auburndale, Massachusetts), and Tryton (Tryton Medical, Newton, Massachusetts).
3. Conical stents for the geometry of the ostium. These may require additional stents to be implanted in the main branch or side branch. Examples include the Axxess stent.

The newer generation of dedicated stents have significantly improved from the initial attempts at bifurcation stents that were difficult to deploy, had large crossing profiles, and had poor trackability. The evaluation of these stents, which is summarized in Table 6 (32,55,148–161), is limited to small-sized studies with short follow-up, many of which have not been published in peer-reviewed journals.

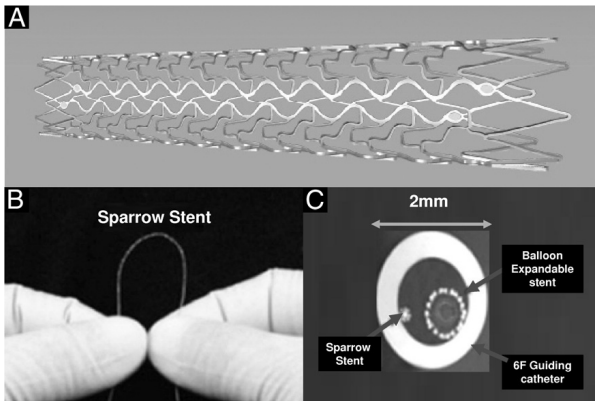


Figure 24 **Self-Expanding Stents**

(A) The vProtect Luminal Shield stent. **(B, C)** The CardioMind Sparrow stent. **(B)** Illustrates the flexibility of the Sparrow stent delivery system, whereas **(C)** demonstrates the smaller profile of the Sparrow stent compared with a conventional balloon-expandable stent, and a 6-F guiding catheter. **(B, C)** Reprinted with permission from Chamie et al. (168).

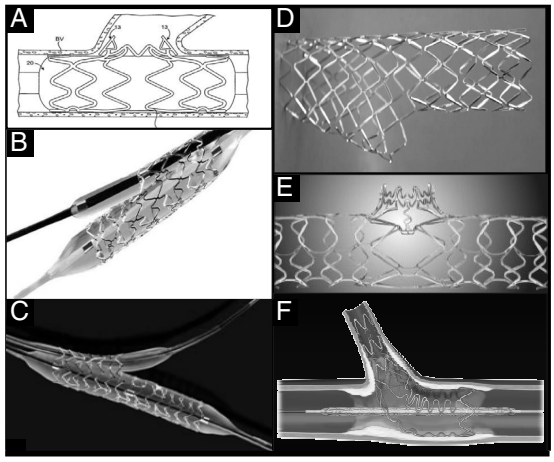


Figure 25 **Balloon-Expandable Dedicated Bifurcation Stents**

(A) Antares, **(B)** Invatec Twin-Rail, **(C)** Multi-Link Frontier, **(D)** Nile Croco/Pax, **(E)** Petal, **(F)** Tryton.

Although device success has been high, studies have reported rates of additional stenting of up to 40%. Moreover, the early devices were bare metal, and subsequent rates of restenosis were similar to those observed with PCI of bifurcation lesions using BMS (182). The consequently high rates of MACE and TLR have prompted second-generation devices that elute antiproliferative drugs and have different stent designs, each with their own associated learning curve. The evaluation of these newer devices is ongoing, and although results appear more promising, randomized trials against conventional DES are still lacking. Conceptually, these dedicated stents would seem the answer to the problem of treating bifurcation lesions; however, clinical evidence is currently absent to support their use as first-line devices in these complex lesions.

Drug-Eluting Balloons (DEBs)

DEBs represent a new coronary device that may provide "healthy" future competition for DES, particularly in specific lesions where DES cannot be delivered or have unproven results such as ISR, torturous vessels, small vessels, and long, calcified lesions.

The development of these devices, which are able to locally deliver antiproliferative drugs without the associated limitations of DES, have in part been stimulated by the previously discussed problems of DES, such as ST and ISR. Moreover, additional impetus has been gained following the discovery that long-lasting antiproliferative effects do not require sustained drug release. For example, the most commonly used agent in DEB is paclitaxel, which is rapidly taken up by vascular smooth muscle cells and retained in these tissues for up to 1 week, resulting in a prolonged antiproliferative effect (183–185).

Potential advantages of DEBs, besides their use in ISR, include the absence of a polymer, which may decrease chronic inflammation, reducing the trigger for ST. This risk of ST may also be reduced by the absence of a rigid stent casing, which not only removes the presence of foreign stent struts, but also allows the original coronary anatomy to be maintained following PCI in tortuous lesions and small vessels, thereby diminishing abnormal flow patterns. The absence of metal struts, and local drug delivery can also diminish the need for prolonged DAPT.

It is important to acknowledge that DEBs cannot overcome some of the mechanical problems previously associated with angioplasty using noncoated balloons, such as acute recoil. In addition, it remains unclear whether the previous problem of late negative remodeling will occur with DEBs.

At present, several DEBs are undergoing clinical evaluation, with most studies assessing their performance in the treatment of ISR, de novo lesions, and bifurcation lesions (186–197).

All current devices use paclitaxel with a typical dose of 3 $\mu g/mm^2$ of balloon surface. The main difference between devices is the formulation used to coat the balloon, which ultimately facilitates drug transfer. The different formulations in use are:

1. Paclitaxel with iopromide coating (Paccocath Technology). This proprietary drug matrix, which is applied to the balloon of an angioplasty catheter, increases the solubility and transfer of paclitaxel such that more than 80% of the drug is released during a single 1-min balloon inflation, with 10% to 15% of the released paclitaxel being delivered to the vessel wall (196). This technology is currently used on the Paccocath (Bayer, Leverkusen, Germany) and SeQuent Please (B. Braun, Melsungen, Germany) DEBs. In addition, the Coroflex DEBlue consists of a cobalt chromium BMS pre-mounted on a SeQuent Please DEB (B. Braun).
2. Paclitaxel with FreePac hydrophilic formulation. FreePac is a proprietary natural coating that frees and separates paclitaxel molecules and facilitates their absorption into the wall of the artery. It is applied to the balloon of an angioplasty catheter, reducing total drug elution time to 30 to 60 s. Importantly, it permits balloon inflation to be maintained beyond 60 s without additional drug release. This technology is in use on the IN.PACT Falcon DEB (Invatec).
3. Paclitaxel without any formulation. Several different devices elute paclitaxel without any formulation.

The DIOR DEB (Eurocor, Bonn, Germany) is loaded with 3 $\mu g/mm^2$ of paclitaxel in its microporous balloon surface. The balloon is triple-folded, which protects the drug from early wash-off during insertion and tracking. A 60-s balloon inflation results in the elution of a clinically effective dose of paclitaxel. Approximately 35% of the drug is eluted after the first 20-s inflation, with another 35% released following a second similar inflation. An extension to the DIOR balloon is the MAGICAL system, which uses a cobalt chromium BMS on the DIOR DEB. Finally the GENIE (Acrostak, Winterthur, Switzerland) is a liquid drug delivery catheter available in various diameters and shaft lengths. After determining the vessel diameter and lesion length, the balloons are inflated with diluted paclitaxel.

DEBs have been assessed for 3 main clinical indications:

1. ISR. The assessment of DEBs in patients with ISR has shown consistent results in favor of DEBs when compared with noncoated balloon angioplasty or stenting with DES. In 2006, Scheller et al. (186) published the results of the PACCOCATH ISR I (Paclitaxel-Coated Balloon Catheter for In-Stent Restenosis) trial that randomized 52 patients with angina and a single restenotic coronary artery lesion to treatment with a paclitaxel-eluting DEB or standard angioplasty balloon. At 6-month follow-up, the primary end point of in-segment late lumen loss was significantly lower in the paclitaxel-eluting balloon group compared with the uncoated balloon group (0.03 ± 0.48 mm vs. 0.74 ± 0.86 mm, $p = 0.002$). Similarly, binary restenosis and MACE were also significantly lower in the DEB group (186). Two-year outcomes of these patients, pooled with a similar number of patients who were of equal risk and who were enrolled in the PACCOCATH ISR II trial, demonstrated continued superiority of the DEB compared with standard angioplasty. Specifically, treatment with the DEB resulted in significantly lower late lumen loss, binary restenosis, and TLR (187).
   Further assessment of DEBs in the management of ISR came in the multicenter PEPCAD II (Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease) study, which randomized 131 patients to treatment with the SeQuent Please DEB or the TAXUS PES (188). At 6-month follow-up, the primary end point of in-segment late lumen loss was significantly lower in the DEB group (0.17 ± 0.42 mm vs. 0.38 ± 0.61 mm, $p = 0.03$), whereas DEB-treated patients also had a trend for a lower rate of binary restenosis (7% vs. 20%, $p = 0.06$). At 12-month follow-up, the rate of MACE for the DEB and PES was 9% and 22%, respectively ($p = 0.08$), which was largely driven by the greater need for TLR with PES (6% vs. 15%, $p = 0.15$). Overall, the study demonstrated that the DEBs were well tolerated, safe, and at least as efficacious as PES in patients with ISR.
2. De novo lesions. The assessment of DEBs for de novo lesions has been less extensive, and results are somewhat inconsistent when compared with the superiority of DEBs in the treatment of ISR. The SeQuent Please DEB was assessed for the treatment of de novo lesions with a reference vessel diameter of 2.25 to 2.8 mm in the 120-patient multicenter, prospective PEPCAD I registry. Of note, approximately one-third of the patients required additional stenting with a BMS following use of the DEB. At 6-month follow-up, the late lumen loss in patients treated with only a DEB was 0.18 mm, compared with 0.73 mm in those receiving both DEB and BMS. Similarly, binary restenosis rates were 5.5% and 44.8%, respectively. Although this study suggested the safety and efficacy of the SeQuent Please, the poor performance of the combination of DEB and BMS was concerning and likely to be secondary to geographic mismatch (189).
   Further evaluation of the DEBs in de novo lesions came in the noninferiority PEPCAD III study, which randomized 637 patients with stable/unstable angina to treatment with a Cypher SES or the Coroflex DEBlue (BMS/DEB combination) (B. Braun) (190). At 9-month follow-up, the in-stent late lumen loss (0.41 mm vs. 0.16 mm, $p < 0.001$) and ISR (10.0% vs. 2.9%, $p < 0.01$) were both significantly higher in the BMS/DEB arm compared with SES. Although mortality was comparable between groups, treatment with a BMS/DEB lead to significantly higher rates of MI, TLR, TVR, and ST ($p < 0.05$ for all) at 9 months follow-up.
   Some have suggested that the failure to prove noninferiority in PEPCAD III was the result of using the Cypher SES as the control arm, particularly as the late loss in the BMS/DEB arm is somewhat comparable to

that seen with PES. However, in the PICCOLETO (Paclitaxel-Eluting Balloon versus Paclitaxel-Eluting Stent in Small Coronary Vessel Disease) study, which randomized 57 patients with stable or unstable angina and small coronary vessels (≤2.75 mm) to PCI with the DIOR DEB or PES, a similarly poor performance was seen in the DEB arm (191). At 6 months follow-up, percentage diameter stenosis (the primary end point) was significantly worse in those treated with DEB compared with PES (43.6 ± 27.4% vs. 24.3 ± 25.1%; p = 0.029). Similarly, binary restenosis and minimal lumen diameter were also significantly worse with the DEB. Although clinical outcomes were comparable in terms of death and MI, there was still a trend towards higher TLR with the DEB.

More promising data on the use of locally delivered paclitaxel have been reported by Herdeg et al., who randomized 204 patients to treatment with either a PES, BMS, or a BMS followed by local delivery of fluid paclitaxel using the GENIE device. At 6 months follow-up, late lumen loss was significantly lower in the BMS/GENIE group compared with the BMS-only group (0.61 mm vs. 0.99 mm, p = 0.0006), and noninferior compared with PES (0.61 mm vs. 0.44 mm, $p_{noninferiority}$ = 0.02). Similarly, TLR rates were 13.4%, 22.1%, and 13.4% for patients treated with BMS/GENIE, BMS only, and PES, respectively (192).

The evaluation of the SeQuent Please is continuing in 2 further studies of patients with de novo lesions. The multicenter PEPCAD IV DM plans to enroll 160 diabetic patients, whereas the PEDCAD CTO will enroll 50 patients with a chronic total occlusion (193).

3. DEB for bifurcation lesions. The use of DEBs in combination with BMS in bifurcation lesions has been assessed in several studies, the largest of which enrolled 120 patients. In principle, the use of a DEB in the side branch may reduce the likelihood of restenosis, thereby reducing the requirement for side-branch stenting. Although within the main branch, the use of a DEB in combination with a BMS is needed to achieve a result comparable with DES.

   The DEBIUT (Drug Eluting Balloon in Bifurcation Trial) registry enrolled 20 patients with bifurcation lesions, who sequentially had the main branch and then the side branch treated with a DIOR balloon, followed by provisional stenting of only the main branch using a BMS. At 4-month follow-up, there were no MACE events; however no angiographic data were reported (194). The second DEBIUT study was considerably larger; randomizing 120 patients, the majority of whom had side-branch involvement, to 1 of 3 treatment arms: BMS + plain balloon angioplasty (POBA), BMS + Dior DEB, or PES + POBA (197). All balloon inflations prior to stenting were performed in the main branch and side branch; all lesions were treated using the provisional T-stent technique, and post-stenting kissing balloon dilation was performed using a plain balloon. At 6-months angiographic follow-up, rates of main-branch binary restenosis were lowest (not significant) in those treated with the DEB. In the side branch, rates of binary restenosis and late loss were also numerically lower in the DEB arm compared with those treated with BMS + POBA; however, both measurements were inferior to those receiving PES. There were no overall significant differences in clinical outcomes between all 3 arms; notably, there were no ST events in the DEB and BMS arms compared with a rate of 2.5% in the PES arm.

   The PEPCAD V study enrolled 28 patients with bifurcation lesions, the majority of which were Medina class 011 or 111. Both branches were treated with the SeQuent Please, followed by provisional stenting of the main branch with a BMS; 14% of side branches eventually received a stent. At 9-month follow-up, although there were significant reductions in both main-branch and side-branch late lumen loss, and only 1 TLR, of concern were the 2 late ST events in patients receiving DEB and BMS in the main branch (195).

Overall, DEBs have been shown to be effective in ISR; however, the comparison with DES in de novo lesions has produced inconsistent results. Currently, no DEBs have FDA approval, and many issues remain to be resolved before these devices can become fully accepted by regulatory authorities.

Conclusions

The previous discussion highlights the wealth of new stent technology, and only time will tell which is the most appropriate design for the ideal coronary stent. It is clear that no single stent design and polymer type will be suitable for all patients and lesion types. Therefore, a more individualized choice of stent, taking into account patient characteristics such as the ability to take long-term DAPT, and lesion characteristics such as presence or not of a bifurcation lesion will be important factors influencing stent selection. Reassuringly, the new stent technology appears to allow interventional cardiologists to make these choices, and there is great anticipation that this will result in improved long-term clinical efficacy and safety.

Acknowledgments

The authors would like to thank (in alphabetic order): Davide Capodanno, MD, Nils le Cerf, Keith Dawkins, MD, Refat Jabara, MD, Susanne Meis, Matthew Pollman, MD, Richard Rapoza, PhD, Steve Rowland, PhD, Professor Corrado Tamburino, MD, Susan Veldhof, RN, and Professor Stephan Windecker, MD, who kindly reviewed some sections of this manuscript.

Reprint requests and correspondence: Prof. Patrick W. Serruys, Ba583a, Thoraxcenter, Erasmus Medical Center, 's-Gravendijkwal 230, 3015 CE Rotterdam, the Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl.

REFERENCES

1. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. Circulation 2007;115:1440–55.
2. Lagerqvist B, James SK, Stenestrand U, et al. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. N Engl J Med 2007;356:1009–19.
3. Nordmann AJ, Briel M, Bucher HC. Mortality in randomized controlled trials comparing drug-eluting vs. bare metal stents in coronary artery disease: a meta-analysis. Eur Heart J 2006;27:2784–814.
4. Garg S, Serruys PW. Benefits of and safety concerns associated with drug-eluting coronary stents. Expert Rev Cardiovasc Ther 2010;8:449–70.
5. Garg S, Serruys PW, Onuma Y, et al. Three year clinical follow up of the XIENCE V Everolimus eluting coronary stent system in the treatment of patients with de novo coronary artery lesions. The SPIRIT II Trial. J Am Coll Cardiol Intv 2009;2:1190–8.
6. Stone GW, Midei M, Newman W, et al. Randomized comparison of everolimus-eluting and paclitaxel-eluting stents: 2-year clinical follow-up from the Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions (SPIRIT) III trial. Circulation 2009;119:680–6.
7. Hamm C. 5 years later and more than 20,000 patients studied: the ENDEAVOR clinical program. Paper presented at: EuroPCR; May 19-22, 2009; Barcelona, Spain. Available at: http://www.pcronline.com/Lectures/2009/5-years-later-and-more-than-20-000-patients-studied-the-ENDEAVOR-clinical-programme. Accessed June 20, 2009.
8. Wilson GJ, Nakazawa G, Schwartz RS, et al. Comparison of inflammatory response after implantation of sirolimus- and paclitaxel-eluting stents in porcine coronary arteries. Circulation 2009;120:141–9, 1–2.
9. Finn AV, Kolodgie FD, Harnek J, et al. Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. Circulation 2005;112:270–8.
10. Finn AV, Nakazawa G, Joner M, et al. Vascular responses to drug eluting stents: importance of delayed healing. Arterioscler Thromb Vasc Biol 2007;27:1500–10.
11. Joner M, Nakazawa G, Finn AV, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. J Am Coll Cardiol 2008;52:333–42.
12. Niemela KO. Biodegradable coating for drug-eluting stents—more than a facelift? Eur Heart J 2008;29:1930–1.
13. Meredith IT, Worthley S, Whitbourn R, et al. Clinical and angiographic results with the next-generation Resolute stent system a prospective, multicenter, first-in-human trial. J Am Coll Cardiol Intv 2009;2:977–85.
14. Costa JR Jr., Abizaid A, Feres F, et al. EXCELLA First-in-Man (FIM) study: safety and efficacy of novolimus-eluting stent in de novo coronary lesions. EuroIntervention 2008;4:53–8.
15. Abizaid A, Costa JR Jr., Feres F, et al. TCT-429: single center, first-in-man study of the elixir novolimus eluting coronary stent system with durable polymer 24-month clinical safety and efficacy results (abstr). Am J Cardiol 2009;104:158D.
16. Kereiakes DJ, Cannon LA, Feldman RL, et al. Clinical and angiographic outcomes after treatment of de novo coronary stenoses with a novel platinum chromium thin-strut stent: primary results of the PERSEUS (Prospective Evaluation in a Randomized Trial of the Safety and Efficacy of the Use of the TAXUS Element Paclitaxel-Eluting Coronary Stent System) trial. J Am Coll Cardiol 2010;56:264–71.
17. Kereiakes D, Cannon LA, Feldman R, et al. TAXUS PERSEUS: a novel platinum chromium, thin-strut TAXUS Element stent for the treatment of de novo coronary stenoses. Paper presentet at: i2summit, American College of Cardiology; March 15, 2010; Atlanta, GA.
18. Meredith IT, Worthley S, Whitbourn R, et al. The next-generation Endeavor Resolute stent: 4-month clinical and angiographic results from the Endeavor Resolute first-in-man trial. EuroIntervention 2007;3:50–3.
19. Udipi K, Melder RJ, Chen M, et al. The next generation Endeavor Resolute stent: role of the BioLinx polymer system. EuroIntervention 2007;3:137–9.
20. Meredith I, Worthley S, Whitbourn R, et al. Long-term clinical outcomes with the next generation Resolute Stent System: a report of the 2-year follow-up from RESOLUTE clinical trial. EuroIntervention 2010;5:692–97.
21. TCT-414: Three-year follow-up of a new zotarolimus-eluting stent: results of the RESOLUTE first-in-man trial (abstr). Am J Cardiol 2009;104:153D–4D.
22. Serruys PW, Silber S, Garg S, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. N Engl J Med 2010;363:123–35.
23. Serruys PW, Garg S, Abizaid A, et al. A randomised comparison of novolimus-eluting and zotarolimus-eluting stents: 9-month results of the EXCELLA II study. EuroIntervention 2010;6:195–205.
24. Kastrati A, Mehilli J, Dirschinger J, et al. Intracoronary Stenting and Angiographic Results : Strut Thickness Effect on Restenosis Outcome (ISAR-STEREO) Trial. Circulation 2001;103:2816–21.
25. Pache J, Kastrati A, Mehilli J, et al. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO-2) trial. J Am Coll Cardiol 2003;41:1283–8.
26. Dani S, Kukreja N, Parikh P, et al. Biodegradable-polymer-based, sirolimus-eluting Supralimus stent: 6-month angiographic and 30-month clinical follow-up results from the series I prospective study. EuroIntervention 2008;4:59–63.
27. Han Y, Jing Q, Xu B, et al. Safety and efficacy of biodegradable polymer-coated sirolimus-eluting stents in "real-world" practice: 18-month clinical and 9-month angiographic outcomes. J Am Coll Cardiol Intv 2009;2:303–9.
28. Abizaid A. The NEVO RES Elution I study: a randomised multicenter comparison of the NEVO reservoir-based Sirolimus eluting-stent with the TAXUS Liberte Paclitaxel-eluting stent: first presentation of the 12-month outcomes. Paper presented at: EuroPCR; May 25–28, 2010; Paris, France. Available at: http://www.pcronline.com/Lectures/2010/The-NEVO-RES-Elution-I-study-a-randomised-multicentre-comparison-of-the-NEVO-reservoir-based-Sirolimus-eluting-stent-with-the-TAXUS-Liberte-Paclitaxel-eluting-stent-first-presentation-of-12-month-outcomes. Accessed May 29, 2010.
29. Garg S, Sarno G, Serruys PW, et al. The twelve-month outcomes of a biolimus eluting stent with a biodegradable polymer compared with a sirolimus eluting stent with a durable polymer. EuroIntervention 2010;6:233–9.
30. Windecker S, Serruys PW, Wandel S, et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet 2008;372:1163–73.
31. Chevalier B, Silber S, Park S-J, et al. Randomized comparison of the Nobori Biolimus A9-eluting coronary stent with the Taxus Liberte paclitaxel-eluting coronary stent in patients with stenosis in native coronary arteries: the NOBORI 1 trial—phase 2. Circ Cardiovasc Interv 2009;2:188–95.
32. Verheye S, Agostoni P, Dubois CL, et al. 9-month clinical, angiographic, and intravascular ultrasound results of a prospective evaluation of the Axxess self-expanding biolimus A9-eluting stent in coronary bifurcation lesions: the DIVERGE (Drug-Eluting Stent Intervention for Treating Side Branches Effectively) study. J Am Coll Cardiol 2009;53:1031–9.
33. Stella PR, Mueller R, Pavlakis G, et al. One year results of a new in situ length-adjustable stent platform with a biodegradable biolimus A9 eluting polymer: results of the CUSTOM-II trial. EuroIntervention 2008;4:200–7.
34. Grube E. Custom clinical program. Paper presented at: EuroPCR; May 13–16, 2008; Barcelona, Spain. Available at: http://www.europcronline.com/fo/lecture/view_slide.php?idCongres=4&id=5514. Accessed June 18, 2009.
35. Dawkins KD. The Element stent technology. Paper presented at: EuroPCR; May 25-28, 2010; Paris, France. Available at: http://

www.pcronline.com/Lectures/2010/The-ELEMENT-stent-technology. Accessed May 29, 2010.
36. Grube E. Bioabsorbable stent. The Boston Scientific and REVA technology. Paper presented at: EuroPCR; May 19–22, 2009; Barcelona, Spain. Available at: http://www.pcronline.com/Lectures/2009/The-Boston-Scientific-technology. Accessed June 10, 2009.
37. Granada JF. The Orbus-Neich EPC-coated bioabsorbable polymer sirolimus-eluting stent program. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 21, 2009; San Francisco, CA. Available at: http://www.tctmd.com/txshow.aspx?tid=939086&id=84030&trid=938634. Accessed October 13, 2009.
38. Rutsch W. Multi-center first-in-man study with the lowest known limus dose on the Elixir Medical myolimus eluting coronary stent system with a durable polymer: nine month clinical and six month angiographic and IVUS follow-up. Paper presented at: EuroPCR; May 19–22, 2009; Barcelona, Spain.
39. Lemos PA, Moulin B, Perin MA, et al. Randomized evaluation of 2 drug-eluting stents with identical metallic platform and biodegradable polymer but different agents (paclitaxel or sirolimus) compared against bare stents: 1-year results of the PAINT trial. Catheter Cardiovasc Interv 2009;74:665–73.
40. Vranckx P, Serruys PW, Gambhir S, et al. Biodegradable-polymer-based, paclitaxel-eluting Infinnium stent: 9-Month clinical and angiographic follow-up results from the SIMPLE II prospective multi-centre registry study. EuroIntervention 2006;2:310–7.
41. Grube E, Schofer J, Hauptmann KE, et al. A novel paclitaxel-eluting stent with an ultrathin abluminal biodegradable polymer 9-month outcomes with the JACTAX HD stent. J Am Coll Cardiol Intv 2010;3:431–8.
42. Waksman R, Pakala R. Coating bioabsorption and chronic bare metal scaffolding versus fully bioabsorbable stent. EuroIntervention 2009;5 Suppl F:F36–42.
43. De Jong WH, Eelco Bergsma J, Robinson JE, Bos RR. Tissue response to partially in vitro predegraded poly-L-lactide implants. Biomaterials 2005;26:1781–91.
44. Costa RA. Complex patients with coronary artery disease treated with the novel supralimus sirolimus-eluting stents: preliminary results of the prospective, multicentre, non-randomised E-Series trial. Paper presented at: EuroPCR; May 19-22, 2009; Barcelona, Spain. Available at: http://www.pcronline.com/Lectures/2009/Complex-patients-with-coronary-artery-disease-treated-with-the-novel-supralimus-sirolimus-eluting-stents-preliminary-results-of-the-prospective-multicentre-non-randomised-E-Series-trial. Accessed June 10, 2009.
45. Serruys PW, Sianos G, Abizaid A, et al. The effect of variable dose and release kinetics on neointimal hyperplasia using a novel paclitaxel-eluting stent platform: the Paclitaxel In-Stent Controlled Elution Study (PISCES). J Am Coll Cardiol 2005;46:253–60.
46. Kaul U, Gupta RK, Mathur A, et al. Cobalt chromium stent with antiproliferative for restenosis trial in India (COSTAR I). Indian Heart J 2007;59:165–72.
47. Dawkins KD, Verheye S, Schuhlen H, et al. The European cobalt STent with Antiproliferative for Restenosis trial (EuroSTAR): 12 month results. EuroIntervention 2007;3:82–8.
48. Krucoff MW, Kereiakes DJ, Petersen JL, et al. A novel bioresorbable polymer paclitaxel-eluting stent for the treatment of single and multivessel coronary disease: primary results of the COSTAR (Cobalt Chromium Stent With Antiproliferative for Restenosis) II study. J Am Coll Cardiol 2008;51:1543–52.
49. Klauss V. LEADERS: two-year follow-up from a prospective randomized trial of Biolimus A9-eluting stents with a bioabsorbable polymer vs. sirolimus-eluting stents with a durable polymer. Paper presented at: Transcatheter Cardiovascular Therapeutics, September 22, 2009; San Francisco, CA.
50. Barlis P, Regar E, Serruys PW, et al. An optical coherence tomography study of a biodegradable vs. durable polymer-coated limus-eluting stent: a LEADERS trial sub-study. Eur Heart J 2010;31:165–76.
51. Ostojic M, Sagic D, Beleslin B, et al. First clinical comparison of Nobori Biolimus A9 eluting stents with Cypher sirolimus eluting stents: Nobori Core nine months angiographic and one year clinical outcomes. EuroIntervention 2008;3:574–9.
52. Hamilos MI, Ostojic M, Beleslin B, et al. Differential effects of drug-eluting stents on local endothelium-dependent coronary vasomotion. J Am Coll Cardiol 2008;51:2123–9.
53. Hamilos M, Sarma J, Ostojic M, et al. Interference of drug-eluting stents with endothelium-dependent coronary vasomotion: evidence for device-specific responses. Circ Cardiovasc Interv 2008;1:193–200.
54. Chevalier B. The NOBORI biolimus-eluting stent: comprehensive update of the clinical trial program. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 21, 2009; San Francisco, CA. Available at: http://www.tctmd.com/txshow.aspx?tid=939082&id=84010&trid=938634. Accessed November 29, 2009.
55. Grube E, Buellesfeld L, Neumann FJ, et al. Six-month clinical and angiographic results of a dedicated drug-eluting stent for the treatment of coronary bifurcation narrowings. Am J Cardiol 2007;99:1691–7.
56. Schofer J. Multicentre, first-in-man study on the Elixir Myolimus-eluting coronary stent system with bioabsorbable polymer: 12-month clinical and angiographic/IVUS results. Paper presented at: EuroPCR; May 25–28, 2010; Paris, France. Available at: http://www.pcronline.com/Lectures/2010/Multicentre-first-in-man-study-on-the-Elixir-Myolimus-eluting-coronary-stent-system-with-bioabsorbable-polymer-12-month-clinical-and-angiographic-IVUS-results. Accessed May 29, 2010.
57. Guagliumi G, Sirbu V, Musumeci G, et al. Strut coverage and vessel wall response to a new-generation paclitaxel-eluting stent with an ultrathin biodegradable abluminal polymer: Optical Coherence Tomography Drug-Eluting Stent Investigation (OCTDESI). Circ Cardiovasc Interv 2010 July 22 [E-pub ahead of print].
58. Turco MA, Ormiston JA, Popma JJ, et al. Polymer-based, paclitaxel-eluting TAXUS Liberte stent in de novo lesions: the pivotal TAXUS ATLAS trial. J Am Coll Cardiol 2007;49:1676–83.
59. Basalus MW, Ankone MJ, van Houwelingen GK, de Man FH, von Birgelen C. Coating irregularities of durable polymer-based drug-eluting stents as assessed by scanning electron microscopy. EuroIntervention 2009;5:157–65.
60. Otsuka Y, Chronos NA, Apkarian RP, Robinson KA. Scanning electron microscopic analysis of defects in polymer coatings of three commercially available stents: comparison of BiodivYsio, Taxus and Cypher stents. J Invasive Cardiol 2007;19:71–6.
61. Dibra A, Kastrati A, Mehilli J, et al. Influence of stent surface topography on the outcomes of patients undergoing coronary stenting: a randomized double-blind controlled trial. Catheter Cardiovasc Interv 2005;65:374–80.
62. Abizaid A. PAX A trial (Amazonia PAX versus TAXUS Liberté): 4-month follow-up: IVUS and optical coherence tomography evaluation. Paper presented at: EuroPCR; May 25–28, 2010; Paris, France. Available at: http://www.pcronline.com/Lectures/2010/PAX-A-trial-Amazonia-PAX-versus-TAXUS-Liberte-4-month-follow-up-IVUS-and-optical-coherence-tomography-evaluation. Accessed May 29, 2010.
63. Grube E. BioFreedom First In Man progress report. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 24, 2009; San Francisco, CA. Available at: http://www.tctmd.com/txshow.aspx?tid=941378&id=84088&trid=938634. Accessed November 10, 2009.
64. Costa JR, Jr., Abizaid A, Costa R, et al. 1-Year results of the hydroxyapatite polymer-free sirolimus-eluting stent for the treatment of single de novo coronary lesions: the VESTASYNC I Trial. J Am Coll Cardiol Intv 2009;2:422–7.
65. Mehilli J, Kastrati A, Wessely R, et al. Randomized trial of a nonpolymer-based rapamycin-eluting stent versus a polymer-based paclitaxel-eluting stent for the reduction of late lumen loss. Circulation 2006;113:273–9.
66. Wessely R, Hausleiter J, Michaelis C, et al. Inhibition of neointima formation by a novel drug-eluting stent system that allows for dose-adjustable, multiple, and on-site stent coating. Arterioscler Thromb Vasc Biol 2005;25:748–53.
67. Hausleiter J, Kastrati A, Wessely R, et al. Prevention of restenosis by a novel drug-eluting stent system with a dose-adjustable, polymer-free, on-site stent coating. Eur Heart J 2005;26:1475–81.
68. Moore P, Barlis P, Spiro J, et al. A randomized optical coherence tomography study of coronary stent strut coverage and luminal protrusion with rapamycin-eluting stents. J Am Coll Cardiol Intv 2009;2:437–44.

69. Ruef J, Storger H, Schwarz F, Haase J. Comparison of a polymer-free rapamycin-eluting stent (YUKON) with a polymer-based paclitaxel-eluting stent (TAXUS) in real-world coronary artery lesions. Catheter Cardiovasc Interv 2008;71:333–9.
70. Byrne RA, Iijima R, Mehilli J, et al. Durability of antirestenotic efficacy in drug-eluting stents with and without permanent polymer. J Am Coll Cardiol Intv 2009;2:291–9.
71. Claessen BE, Beijk MA, Legrand V, et al. Two-year clinical, angiographic, and intravascular ultrasound follow-up of the XIENCE V Everolimus-Eluting Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions: the SPIRIT II trial. Circ Cardiovasc Interv 2009;2:339–47.
72. Raber L. SIRTAX-LATE: five-year clinical and angiographic follow-up from a prospective randomized trial of sirolimus-eluting and paclitaxel-eluting stents. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 22, 2009; San Francisco, CA.
73. Aoki J, Abizaid AC, Ong AT, Tsuchida K, Serruys PW. Serial assessment of tissue growth inside and outside the stent after implantation of drug-eluting stent in clinical trials. Does delayed neointimal growth exist? EuroIntervention 2005;1:235–55.
74. Leon M. The ENDEAVOR and ENDEAVOR Resolute zotarolimus-eluting stent: comprehensive update of the clinical trial program (featuring the first presentation of the ENDEAVOR IV 3-year results). Paper presented at: Transcatheter Cardiovascular Therapeutics; September 21, 2009; San Francisco, CA. Available at: http://www.tctmd.com/txshow.aspx?tid=939082&id=84004&trid=938634. Accessed October 28, 2009.
75. Tada N, Virmani R, Grant G, et al. Polymer-free biolimus a9-coated stent demonstrates more sustained intimal inhibition, improved healing, and reduced inflammation compared with a polymer-coated sirolimus-eluting cypher stent in a porcine model. Circ Cardiovasc Interv 2010;3:174–83.
76. Virmani R. Are polymer-free DES safer? Observations from experimental studies in animal models. Paper presented at: Transcatheter Therapeutics; September 21, 2009; San Francisco, CA.
77. van der Giessen WJ, Sorop O, Serruys PW, Peters-Krabbendam I, van Beusekom HMM. Lowering the dose of sirolimus, released from a nonpolymeric hydroxyapatite coated coronary stent, reduces signs of delayed healing. J Am Coll Cardiol Intv 2009;2:284–90.
78. Abizaid A. The MIV VESTASYNC polymer-free sirolimus-eluting stent program (micorporous hydroxyapatite surface). Paper presented at: Transcatheter Cardiovascular Therapeutics; September 21, 2009; San Francisco, CA. Available at: http://www.tctmd.com/txshow.aspx?tid=939088&id=84036&trid=938634. Accessed October 10, 2009.
79. Fajadet J. The Minvasys Amazonia Pax & Nile Pax polymer free paclitaxel eluting stent programme. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 21, 2009; San Francisco, CA. Available at: http://www.tctmd.com/txshow.aspx?tid=939088&id=84034&trid=938634. Accessed October 10, 2009.
80. Mehilli J, Byrne RA, Wieczorek A, et al. Randomized trial of three rapamycin-eluting stents with different coating strategies for the reduction of coronary restenosis. Eur Heart J 2008;29:1975–82.
81. Byrne RA, Kufner S, Tiroch K, et al. Randomised trial of three rapamycin-eluting stents with different coating strategies for the reduction of coronary restenosis: 2-year follow-up results. Heart 2009;95:1489–94.
82. Byrne RA, Mehilli J, Iijima R, et al. A polymer-free dual drug-eluting stent in patients with coronary artery disease: a randomized trial vs. polymer-based drug-eluting stents. Eur Heart J 2009;30:923–31.
83. Byrne RA, Kastrati A, Tiroch K, et al. 2-year clinical and angiographic outcomes from a randomized trial of polymer-free dual drug-eluting stents versus polymer-based Cypher and Endeavor, drug-eluting stents. J Am Coll Cardiol 2010;55:2536–43.
84. Tardif JC, Cote G, Lesperance J, et al. Probucol and multivitamins in the prevention of restenosis after coronary angioplasty. Multivitamins and Probucol Study Group. N Engl J Med 1997;337:365–72.
85. Tamburino C, La Manna A, Di Salvo ME, et al. First-in-man 1-year clinical outcomes of the Catania coronary stent system with nanothin Polyzene-F in de novo native coronary artery lesions: the ATLANTA (Assessment of The LAtest Non-Thrombogenic Angioplasty stent) trial. J Am Coll Cardiol Intv 2009;2:197–204.
86. Windecker S, Simon R, Lins M, et al. Randomized comparison of a titanium-nitride-oxide-coated stent with a stainless steel stent for coronary revascularization: the TiNOX trial. Circulation 2005;111:2617–22.
87. Beijk MA, Klomp M, Verouden N, et al. Genous endothelial progenitor cell capturing stent versus the Taxus Liberte stent in patients with de novo coronary lesions with a high-risk of coronary restenosis: a randomised, single-centre, pilot study. Eur Heart J 2010;31:1055–64.
88. La Manna A, Capodanno D, Cera M, et al. Optical coherence tomographic results at six-month follow-up evaluation of the CATANIA coronary stent system with nanothin Polyzene-F surface modification (from the Assessment of The LAtest Non-Thrombogenic Angioplasty Stent [ATLANTA] trial). Am J Cardiol 2009;103:1551–5.
89. La Manna A, Sanfilippo A, Di Salvo ME, et al. Short and mid-term benefits of CATANIA stent in acute coronary syndromes [abstract]. Am J Cardiol 2009;104:111D.
90. La Manna A, Sanfilippo A, Di Salvo ME, et al. One-year outcomes of CATANIA coronary stent system with nanothin polyzene-F in a real-world unselected population: assessment of the latest non-thrombogenic angioplasty stent 2 (Atlanta-2) study. Paper presented at: EuroPCR; May 25-28, 2010; Paris, France.
91. Moschovitis A, Simon R, Seidenstucker A, et al. Randomised comparison of titanium-nitride-oxide coated stents with bare metal stents: five year follow-up of the TiNOX trial. EuroIntervention 2010;6:63–8.
92. Karjalainen PP, Ylitalo A, Niemela M, et al. Two-year follow-up after percutaneous coronary intervention with titanium-nitride-oxide-coated stents versus paclitaxel-eluting stents in acute myocardial infarction. Ann Med 2009;41:599–607.
93. Karjalainen PP, Annala AP, Ylitalo A, Vahlberg T, Airaksinen KE. Long-term clinical outcome with titanium-nitride-oxide-coated stents and paclitaxel-eluting stents for coronary revascularization in an unselected population. Int J Cardiol 2009 Apr 27 [E-pub ahead of print].
94. Windecker S. Randomized comparison of titanium-nitride-oxide-coated stents with zotarolimus-eluting stents for coronary revascularisation. Paper presented at: EuroPCR; May 25-28, 2010, Paris, France. Available at: http://www.pcronline.com/Lectures/2010/Comparison-of-titanium-nitride-oxide-coated-stents-with-Zotarolimus-eluting-stents-for-coronary-revascularisation-TIDE-a-randomised-controlled-trial. Accessed May 29, 2010.
95. Inoue T, Sata M, Hikichi Y, et al. Mobilization of CD34-positive bone marrow-derived cells after coronary stent implantation: impact on restenosis. Circulation 2007;115:553–61.
96. Garg S, Duckers HJ, Serruys PW. Endothelial progenitor cell capture stents: will this technology find its niche in contemporary practice? Eur Heart J 2010;31:1032–5.
97. Aoki J, Serruys PW, van Beusekom H, et al. Endothelial progenitor cell capture by stents coated with antibody against CD34: the HEALING-FIM (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth-First In Man) Registry. J Am Coll Cardiol 2005;45:1574–9.
98. Duckers HJ, Silber S, de Winter R, et al. Circulating endothelial progenitor cells predict angiographic and intravascular ultrasound outcome following percutaneous coronary interventions in the HEALING-II trial: evaluation of an endothelial progenitor cell capturing stent. EuroIntervention 2007;3:67–75.
99. Duckers H, Onuma Y, Benit E, et al. Final results of the HEALING 2B Trial to evaluate a bioengineered CD34 antibody coated stent (Genous Stent) designed to promote vascular healing by capture of circulating endothelial progenitor cells in CAD patients. Paper presented at: American Heart Association Scientific Sessions; November 8–12, 2008; Orlando, FL.
100. Beijk M. Two year follow-up of the endothelial progenitor cell capturing stent versus a paclitaxel-eluting stent in patients with de novo coronary lesions with a high-risk of coronary restenosis: the single-centre randomised TRIAS study. Paper presented at: EuroPCR 2009; May 19-22, 2009; Barcelona, Spain.
101. Winter Rd. Can a pro-healing stent make a difference? Final 12-month outcomes from the e-HEALING 5,000 patient registry using the EPC-coated Genous stent. Paper presented at: Transcath-

eter Cardiovascular Therapeutics; September 22, 2009; San Francisco, CA.
102. Granada JF, Inami S, Aboodi MS, et al. Development of a novel prohealing stent designed to deliver sirolimus from a biodegradable abluminal matrix. Circ Cardiovasc Interv 2010;3:257–66.
103. Ellis SG, Popma JJ, Lasala JM, et al. Relationship between angiographic late loss and target lesion revascularization after coronary stent implantation: analysis from the TAXUS-IV trial. J Am Coll Cardiol 2005;45:1193–200.
104. Spuentrup E, Ruebben A, Mahnken A, et al. Artifact-free coronary magnetic resonance angiography and coronary vessel wall imaging in the presence of a new, metallic, coronary magnetic resonance imaging stent. Circulation 2005;111:1019–26.
105. Ormiston JA, Serruys PWS. Bioabsorbable coronary stents. Circ Cardiovasc Interv 2009;2:255–60.
106. Pietrzak WS, Sarver DR, Verstynen ML. Bioabsorbable polymer science for the practicing surgeon. J Craniofac Surg 1997;8:87–91.
107. Waksman R. Biodegradable stents: they do their job and disappear. J Invasive Cardiol 2006;18:70–4.
108. van der Giessen WJ, Lincoff AM, Schwartz RS, et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. Circulation 1996; 94:1690–7.
109. Tamai H, Igaki K, Kyo E, et al. Initial and 6-month results of biodegradable poly-l-lactic acid coronary stents in humans. Circulation 2000;102:399–404.
110. Nishio S, Kosuga K, Okada M, et al. Long-term (>10 years) clinical outcomes of first-in-man biodegradable poly-l-lactic acid coronary stents. Paper presented at: EuroPCR; May 25-28, 2010; Paris, France.
111. Tsuji T, Tamai H, Igaki K, et al. Four-year follow-up of the biodegradable stent (IGAKI-TAMAI stent). Circ J 2004;68:135.
112. Ormiston JA, Serruys PW, Regar E, et al. A bioabsorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions (ABSORB): a prospective open-label trial. Lancet 2008;371:899–907.
113. Serruys PW, Ormiston JA, Onuma Y, et al. A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. Lancet 2009;373: 897–910.
114. Serruys PW. ABSORB Cohort B trial: 6-month clinical and imaging results of the evaluation of the bioresorbable everolimus-eluting vascular scaffold (BVS) in the treatment of patients with de novo native coronary artery lesions. Paper presented at: EuroPCR; May 25–28, 2010; Paris, France. Available at: http://www.pcronline.com/Lectures/2010/ABSORB-Cohort-B-trial-6-month-clinical-and-imaging-results-of-the-evaluation-of-the-bioresorbable-Everolimus-eluting-vascular-scaffold-BVS-in-the-treatment-of-patients-with-de-novo-native-coronary-artery-lesions. Accessed May 29, 2010.
115. Jabara R. Poly-anhydride based on salicylic acid and adipic acid anhydride. Paper presented at: EuroPCR; May 19–22, 2009; Barcelona, Spain. Available at: http://www.pcronline.com/Lectures/2009/Poly-anhydride-based-on-salicylic-acid-and-adipic-acid-anhydride. Accessed June 11, 2009.
116. Erbel R, Di Mario C, Bartunek J, et al. Temporary scaffolding of coronary arteries with bioabsorbable magnesium stents: a prospective, non-randomised multicentre trial. Lancet 2007;369:1869–75.
117. Onuma Y, Garg S, Okamura T, et al. Ten-year follow-up of the IGAKI-TAMAI stent. A post-humous tribute to the scientific work of Dr. Hideo Tamai. EuroIntervention 2009;5 Suppl F:F109–11.
118. Douek PC, Correa R, Neville R, et al. Dose-dependent smooth muscle cell proliferation induced by thermal injury with pulsed infrared lasers. Circulation 1992;86:1249–56.
119. Post MJ, de Graaf-Bos AN, van Zanten HG, de Groot PG, Sixma JJ, Borst C. Thrombogenicity of the human arterial wall after interventional thermal injury. J Vasc Res 1996;33:156–63.
120. Yamawaki T, Shimokawa H, Kozai T, et al. Intramural delivery of a specific tyrosine kinase inhibitor with biodegradable stent suppresses the restenotic changes of the coronary artery in pigs in vivo. J Am Coll Cardiol 1998;32:780–6.
121. Vogt F, Stein A, Rettemeier G, et al. Long-term assessment of a novel biodegradable paclitaxel-eluting coronary polylactide stent. Eur Heart J 2004;25:1330–40.
122. Tanimoto S, Serruys PW, Thuesen L, et al. Comparison of in vivo acute stent recoil between the bioabsorbable everolimus-eluting coronary stent and the everolimus-eluting cobalt chromium coronary stent: insights from the ABSORB and SPIRIT trials. Catheter Cardiovasc Interv 2007;70:515–23.
123. ABBOTT V. ABSORB trial investigator brochure. Santa Clara, CA: ABBOTT Vascular, 2006.
124. Ormiston JA, Webster MW, Armstrong G. First-in-human implantation of a fully bioabsorbable drug-eluting stent: the BVS poly-L-lactic acid everolimus-eluting coronary stent. Catheter Cardiovasc Interv 2007;69:128–31.
125. Onuma Y, Serruys PW, Ormiston JA, et al. Three-year results of clinical follow-up after a bioresorbable everolimus-eluting scaffold in patients with de novo coronary artery disease: the ABSORB trial. EuroIntervention 2010 June 6 [E-pub ahead of print].
126. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221–31.
127. Serruys PW, Ong ATL, Piek JJ, et al. A randomised comparison of a durable polymer everolimus-eluting stent with a bare metal coronary stent: the SPIRIT First trial. EuroIntervention 2005;1:58–65.
128. Serruys PW, Ruygrok P, Neuzner J, et al. A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent: the SPIRIT II trial. EuroIntervention 2006;2:286–94.
129. Sarno G, Onuma Y, Garcia HM, et al. IVUS radiofrequency analysis in the evaluation of the polymeric struts of the bioabsorbable everolimus-eluting device during the bioabsorption process. Catheter Cardiovasc Interv 2010;75:914–8.
130. Garcia-Garcia HM, Gonzalo N, Pawar R, et al. Assessment of the absorption process following bioabsorbable everolimus-eluting stent implantation: temporal changes in strain values and tissue composition using intravascular ultrasound radiofrequency data analysis. A substudy of the ABSORB clinical trial. EuroIntervention 2009;4: 443–8.
131. Okamura T, Garg S, Gutierrez-Chico JL, et al. In-vivo evaluation of stent strut distribution patterns in the bioabsorbable everolimus-eluting device: an OCT ad hoc analysis of the Revision 1.0 and Revision 1.1 stent design in the ABSORB clinical trial. EuroIntervention 2010;5:932–8.
132. Pollman MJ. Engineering a bioresorbable stent: REVA programme update. EuroIntervention 2009;5 Suppl F:F54–7.
133. Abizaid A. The REVA tyrosine polycarbonate bioabsorbable stent: lessons learned and future directions. Paper presented at: Transcatheter Therapeutics, September 22, 2009; San Francisco, CA. Available at: http://www.tctmd.com/txshow.aspx?tid=939090&id=84050&trid=938634. Accessed October 14, 2009.
134. Jabara R, Chronos N, Robinson K. Novel bioabsorbable salicylate-based polymer as a drug-eluting stent coating. Catheter Cardiovasc Interv 2008;72:186–94.
135. Lafont A, Durand E. A.R.T.: concept of a bioresorbable stent without drug elution. EuroIntervention 2009;5 Suppl F:F83–7.
136. Yan J, Bhat V. Elixir Medical's bioresorbable drug eluting stent programme: an overview. EuroIntervention 2009;5 Suppl F:F80–2.
137. Cottone R, Thatcher GL, Paker S, et al. Orbus Neich fully absorbable coronary stent platform incorporating dual partitioned coatings. EuroIntervention 2009;5 Suppl F:F65–71.
138. Waksman R, Pakala R, Kuchulakanti PK, et al. Safety and efficacy of bioabsorbable magnesium alloy stents in porcine coronary arteries. Catheter Cardiovasc Interv 2006;68:607–17; discussion 618–9.
139. Heublein B, Rohde R, Kaese V, Niemeyer M, Hartung W, Haverich A. Biocorrosion of magnesium alloys: a new principle in cardiovascular implant technology? Heart 2003;89:651–6.
140. Waksman R, Erbel R, Di Mario C, et al. Early- and long-term intravascular ultrasound and angiographic findings after bioabsorbable magnesium stent implantation in human coronary arteries. J Am Coll Cardiol Intv 2009;2:312–20.
141. Waksman R. Current state of the absorbable metallic (magnesium) stent. EuroIntervention 2009;5 Suppl F:F94–8.
142. Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med 1987;316:701–6.
143. Hirayama A, Kodama K, Adachi T, et al. Angiographic and clinical outcome of a new self-expanding intracoronary stent (RADIUS):

results from multicenter experience in Japan. Catheter Cardiovasc Interv 2000;49:401–7.
144. Konig A, Schiele TM, Rieber J, Theisen K, Mudra H, Klauss V. Stent design-related coronary artery remodeling and patterns of neointima formation following self-expanding and balloon-expandable stent implantation. Catheter Cardiovasc Interv 2002;56: 478–86.
145. Joner M, Nakazawa G, Bonsignore C, et al. Histopathologic evaluation of nitinol self-expanding stents in an animal model of advanced atherosclerotic lesions. EuroIntervention 2010;5:737–44.
146. Tanaka N, Martin JB, Tokunaga K, et al. Conformity of carotid stents with vascular anatomy: evaluation in carotid models. AJNR Am J Neuroradiol 2004;25:604–7.
147. Kaneda H, Ikeno F, Lyons J, Rezaee M, Yeung AC, Fitzgerald PJ. Long-term histopathologic and IVUS evaluations of a novel coiled sheet stent in porcine carotid arteries. Cardiovasc Intervent Radiol 2006;29:413–9.
148. Hermiller J. The TriReme Medical Antares sidebranch access stent: design specifications and clinical trial results. Paper presented at Transcatheter Cardiovascular Therapeutics; September 21, 2009; San Francisco, CA. Available at: http://www.tctmd.com/txshow.aspx?tid=938900&id=83226&trid=938634. Accessed November 12, 2009.
149. Lefevre T. Invatec twin rail bifurcation stent. Paper presented at: Transcatheter Cardiovascular Therapeutics; October 17–21, 2005; Washington, DC. Available at: http://www.tctmd.com/Show.aspx?id=68990. Accessed November 12, 2009.
150. Lefevre T, Ormiston J, Guagliumi G, et al. The Frontier stent registry: safety and feasibility of a novel dedicated stent for the treatment of bifurcation coronary artery lesions. J Am Coll Cardiol 2005;46:592–8.
151. Van Geuns RJ. The Minvasys Nile paclitaxel-eluting sidebranch access stent: results from the BiPAX study. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 21, 2009; San Francisco, CA.
152. Costa RA. BIPAX bifurcation study: first results. Paper presented at: EuroPCR; May 25-28, 2010; Paris, France. Available at: http://www.pcronline.com/Lectures/2010/Bipax-bifurcation-study-first-results. Accessed May 29, 2010.
153. Ormiston J, Webster M, El-Jack S, McNab D, Plaumann SS. The AST petal dedicated bifurcation stent: first-in-human experience. Catheter Cardiovasc Interv 2007;70:335–40.
154. Ormiston J, Lefevre T, Grube E, Allocco D, Dawkins KD. First Human Use of the TAXUS Petal Paclitaxel-Eluting Bifurcation Stent. EuroIntervention 2010;6:46–53.
155. Solar RJ. The Y Med sidekick stent delivery system for the treatment of coronary bifurcation and ostial lesions. Paper presented at: Cardiovascular Revascularization Therapies; March 8, 2007; Washington, DC. Available at: http://www.crtonline.org/flash.aspx?PAGE_ID=4328. Accessed November 12, 2009.
156. Ikeno F, Kim YH, Luna J, et al. Acute and long-term outcomes of the novel side access (SLK-View) stent for bifurcation coronary lesions: a multicenter nonrandomized feasibility study. Catheter Cardiovasc Interv 2006;67:198–206.
157. Onuma Y, Muller R, Ramcharitar S, et al. Tryton I, First-In-Man (FIM) study: six month clinical and angiographic outcome, analysis with new quantitative coronary angiography dedicated for bifurcation lesions. EuroIntervention 2008;3:546–52.
158. Doi H, Maehara A, Mintz GS, Dani L, Leon MB, Grube E. Serial intravascular ultrasound analysis of bifurcation lesions treated using the novel self-expanding sideguard side-branch stent. Am J Cardiol 2009;104:1216–21.
159. Hauptman K. Bifurcation management using Cappella technology. Paper presented at: EuroPCR; May 25-28, 2010; Paris, France. Available at: http://www.pcronline.com/index.php/Lectures/2010/Bifurcation-management-using-Cappella-technology. Accessed May 30, 2010.
160. Verheye S, Grube E, Ramcharitar S, et al. First-in-man (FIM) study of the Stentys bifurcation stent—30 days results. EuroIntervention 2009;4:566–71.
161. Verheye S. The Stentys self-expanding stent: design specification and clinical trial results. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 21, 2009; San Francisco, CA. Available at: http://www.tctmd.com/txshow.aspx?tid=938900&id=83230&trid=938634. Accessed November 14, 2009.
162. Abizaid A, de Ribamar Costa J Jr., Alfaro VJ, et al. Bifurcated stents: giving to Caesar what is Caesar's. EuroIntervention 2007;2:518–25.
163. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol 2000;20:1262–75.
164. Farb A, Burke AP, Kolodgie FD, Virmani R. Pathological mechanisms of fatal late coronary stent thrombosis in humans. Circulation 2003;108:1701–6.
165. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193–202.
166. Granada JF, Pomeranz M, Heringes J, Odess I. vProtect luminal shield system. EuroIntervention 2007;3:416–9.
167. Ramcharitar S, Gonzalo N, van Geuns RJ, et al. First case of stenting of a vulnerable plaque in the SECRITT I trial-the dawn of a new era? Nat Rev Cardiol 2009;6:374–8.
168. Chamie D, Costa JR Jr., Abizaid A, et al. Serial angiography and intravascular ultrasound: results of the SISC Registry (Stents In Small Coronaries). J Am Coll Cardiol Intv 2010;3:191–202.
169. Abizaid A. CardioMind stent. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 24, 2009; San Francisco, CA. Available at: http://www.tctmd.com/txshow.aspx?tid=939038&id=81898&trid=938634. Accessed January 26, 2010.
170. Botelho R. The CARDIOMIND Sparrow DES program (CARE II): a bioabsorbable polymer sirolimus-eluting "micro-stent." Paper presented at: Transcatheter Cardiovascular Therapeutics; September 21, 2009; San Francisco, CA. Available at: http://www.tctmd.com/txshow.aspx?tid=939086&&id=84612&trid=938634. Accessed October 16, 2009.
171. Latib A, Colombo A, Sangiorgi GM. Bifurcation stenting: current strategies and new devices. Heart 2009;95:495–504.
172. Pan M, de Lezo JS, Medina A, et al. Rapamycin-eluting stents for the treatment of bifurcated coronary lesions: a randomized comparison of a simple versus complex strategy. Am Heart J 2004; 148:857–64.
173. Colombo A, Moses JW, Morice MC, et al. Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. Circulation 2004;109:1244–9.
174. Jensen JS, Galløe A, Lassen JF, et al. Safety in simple versus complex stenting of coronary artery bifurcation lesions. The nordic bifurcation study 14-month follow-up results. EuroIntervention 2008;4:229.
175. Hildick-Smith D, de Belder AJ, Cooter N, et al. Randomized trial of simple versus complex drug-eluting stenting for bifurcation lesions: the British Bifurcation Coronary Study: old, new, and evolving strategies. Circulation 2010;121:1235–43.
176. Colombo A, Bramucci E, Sacca S, et al. Randomized study of the crush technique versus provisional side-branch stenting in true coronary bifurcations: the CACTUS (Coronary Bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents) study. Circulation 2009;119:71–8.
177. Brar S, Gray W, Dangas G, et al. Bifurcation stenting with drug-eluting stents: a meta-analysis. EuroIntervention 2009;5: 475–84.
178. Zhang F, Dong L, Ge J. Simple versus complex stenting strategy for coronary artery bifurcation lesions in the drug-eluting stent era: a meta-analysis of randomized trials. Heart 2009;95:1676–81.
179. Katritsis DG, Siontis GCM, Ioannidis JPA. Double versus single stenting for coronary bifurcation lesions: a meta-analysis. Circ Cardiovasc Intervent 2009;2:409–15.
180. Erglis A, Kumsars I, Niemela M, et al. Randomized comparison of coronary bifurcation stenting with the crush versus the culotte technique using sirolimus eluting stents: the Nordic Stent Technique study. Circ Cardiovasc Interv 2009;2:27–34.
181. Ge L, Iakovou I, Cosgrave J, et al. Treatment of bifurcation lesions with two stents: one year angiographic and clinical follow up of crush versus T stenting. Heart 2006;92:371–6.
182. Yamashita T, Nishida T, Adamian MG, et al. Bifurcation lesions: two stents versus one stent—immediate and follow-up results. J Am Coll Cardiol 2000;35:1145–51.

183. Axel DI, Kunert W, Goggelmann C, et al. Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery. Circulation 1997;96:636–45.
184. Herdeg C, Oberhoff M, Baumbach A, et al. Local paclitaxel delivery for the prevention of restenosis: biological effects and efficacy in vivo. J Am Coll Cardiol 2000;35:1969–76.
185. Mori T, Kinoshita Y, Watanabe A, Yamaguchi T, Hosokawa K, Honjo H. Retention of paclitaxel in cancer cells for 1 week in vivo and in vitro. Cancer Chemother Pharmacol 2006;58:665–72.
186. Scheller B, Hehrlein C, Bocksch W, et al. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. N Engl J Med 2006;355:2113–24.
187. Scheller B, Hehrlein C, Bocksch W, et al. Two year follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. Clin Res Cardiol 2008;97:773–81.
188. Unverdorben M, Vallbracht C, Cremers B, et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. Circulation 2009;119:2986–94.
189. Maier LS, Maack C, Ritter O, Bohm M. Hotline update of clinical trials and registries presented at the German Cardiac Society meeting 2008. (PEPCAD, LokalTax, INH, German ablation registry, German device registry, DES.DE registry, DHR, Reality, SWEETHEART registry, ADMA, GERSHWIN). Clin Res Cardiol 2008;97:356–63.
190. Hamm C. Paclitaxel-eluting PTCA-balloon in combination with the Coroflex Blue stent vs. the sirolimus coated Cypher stent in the treatment of advanced coronary artery disease. Paper presented at: American Heart Association Scientific Sessions 2009; November 14, 2009; Orlando, FL.
191. Cortese B, Micheli A, Picchi A, et al. Paclitaxel-coated balloon versus drug-eluting stent during PCI of small coronary vessels, a prospective randomised clinical trial. The PICCOLETO Study. Heart 2010;96:1291–6.
192. Herdeg C, Gohring-Frischholz K, Haase KK, et al. Catheter-based delivery of fluid paclitaxel for prevention of restenosis in native coronary artery lesions after stent implantation. Circ Cardiovasc Interv 2009;2:294–301.
193. Unverdorben M. Summarizing the B. Braun PEPCAD coronary paclitaxel-eluting balloon clinical studies. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 22, 2009; San Francisco, CA. Available at: http://www.tctmd.com/txshow.aspx?tid=939092&id=84062&trid=938634. Accessed January 14, 2010.
194. Fanggiday JC, Stella PR, Guyomi SH, Doevendans PA. Safety and efficacy of drug-eluting balloons in percutaneous treatment of bifurcation lesions: the DEBIUT (drug-eluting balloon in bifurcation Utrecht) registry. Catheter Cardiovasc Interv 2008;71:629–35.
195. Mathey DG. The PEPCAD V bifurcation study. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 22, 2009; San Francisco, CA. Available at: http://www.tctmd.com/txshow.aspx?tid=939092&id=84154&trid=938634. Accessed January 14, 2010.
196. Scheller B, Speck U, Abramjuk C, Bernhardt U, Bohm M, Nickenig G. Paclitaxel balloon coating, a novel method for prevention and therapy of restenosis. Circulation 2004;110:810–4.
197. Stella P. Drug eluting balloons in coronary bifurcations: the Drug Eluting Balloon In Bifurcation trial. Paper presented at: EuroPCR; May 25–28, 2010; Paris, France. Available at: http://www.pcronline.com/Lectures/2010/The-DEBIUT-trial. Accessed May 29, 2010.

Key Words: drug-eluting stents ■ biodegradable stents ■ biodegradable polymer stents ■ polymer-free drug-eluting stents ■ coronary stents.

APPENDIX

For a list of all study acronyms and their definitions, please see Appendix I in the online version of this article; and for a list of all study devices and their manufacturers, please see Appendix II in the online version of this article.

Appendix I Trial Acronyms

Trial Acronyms	Trial	Reference
ABSORB	A bioresorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions	112-114, 125
ATLANTA	Assessment of The Latest Non-Thrombogenic Angioplasty stent	85, 88, 90
CARE	Cardiomind Sparrow DES Trials	169
COSTAR	Cobalt Chromium Stent With Anti-proliferative for Restenosis	46, 48
CREATE	Multi-Center Registry of Excel Biodegradable Polymer Drug Eluting Stents	27
CUSTOM	XTENT studies	33, 34
DEBIUT	Drug Eluting Balloon in Bifurcation Trial	194, 197
DESIRE	Double versus Single balloon stent delivery systems for bifurcation lesions	149
DIVERGE	Drug Eluting Stent Intervention for Treating Side Branches Effectively	32
EuroSTAR	The European cobalt Stent with Anti-proliferative for Restenosis trial	47
EVOLVE	Randomised comparison of the standard and low dose SYNERGY everolimus eluting stent with the PROMUS Element stent.	35
EXCELLA	Elixir Medical Clinical Evaluation of the Novolimus-Eluting Coronary Stent System	14, 15, 23
HEALING-II	Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth	97-99
ISAR-TEST	Intracoronary Stenting and Angiographic Restenosis–Test Equivalence Between 2 Drug-Eluting Stents	65
ISAR-TEST 2	Intracoronary Stenting and Angiographic Restenosis – Test Efficacy of Three Limus Eluting Stents	82, 83
ISAR-TEST 3	Intracoronary Stenting and Angiographic Restenosis Investigators – Test Efficacy of Rapamycin-eluting Stents with Different Polymer Coating Strategies	80, 81
JACTAX	Juxtaposed Abluminal Coating TAXUS stent study	41
LEADERS	Limus Eluted from A Durable versus Erodable Stent coating	29, 30
NEVO-RES	NEVO RES-ELUTION	28
NOBORI	NOBORI stent trials	31, 51, 54
OCTDESI	The Optical Coherence Tomography Drug Eluting Stent Investigation	57
OPEN	Stentys coronary bifurcation stent system for the Percutaneous Treatment of *de novo* lesions in native bifurcated coronary arteries	160, 161
PACCOCATH ISR	Paclitaxel-Coated Balloon Catheter for In-Stent Restenosis	186, 187
PAINT	Percutaneous Intervention with biodegradable-polymer based paclitaxel-eluting, sirolimus-eluting, or bare stents for the treatment of de novo coronary lesions	39
PEPCAD	Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease	188-190, 193, 195
PERSEUS	A Prospective Evaluation in a Randomized Trial of the Safety and Efficacy of the Use of the TAXUS Element Paclitaxel-Eluting Coronary Stent System for the Treatment of De Novo Coronary Artery Lesions	16, 17
PICCOLETO	Paclitaxel-eluting balloon versus paclitaxel-eluting stent in small coronary vessel disease	191
PISCES	The Paclitaxel In-Stent Controlled Elution Study	45
PLATINUM	A Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of up to Two De Novo Coronary Artery Lesions	35
PROGRESS AMS	Clinical Performance and Angiographic Results in Absorbable Metal Stents study	116, 140

Trial Acronyms	Trial	Reference
REMEDEE	Randomized Evaluation of an Abluminal sirolimus coated Bio-Engineered Stent	37
RESOLUTE	Evaluation of the new generation zotarolimus-eluting coronary stent system	13, 18, 20-22
RESORB	REVA Endovascular Study of a Bioresorbable Coronary Stent	36
SECRITT	Santorini Criteria for Investigating and Treating Thin Capped Fibroatheroma Trial	167
SERIES	Study of the Supralimus® Sirolimus Eluting Stent in the treatment of patients with real world coronary artery lesions	26, 44
SIMPLE	Safety and Efficacy of the Infinnium Paclitaxel-Eluting Stent	40
TIDE	Randomized Trial Comparing Titan vs. Endeavor-stents.	94
TiNOX	Randomized Comparison of a Titanium-Nitride-Oxide–Coated Stent With a Stainless Steel Stent for Coronary Revascularization	86, 91
TITAX-AMI	A Prospective, Randomized Trial Comparing TITAN-2® Stent and TAXUS-Liberte® Stent in Acute Myocardial Infarction	92, 93
TOP	TMI Ostial Preservation	148
TRIAS-HR	TRI-stent Adjudication Study	87, 100
VESTASYNC	Hydroxyapatite Polymer-Free Sirolimus-Eluting Stent for the Treatment of Single De Novo Coronary Lesions	64, 78
WHISPER	FIM study of the IDEAL Poly (Anhydride Ester) Salicylic acid stent	115

Appendix II Devices and Manufacturers

Device	Manufacturer
Adsorbable Metal Stent (AMS)	Biotronik, Berlin, Germany
Amazonia PAX	Minvasys, Genevilliers, France
Antares	TriReme Medical Inc., Pleasanton, CA, USA
Axxess	Devax, Lake Forest, CA, USA
BioFREEDOM	Biosensors, Morges, Switzerland
BioMatrix Flex	Biosensors, Morges, Switzerland
Bioresorbable Vascular Scaffold (BVS)	Abbott Vascular, Santa Clara, CA, USA
Cardiomind Sparrow	Cardiomind Inc, Sunnyvale, CA, USA
Catania	CeloNova Biosciences, Newnan, GA, USA
Combo stent	Orbus Neich, Fort Lauderdale, Fl, USA
Coroflex DEBlue	B.Braun, Melsungen, Germany
Cypher	Cordis, Johnson and Johnson, Warren, NJ, USA
DIOR	Eurocor, Bonn, Germany
Elixir DESyne	Elixir Medical, Sunnyvale, CA, USA
ENDEAVOR	Medtronic, Santa Rosa, CA, USA
ENDEAVOR Resolute	Medtronic, Santa Rosa, CA, USA
Excel	JW Medical System, Weihai, China
GENIE	Acrostak, Winterthur, Switzerland
Genous	Orbus Neich, Fort Lauderdale, Fl, USA
IDEAL	Bioabsorbable Therapeutics, Inc. Menlo Park, Ca, USA
Igaki-Tamai	Kyoto Medical Planning. Co. Ltd., Kyoto, Japan
IN.PACT Falcon	Invatec S.r.l., Brescia, Italy
Infinnium	Sahajanand Medical, Gujrat, India
Invatec Twin-Rail	Invatec S.r.l., Brescia, Italy
JacPro	Boston Scientific, Natick, MA, USA
JACTAX	Boston Scientific, Natick, MA, USA
Labcoat Element	Boston Scientific, Natick, MA, USA
Multi-Link Frontier	Abbott Vascular, Santa Clara, CA, USA
NEVO	Cordis, Johnson and Johnson, Warren, NJ, USA
Nile Croco	Minvasys, Genevilliers, France
Nile Pax	Minvasys, Genevilliers, France
NOBORI	Terumo, Leuven, Belgium
Paccocath	Bayer AG, Leverkusen, Germany
Petal	Boston Scientific, Natick, MA, USA
Promus Element	Boston Scientific, Natick, MA, USA
REVA Generation I	REVA Medical, Inc., San Diego, CA, USA
REZolve	REVA Medical, Inc., San Diego, CA, USA
SeQuent Please	B.Braun, Melsungen, Germany
Sideguard	Cappella, Auburndale, MA, USA
SideKick	Y-Med, San Diego, CA, USA
SLK-View	Advance Stent Technologies, Pleasanton, CA, USA
Stentys	Stentys SAS, Clichy, France
Supralimus	Sahajanand Medical, Gujarat, India
SYNERGY	Boston Scientific, Natick, MA, USA
TAXUS Liberté	Boston Scientific, Natick, MA, USA
TAXUS Element	Boston Scientific, Natick, MA, USA

Device	Manufacturer
TiNOX	Hexacath, Rueil-Malmaison, France
Tryton	Tryton Medical, Newton, MA, USA
VESTAsync	MIV Therapeutics, Atlanta, GA, USA
vPROTECT	Prescient Medical, Inc., Doylestown, PA, USA
Xience V	Abbott Vascular, Santa Clara, CA, USA
XTENT	Xtent Inc, Menlo Park, CA, USA
Yukon	Translumina, Hechingen, Germany

Chapter 2.3

Stent Thrombosis

J Am Coll Cardiol 2010;56(10):1357-1365

David R. Holmes JR, Dean Kereiakes, Scot Garg, Patrick W. Serruys, Gregory Dehmer, Stephen Ellis, David Williams, Takeshi Kimura, David Moliterno

JACC White Paper

Stent Thrombosis

David R. Holmes, JR, MD,* Dean J. Kereiakes, MD,† Scot Garg, MD,§
Patrick W. Serruys, MD, PHD,§ Gregory J. Dehmer, MD,‖ Stephen G. Ellis, MD,‡
David O. Williams, MD,¶ Takeshi Kimura, MD,# David J. Moliterno, MD**

Rochester, Minnesota; Cincinnati and Cleveland, Ohio; Rotterdam, the Netherlands; Temple, Texas; Boston, Massachusetts; Kyoto, Japan; and Lexington, Kentucky

Intense investigation continues on the pathobiology of stent thrombosis (ST) because of its morbidity and mortality. Because little advance has been made in outcomes following ST, ongoing research is focused on further understanding predictive factors as well as ST frequency and timing in various patient subsets, depending upon whether a drug-eluting stent or bare-metal stent has been implanted. Although the preventive role of antiplatelet therapies remains unchallenged, new data on genomics and variability in response to antiplatelet therapy, as well as the effects of novel therapeutic agents and duration of therapy, have become available. The goal remains identification of patients at particularly increased risk of ST so that optimal prevention strategies can be developed and employed.

Prior to the development of coronary artery stents, interventional cardiologists focused on procedural dissection-related acute vessel closure and late restenosis. Stents, particularly drug-eluting stents (DES), significantly ameliorated these problems. Unfortunately, by delaying endoluminal healing of the angioplasty site, stent thrombosis (ST) can occur. Thus, interest from the scientific community as well as regulatory agencies and the public is now focused on ST because of the associated incidences of death (~20% to 40%), myocardial infarction (~50% to 70%) and repeat revascularization (1–7).

Definitions

Early reports of ST utilized varying definitions, making comparisons among different datasets challenging (8–10). Uniform definitions were subsequently developed by the Academic Research Consortium (ARC) incorporating timing as well as diagnostic certainty (Table 1) (11). Although ARC definitions added uniformity, they remain an imperfect balance of sensitivity and specificity: "definite" ST is highly specific but likely underestimates true frequency, whereas "possible" ST, although more sensitive, lacks diagnostic certainty. Most contemporary studies exclude the

From the *Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic, Rochester, Minnesota; †Christ Hospital Heart and Vascular Center, Cincinnati, Ohio; ‡Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio; §Department of Interventional Cardiology, Thoraxcentre, Erasmus Medical Centre, Rotterdam, the Netherlands; ‖Division of Cardiology, the Scott and White Clinic, Temple, Texas; ¶Cardiovascular Division, Brigham & Women's Hospital, Boston, Massachusetts; #Department of Cardiovascular Medicine, Kyoto University Hospital, Kyoto, Japan; and the **Division of Cardiology, Department of Medicine, University of Kentucky, Lexington, Kentucky. Dr. Kereiakes has received a grant and/or research support from Abbott Vascular, Cordis/Johnson & Johnson, Boston Scientific, and Medtronic; and consulting fees from Abbott Vascular, Boston Scientific, Cordis/Johnson & Johnson, Devax, and REVA Medical Inc. Dr. Ellis is a consultant for Abbott Vascular, Boston Scientific, and Cordis. Dr. Williams is a consultant for Cordis. Dr. Kimura is an advisory board member for Codis Cardiology and Abbott Vascular. Dr. Moliterno is a consultant for Boston Scientific, Merck/Schering-Plough, Daiichi-Sankyo, and Sanofi-Aventis. All other authors report that they have no relationships to disclose.

Manuscript received February 1, 2010; revised manuscript received July 1, 2010, accepted July 5, 2010.

Table 1

ARC Definition of ST to Standardize ST and Ensure Unified Assessment Across Trials

Term	Definition
"Definite" ST	The highest level of certainty Either angiographic or post-mortem evidence of thrombotic stent occlusion
"Probable" ST	Any unexpected death within 30 days of stent implantation, or any myocardial infarction in the territory of the implanted stent irrespective of time
"Possible" ST	Any unexplained death beyond 30 days until the end of follow-up
Early ST	ST occurring in the first 30 days after stent implantation
Late ST	ST occurring between 1 month and 1 yr after stent implantation
Very late ST	ST occurring beyond 1 yr

ARC = Academic Research Consortium; ST = stent thrombosis.

category of "possible" ST and select the end points of "definite" or "probable" ST to provide a balance of specificity and sensitivity.

Pathophysiology of ST

The pathophysiology of ST includes stent-, procedure-, and patient-related factors (Table 2). ST can occur with either bare-metal stents (BMS) or DES (8–10,12). Early events may be related to residual target lesion thrombus or dissection, stasis, stent underexpansion, or a combination of these (13). Following DES deployment, late incomplete stent apposition (ISA) demonstrated by intravascular ultrasound, due to the gradual dissolution of thrombus or positive arterial remodeling, has not been convincingly linked to adverse outcomes (14). Late ST may be more frequently related to incomplete healing and/or inadequate neointimal coverage. Serial angioscopic, optical coherence tomography, and evaluations at autopsy suggest that stent endothelialization is delayed or incomplete with DES (15–17). Although a correlation has been observed between uncovered DES struts and ST, endoluminal mural thrombus may be present despite neointimal coverage and may reflect underlying inflammation related to the drug-delivery polymer. The role of inflammation in vessel remodeling, ISA, and very late ST is supported by the preponderance of inflammatory cells associated with ISA (18). Histopathologic differences (the prevalence of eosinophils, giant cells, and fibrin) among DES platforms have been observed; this may reflect unique responses to the specific polymer/drug. Finally, very late atherothrombosis within a previously deployed stent may be related to the intercurrent development of yellow plaque and plaque rupture (19,20). This point was emphasized in an analysis of histopathological findings of new in-stent lesions that developed beyond 5 years. These tissues, which were obtained using directional coronary atherectomy, did not display persistent peri-stent inflammation; rather, there were findings of acute, unstable coronary lesions (21).

Clinical evidence for a relationship between underlying vascular inflammation and ST has been found in patients with ruptured plaque. Risk of ST is directly related to the acuity of the index clinical syndrome preceding stenting. Patients presenting with an acute coronary syndrome (ACS) have a several-fold increased risk for ST regardless of stent type compared with patients with stable symptoms (22–24). Possible histopathologic mechanisms include the thin fibrous cap that characterizes vulnerable plaque, abundant inflammatory cells, and a necrotic lipid core. In registry series, ST beyond 6 to 12 months following ACS treatment is more frequent with DES (vs. BMS) (25–27). DES struts imbedded in the necrotic lipid core demonstrate incomplete healing and reduced neointimal coverage compared with struts imbedded in adjacent fibro-calcific stable plaque.

In contrast, the theory that neointimal thickness, as reflected by in-stent late lumen loss, may "protect" against ST has been dispelled by both recent clinical trials and a recent meta-regression meta-analysis (28) in which stents with lower late lumen loss demonstrated both a lower incidence of target lesion revascularization and ST (29,30).

Table 2

Selected Multifactorial Causes of ST

	Precipitant of Stent Thrombosis
Stent factors	Hypersensitivity to drug coating or polymer Incomplete endothelialization Stent design Covered stents (64,65)
Patient factors	PCI for acute coronary syndrome/ST-segment elevation MI Diabetes mellitus Renal failure Impaired left ventricular function Premature cessation of dual antiplatelet therapy Aspirin nonresponsiveness Clopidogrel nonresponsiveness Glycoprotein IIb/IIIa inhibitors Prior brachytherapy Malignancy Saphenous vein graft disease
Lesion characteristics	Lesion/stent length Vessel/stent diameter Complex lesions (bifurcation lesions, chronic total occlusions) Saphenous vein graft target lesion Stasis
Procedural factors	Inadequate stent expansion/sizing Incomplete stent apposition Stent deployment in necrotic core Residual edge dissection

MI = myocardial infarction; PCI = percutaneous coronary intervention; ST = stent thrombosis.

Nevertheless, both histopathologic and invasive imaging studies following ST identify that DES deployment in yellow, vulnerable, or ruptured plaque appears to be associated with incomplete endothelialization, less neointima formation, and a greater subsequent risk for late or very late ST (17,18). Finally, the physical presence of endothelial coverage may not confer functional integrity, and chronic vascular/endothelial dysfunction may contribute to very late ST (31,32).

Predictors of ST

Predictors of early and late ST following stenting have been studied in registries and post hoc analyses from clinical trials (33,34) and may be categorized into those related to the: 1) stent; 2) patient; 3) procedure; and 4) type and duration of antiplatelet therapy (Table 2).

ST in BMS Versus DES

The frequency of ST has been evaluated in clinical trials, "real-world" registries, and meta-analyses. The quality and applicability of data vary by study; most studies did not employ routine angiographic follow-up, but instead monitored death, myocardial infarction (MI), and repeat revascularization (which may or may not be related to ST). Using these surrogates is confounded because coronary atherothrombosis is progressive, and the portion of events related to the stented versus nontarget site changes over time.

Randomized Clinical Trials

Kirtane et al. (7) identified 9,470 patients from 22 randomized clinical trials (RCTs) and 182,901 patients from 34 observational studies that compared the first generation Cypher (Cordis, Warren, New Jersey) sirolimus-eluting stent (SES) and Taxus (Boston Scientific, Natick, Massachusetts) paclitaxel-eluting stent (PES) with BMS. In RCTs, at 2.9 years, the hazard ratio (HR) (DES vs. BMS) for mortality was 0.97 ($p = 0.72$). For the 12 trials that evaluated "off-label" versus "on-label" indications, the mortality HR was 0.84 ($p = 0.24$) at 1.5 years. No differences in MI were observed comparing DES with BMS (HR: 0.95, $p = 0.54$) regardless of the indication for stenting. A substantial reduction in target vessel revascularization (TVR) was observed with DES (HR: 0.45, $p < 0.001$) irrespective of follow-up duration; this was particularly marked with "off-label" DES indications (HR: 0.38, $p < 0.001$).

These findings are similar to another analysis of 28 RCTs involving 10,727 patients treated with DES or BMS in which no differences in mortality were observed between stent types either at 1 year (relative risk [RR]: 0.91, $p = 0.47$) or beyond (RR: 1.03, $p = 0.79$) (6). Using the original per protocol definitions, however, ST was observed beyond 1 year in 0.7% DES-treated versus 0.1% BMS-treated patients (RR: 4.57, $p = 0.006$).

Observational Studies

In observational studies including 169,595 subjects, there was a significant mortality reduction with DES (HR: 0.78, $p < 0.01$) (7). Survival varied substantially depending on follow-up duration, study size, and covariate adjustment. Following multivariable adjustments, DES continued to be associated with a mortality reduction (HR: 0.79, $p < 0.001$) as well as fewer subsequent MIs (HR: 0.91, $p = 0.01$) and TVRs (HR: 0.54, $p < 0.01$).

Patient Subgroups

Meta-analyses comparing DES versus BMS have also been performed in patients with either ST-segment elevation myocardial infarction (STEMI) or diabetes. In 13 RCTs involving 7,352 STEMI patients, no reduction was observed in mortality (3.7% DES vs. 4.3% BMS, RR: 0.89, $p = 0.36$) or recurrent MI (3.5% DES vs. 3.8% BMS, RR: 0.82, $p = 0.12$) (27). TVR was reduced by DES (7.7% vs. 11.5%, RR: 0.44, $p < 0.001$). In 18 registry studies including 26,251 STEMI patients, the pooled treatment effect demonstrated a 32% mortality reduction at 1 year with DES (RR: 0.68, $p < 0.01$) (35). Beyond 1 year, mortality remained lower with DES but was not statistically significant (RR: 0.89, $p = 0.45$). No differences in recurrent MI were observed. Finally, TVR was reduced by DES at both 1 and 2 years (RR: 0.71; $p < 0.01$). In the Massachusetts State Database of 7,217 patients treated with DES or BMS using propensity score matching techniques for STEMI or non-STEMI, adjusted 2-year clinical outcomes demonstrated reduced mortality (10.7% vs. 12.8%; $p = 0.02$) and recurrent MI (8.8% vs. 10.2%; $p = 0.09$) following DES (36). The mortality reductions observed in these nonrandomized registries may reflect the effect of confounding due to covariate imbalance despite attempts at adjustment. For example, a mortality difference favoring DES was evident prior to hospital discharge in the Massachusetts State experience (36).

In diabetic patients, periprocedural as well as late adverse clinical outcomes (including ST) appear to be increased with DES and BMS. In 35 trials including 3,852 patients with and 10,947 without diabetes, no mortality differences were observed by stent type in diabetic patients who received dual antiplatelet therapy (DAPT) for ≥6 months (37). Improved TVR rates were seen with DES. In an analysis of 9 trials involving 1,141 patients treated with DES or BMS with follow-up >6 months, no difference in mortality was observed by stent type (2.4% DES vs. 2.3% BMS, odds ratio [OR]: 1.05, $p = 0.91$). Of note, DES was associated with

reductions in MI (3.5% vs. 7.2%, OR: 0.48, p = 0.02) and TLR (8% vs. 27%, OR: 0.23, p < 0.00001) (38).

Summary

Surrogate markers (death or MI) have been used for ST in multiple meta-analyses involving both RCT and observational data. Several conclusions regarding these outcomes following DES versus BMS can be drawn:

- RCT and observational data differ regarding the frequency of reported clinical outcomes.
- Although RCTs have demonstrated similar incidences of death and MI for both stent types, observational (real-world) datasets demonstrate an apparent reduction in mortality favoring DES.
- Both RCTs and observational studies demonstrate a substantial reduction in TVR with DES.

Comparison of true ST rates (not surrogate outcomes) between BMS and DES is more difficult. Given the low incidence occurrence of ST (0.5% to 1% per year), RCTs have not included ST as a primary end point. In a meta-analysis of RCTs (6), ST at 1 year was similar for DES and BMS. Beyond 1 year, the risk of ST appeared greater with DES. An additional meta-analysis of 28 RCTs involving 5,612 DES and 7,639 BMS patients demonstrated no difference in ST by stent type to 15 months (OR: 0.86, p < 0.48) (39). In a meta-analysis of 13 RCTs restricted to primary percutaneous coronary intervention (PCI), ST was observed with similar frequency to 1-year follow-up (2.7% DES, 2.6% BMS) (35), and similar results were seen in the 4 studies of outcomes beyond 1 year. In observational studies of primary PCI, ST was lower at 1 year following DES (RR: 0.52, p = 0.01) but not significantly different at 2 years (35). Finally, in studies confined to diabetic patients, a pooled analysis of RCTs of PES versus BMS demonstrated a similar rate of ST (1.4% vs. 1.2%) at 4 years (40).

Class Effect Analyses

Whether ST rates vary among different DES remains controversial. In a network meta-analysis (12), ST was higher following PES versus SES. Similar observations were noted in other series (5,41). In contrast, in the 5-year follow-up of the randomized SIRTAX (Sirolimus-Eluting Stent Compared With Paclitaxel-Eluting Stent for Coronary Revascularization) trial of PES versus SES, ST was observed in 4.1% and 4.6% of patients, respectively (p = 0.74) (42). The SPIRIT IV (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with De Novo Native Coronary Artery Lesions IV) RCT compared Xience V everolimus-eluting stents (Abbott Vascular, Santa Clara, California) with Taxus Express PES (29). At 1 year, definite/probable ST occurred less frequently following Xience V (0.3% vs. 1.1%; p = 0.003). Likewise, the COMPARE (Second-Generation Everolimus-Eluting and Paclitaxel-Eluting Stents in Real-Life Practice) study of 1,800 real-world patients found that definite/probable ST at 1 year was less frequent following the Xience V versus the Taxus Liberté (0.7% and 2.6%, respectively; p = 0.002) despite similar DAPT compliance (30). In addition, a landmark analysis at 1 to 3 years from the Endeavor IV trial (Randomized, Controlled Trial of the Medtronic Endeavor Drug-Eluting Coronary Stent System Versus the Taxus Paclitaxel-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions) demonstrated a relatively lower incidence of very late (>1 year) ST with Endeavor zotarolimus-eluting stents (Medtronic, Minneapolis, Minnesota) versus Taxus DES (0.1% vs. 1.5%, respectively; p = 0.004) (43). Although these trials suggest a relative increased risk for ST associated with the Taxus Express or Liberté PES to ≥1 year, in comparison with either everolimus- or zotarolimus-eluting stents, results vary (44), and each was underpowered for ST as a primary end point. Thus, there are no adequately powered RCTs for definitive conclusions regarding the relative risk of ST among currently available DES.

Summary

Despite the number of meta-analyses involving patients treated with BMS and DES, it is difficult to draw definitive conclusions regarding relative risks for ST. Although no single trial has adequate power to evaluate ST as a primary end point, several broad conclusions may be reached:

- There appear to be differences in ST frequency between RCTs and registries, probably reflecting differences in complexity and acuity of patient cohorts.
- There is no appreciable difference in ST rates to 1 year between DES and BMS.
- Beyond 1-year follow-up, a small but definite increased risk for very late ST accompanies DES.
- There may be differences in frequency of ST among different DES, the magnitude of which is difficult to discern.
- Although DAPT compliance for <6 months is associated with adverse outcomes following DES, its optimal duration awaits definition by adequately powered, prospective RCTs. Current recommendations for ≥12 months DAPT are based on landmark analyses, which may be confounded by statistical bias.

Prognosis Following ST

Infarction due to ST may differ from de novo native-vessel infarction in that it is associated with larger thrombus burden, more frequent distal embolization, and less successful catheter-based PCI reperfusion (45–47). Many patients with ST present with STEMI, and in a series of 431 definite ST cases, subsequent death or recurrent ST occurred in 18% by 30-day follow-up (46). Such patients remain at increased risk for recurrent ST, recurrent MI, and death for up to 3 years. Thus, efforts should be made to ensure optimal stent expansion (including intravascular ultrasound guidance if available) as well as adequate treatment of residual intimal dissection during primary PCI for ST.

Prevention of ST

By virtue of the adverse clinical consequences typically associated with ST, including death and MI, preventive strategies have assumed a position of central importance. It must be remembered that such strategies carry risks of their own, most prominently bleeding, which can also have severe clinical consequences. The risk-benefit ratio of these preventive strategies must be considered relative to the risk of ST for each individual patient.

DAPT

The focus on DAPT has grown in parallel with concerns regarding ST. A consensus science advisory regarding DAPT for DES-treated patients (48) recommended: 1) DAPT for at least 1 year; 2) deferring elective surgical procedures for 1 year; 3) continuing 81 mg aspirin daily if thienopyridine therapy must be stopped; 4) discussing need for DAPT with the patient before the procedure; 5) educating patients and health care providers regarding DAPT compliance; and 6) consulting with the cardiologist prior to surgical procedures. Lacking adequately powered RCTs with ST as a primary end point, strategic approaches to extended DAPT have developed from observational studies.

In a prospective observational cohort of 6,816 successful DES patients, the incidence, timing, and relationship of ST to duration of clopidogrel therapy were analyzed during 4-year follow-up (49). "Definite" ST was observed in 1.2% of patients, with the greatest risk early after index PCI. The "protective" effect of clopidogrel was largely confined to the first 6 months. The Bern/Rotterdam Registry of 8,146 DES patients found no significant differences in ST between treatment with clopidogrel for 12 months versus 3 to 6 months (5). However, a large, prospective, single-center registry of DES versus BMS patients (50) found that DES-treated patients who discontinued clopidogrel within 6 months of stenting had an increased risk of death or MI during follow-up, whereas DES-treated patients who remained compliant with clopidogrel at both 6- and 12-month follow-up enjoyed a survival advantage over BMS-treated patients irrespective of the clopidogrel treatment status of BMS patients. The risk of adverse clinical outcomes including death appeared greatest for patients undergoing primary DES PCI for STEMI who were noncompliant with clopidogrel during the first 30 days post-procedure (50).

Although clopidogrel noncompliance was raised in 2 registries (5,51), subsequent analyses using the population-attributable risk percentage methodology suggested that 68% to 85% of ST observed could not be attributed to clopidogrel compliance alone (52). The relative importance of "other" factors such as clopidogrel resistance, polymer hypersensitivity, and drug–drug interactions has been supported by studies showing that discontinuation of clopidogrel within the first 6 months, but not thereafter, is a strong predictor of increased ST (53). Finally, extended duration DAPT may also influence nontarget site–related ischemic events. Indeed, late follow-up in both BMS and DES suggests that extended duration DAPT exerts a salutary effect, at least in part, mediated by suppression of nontarget site events (54). The question of efficacy versus safety of extended duration DAPT (12 vs. 30 months) is being evaluated in a >20,000-patient RCT. Conversely, the ISAR-SAFE (Intracoronary Stenting and Antithrombotic Regimen: Safety and Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting) and OPTIMIZE (Effect of Image Optimization With Contrast on the Diagnostic Accuracy of Dobutamine Echocardiography in Coronary Artery Disease) studies are both currently randomizing patients treated with DES to standard 12- or 3-month (OPTIMIZE) versus 6-month (ISAR-SAFE) DAPT (55). Finally, preliminary data, although underpowered, suggest no additional benefit of DAPT beyond 1 year in patients free from major adverse cardiovascular events to 1 year (56).

DAPT-compliant patients who experience ST should be considered for evaluation of aspirin and/or clopidogrel resistance with appropriate modification in the oral platelet inhibitor therapy regimen. Roughly one-fourth of patients undergoing stenting may be "resistant" to the platelet-inhibiting effects of clopidogrel (57,58). Furthermore, patients who respond inadequately to one agent (either aspirin or clopidogrel) are more likely to be hyporesponsive to the other agent, and the risk of ischemic events appears greatest in patients with "dual" resistance (59,60). Resistance to clopidogrel can be related to genetic variation in 1 or more of the cytochrome P450 hepatic enzymes required to convert clopidogrel from prodrug to active metabolite, partic-

ularly the reduced-functioning CYP2C19*2 allele (61). Although risk for stent thrombosis is greatest in homozygotes (2% to 14% of population), heterozygotes (25% to 30% of population) appear to have a variable but increased risk for ischemic events as well (62). Nevertheless, it has been suggested that the CYP2C19*2 genotype accounts for only ~12% of clopidogrel response variability (63), which in turn may not be overcome by increasing the dosage (64). Alternate strategies such as switching to prasugrel (not influenced by genetic polymorphisms) (65) or the use of a "triple" antiplatelet regimen that includes aspirin, clopidogrel, and cilostazol, may be more attractive (66). The latter has been demonstrated to provide significantly higher levels of measured platelet aggregation inhibition in clopidogrel-resistant patients compared with 150 mg daily clopidogrel (66). Finally, multiple drug–drug interactions may exist that modify clopidogrel metabolism/conversion (67). The coadministration of clopidogrel with proton pump inhibitors (especially omeprazole) (68), lipophilic statins (especially atorvastatin) (69), calcium channel blockers (especially amlodipine) (70), or warfarin (71) may reduce clopidogrel conversion from prodrug to active metabolite via the CYP2C19, CYP3A4/5, or CYP2C9 enzyme paths. Although concomitant administration of proton pump inhibitors with either clopidogrel or prasugrel has been associated with a reduction in measured platelet inhibition (72), the clinical relevance of this interaction remains unclear. Observational data are discrepant and confounded, and 1 RCT involving 3,600 clopidogrel-treated patients demonstrated no difference in cardiovascular outcomes by omeprazole treatment (73). This interaction, as well as the issue of the interaction of clopidogrel responsiveness as a function of genetic polymorphisms, is the subject of current expert consensus documents by the American College of Cardiology/American Heart Association.

Preventive Strategies

Although the importance of DAPT has been emphasized, it may be impossible to predict long-term compliance in a specific patient. In 10,778 SES-treated patients over 2 years, definite ST was observed at 30 days in 0.34%, at 1 year in 0.54%, and at 2 years in 0.77% (74). In patients who discontinued both aspirin and thienopyridine 31 to 180 days following stent deployment, ST was 1.76% versus 0.1% with continued compliance ($p < 0.001$); at 366 to 548 days, the rates were 2.1% and 0.14%, respectively ($p = 0.004$). Other studies analyzing death and/or MI over time after treatment with DES or BMS stratified by duration of DAPT found clopidogrel therapy ≥12 months was associated with reduction in death or death/MI in DES- but not BMS-treated patients (75). Similarly, in the TYCOON (Two-Year Clopidogrel Need) registry, DES-treated patients receiving clopidogrel for 24 months had improved cumulative survival versus patients discontinuing clopidogrel after 12 months (76). Preliminary results from an underpowered randomized trial suggested no benefit of extended DAPT beyond 1 year (56); conclusive recommendations await the result of ongoing, adequately powered RCTs. Finally, 1 of the most important observations made in the TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis In Myocardial Infarction 38) trial was that ST occurred in 2.4% of clopidogrel-treated versus 1.1% of prasugrel-treated patients at 14.5 months (HR: 0.48; $p < 0.0001$) (77). How much of prasugrel benefit can be ascribed to a higher level of platelet inhibition (vs. clopidogrel) or to the lack of influence of genetic polymorphisms (CYP2C19*2) on prasugrel pharmacokinetics is unknown.

Among patients with STEMI, the potential benefits of triple antiplatelet therapy (aspirin, thienopyridine, and cilostazol) were available in 4,203 DES STEMI patients; 2,569 received aspirin plus clopidogrel, whereas 1,634 received aspirin, clopidogrel, and cilostazol (78). Although ST was not a primary end point, patients on triple therapy had reduced mortality and major adverse cardiac events versus those on DAPT alone, perhaps mediated in part by a reduction in ST.

New Stent Design and ST

The potential for durable polymers to influence local arterial injury and repair has been known for >10 years (79). Increasing attention has been paid to the potential effect of polymers on subsequent hypersensitivity and inflammation (80–85). Concerns about the effect of polymers on vascular repair have driven efforts to either design DES with biodegradable polymers or develop nonpolymeric drug delivery. The LEADERS (Limus Eluted from A Durable vs. ERodable Stent coating) trial randomized patients to the conventional "biostable" durable polymer (Cypher) SES or the Biomatrix (Biosensors, Morges, Switzerland) biolimus A9-eluting stent with a biodegradable polylactic acid polymer (85). At 2-year follow-up, the respective rate of definite ST was similar for the 2 stents (2.5% vs. 2.2%). Finally, completely bioresorbable stent platforms are currently undergoing clinical trials. Angiographic follow-up at 2 years in the ABSORB (A Bioabsorbable Everolimus-Eluting Coronary Stent System for Patients With Single De-Novo Coronary Artery Lesions) trial of an everolimus-eluting platform demonstrated complete stent resorption, arterial healing, and apparent restoration of normal vascular function (86) with no ST at 3 years (87).

Conclusions

ST with either DES or BMS remains catastrophic and, although infrequent, occupies a central place in the risk-benefit equation of PCI. The timing of ST between DES and BMS differs, occurring more frequently earlier after BMS but continuing later after DES. This may relate to delayed endothelialization that has been documented with DES. Factors associated with ST may be categorized into several groups: 1) the stent, including its geometry, polymer, and drug; 2) the patient, including clinical presentation and comorbid conditions; 3) the procedure, including residual dissection or incomplete expansion; and 4) the extent and duration of antiplatelet therapy and the patient-specific response to this therapy. Improved understanding of these factors will facilitate identification of optimal preventive strategies.

Reprint requests and correspondence: Dr. David R. Holmes, Jr., Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905. E-mail: holmes.david@mayo.edu.

REFERENCES

1. Holmes DR Jr., Kereiakes DJ, Laskey WK, et al. Thrombosis and drug-eluting stents: an objective appraisal. J Am Coll Cardiol 2007; 50:109–18.
2. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293:2126–30.
3. Cutlip DE, Baim DS, Ho KK, et al. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. Circulation 2001;103:1967–71.
4. Doyle B, Rihal CS, O'Sullivan CJ, et al. Outcomes of stent thrombosis and restenosis during extended follow-up of patients treated with bare-metal coronary stents. Circulation 2007;116:2391–8.
5. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;369:667–78.
6. Roukoz H, Bavry AA, Sarkees ML, et al. Comprehensive meta-analysis on drug-eluting stents versus bare-metal stents during extended follow-up. Am J Med 2009;122:581.e1–10.
7. Kirtane AJ, Gupta A, Iyengar S, et al. Safety and efficacy of drug-eluting and bare metal stents: comprehensive meta-analysis of randomized trials and observational studies. Circulation 2009;119: 3198–206.
8. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl J Med 2007;356:1020–9.
9. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. N Engl J Med 2007;356: 998–1008.
10. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:989–97.
11. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
12. Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet 2007;370:937–48.
13. Fujii K, Carlier SG, Mintz GS, et al. Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: an intravascular ultrasound study. J Am Coll Cardiol 2005;45:995–8.
14. Cook S, Wenaweser P, Togni M, et al. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. Circulation 2007;115:2426–34.
15. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193–202.
16. Oyabu J, Ueda Y, Ogasawara N, Okada K, Hirayama A, Kodama K. Angioscopic evaluation of neointima coverage: sirolimus drug-eluting stent versus bare metal stent. Am Heart J 2006;152:1168–74.
17. Gonzalo N, Barlis P, Serruys PW, et al. Incomplete stent apposition and delayed tissue coverage are more frequent in drug-eluting stents implanted during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction than in drug-eluting stents implanted for stable/unstable angina: insights from optical coherence tomography. J Am Coll Cardiol Intv 2009;2:445–52.
18. Cook S, Ladich E, Nakazawa G, et al. Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. Circulation 2009;120:391–9.
19. Takano M, Yamamoto M, Mizuno K. Two cases of coronary stent thrombosis very late after bare-metal stenting. J Am Coll Cardiol Intv 2009;2:1286–7.
20. Takano M, Yamamoto M, Inami S, et al. Appearance of lipid-laden intima and neovascularization after implantation of bare-metal stents. J Am Coll Cardiol 2010;55:26–32.
21. Hasegawa K, Tamai H, Kyo E, et al. Histopathological findings of new in-stent lesions developed beyond five years. Catheter Cardiovasc Interv 2006;68:554–8.
22. de la Torre-Hernandez JM, Alfonso F, Hernandez F, et al. Drug-eluting stent thrombosis: results from the multicenter Spanish registry ESTROFA (Estudio ESpanol sobre TROmbosis de stents FArmacoactivos). J Am Coll Cardiol 2008;51:986–90.
23. Leibundgut G, Nietlispach F, Pittl U, Brunner-La Rocca H, Kaiser CA, Pfisterer ME. Stent thrombosis up to 3 years after stenting for ST-segment elevation myocardial infarction versus for stable angina—comparison of the effects of drug-eluting versus bare-metal stents. Am Heart J 2009;158:271–6.
24. Kukreja N, Onuma Y, Garcia-Garcia HM, Daemen J, van Domburg R, Serruys PW. The risk of stent thrombosis in patients with acute coronary syndromes treated with bare-metal and drug-eluting stents. J Am Coll Cardiol Intv 2009;2:534–41.
25. Brodie BR, Stuckey T, Downey W, et al. Outcomes and complications with off-label use of drug-eluting stents: results from the STENT (Strategic Transcatheter Evaluation of New Therapies) group. J Am Coll Cardiol Intv 2008;1:405–14.
26. Wenaweser P, Daemen J, Zwahlen M, et al. Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice. 4-year results from a large 2-institutional cohort study. J Am Coll Cardiol 2008;52:1134–40.
27. Park D-W, Yun S-C, Lee S-W, et al. Stent thrombosis, clinical events, and influence of prolonged clopidogrel use after placement of drug-eluting stent: data from an observational cohort study of drug-eluting versus bare-metal stents. J Am Coll Cardiol Intv 2008;1:494–503.
28. Rivero F, Moreno R, Barreales L, et al. Lower levels of in-stent late loss are not associated with the risk of stent thrombosis in patients receiving drug-eluting stents. EuroIntervenion 2008;4:124–32.
29. Stone GW. SPIRIT IV. Late breaking clinical trial. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 23, 2009; San Francisco, CA.
30. Smits P. COMPARE Trial. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 23, 2009; San Francisco, CA.
31. van Beusekom HM, Serruys PW. Drug-eluting stent endothelium. J Am Coll Cardiol Intv 2010;3:76–7.
32. Nakazawa G, Granada JF, Alviar CL, et al. Anti-CD34 antibodies immobilized on the surface of sirolimus-eluting stents enhance endothelialization. J Am Coll Cardiol Intv 2010;3:68–75.
33. van Werkum JW, Heestermans AA, Zomer AC, et al. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. J Am Coll Cardiol 2009;53:1399–409.
34. Dangas GD, Lansky AJ, Brodie BR, et al. Predictors of stent thrombosis after primary angioplasty in acute myocardial infarction. The HORIZONS-AMI Trial. Paper presented at: American College of Cardiology 2009 Scientific Sessions; March 29, 2009; Orlando, FL.

35. Brar SS, Leon MB, Stone GW, et al. Use of drug-eluting stents in acute myocardial infarction: a systematic review and meta-analysis. J Am Coll Cardiol 2009;53:1677–89.
36. Mauri L, Silbaugh TS, Garg P, et al. Drug-eluting or bare-metal stents for acute myocardial infarction. N Engl J Med 2008;359:1330–42.
37. Stettler C, Allemann S, Wandel S, et al. Drug eluting and bare metal stents in people with and without diabetes: collaborative network meta-analysis. BMJ 2008;337:a1331.
38. Patti G, Nusca A, Di Sciascio G. Meta-analysis comparison (nine trials) of outcomes with drug-eluting stents versus bare metal stents in patients with diabetes mellitus. Am J Cardiol 2008;102:1328–34.
39. Fuchs AT, Kuehnl A, Pelisek J, et al. Meta-analysis shows similar risk of thrombosis after drug-eluting stent, bare-metal stent, or angioplasty. Endothelium 2008;15:93–100.
40. Kirtane AJ, Ellis SG, Dawkins KD, et al. Paclitaxel-eluting coronary stents in patients with diabetes mellitus: pooled analysis from 5 randomized trials. J Am Coll Cardiol 2008;51:708–15.
41. Kaltoft A, Jensen LO, Maeng M, et al. 2-year clinical outcomes after implantation of sirolimus-eluting, paclitaxel-eluting, and bare-metal coronary stents: results from the WDHR (Western Denmark Heart Registry). J Am Coll Cardiol 2009;53:658–64.
42. Raber L. SIRTAX-LATE: five-year clinical and angiographic follow-up from a prospective randomized trial of sirolimus-eluting and paclitaxel-eluting stents. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 22, 2009; San Francisco, CA.
43. Leon M. The ENDEAVOR and ENDEAVOR resolute zotarolimus-eluting stent: comprehensive update of the clinical trial program (featuring the first presentation of the ENDEAVOR IV 3-year results). Paper presented at: Transcatheter CardiovascularTherapeutics; September 21, 2009; San Francisco, CA. Available at: http://www.tctmd.com/txshow.aspx?tid=939082&id=84004&trid=938634. Accessed October 28, 2009.
44. Park SJ. Comparison of sirolimus- and paclitaxel-eluting stents vs zotarolimus-eluting stents in real world practice: the ZEST randomized controlled trial. Paper presented at: i2 Summit at the American College of Cardiology Scientific Sessions; March 29–31, 2009; Orlando, FL.
45. Slottow TLP, Steinberg DH, Roy P, et al. Abstract 4483: long-term clinical outcomes of 233 patients who presented with definite/probable stent thrombosis. Circulation 2008;118:S897b.
46. van Werkum JW, Heestermans AA, de Korte FI, et al. Long-term clinical outcome after a first angiographically confirmed coronary stent thrombosis: an analysis of 431 cases. Circulation 2009;119:828–34.
47. Sianos G, Papafaklis MI, Daemen J, et al. Angiographic stent thrombosis after routine use of drug-eluting stents in ST-segment elevation myocardial infarction: the importance of thrombus burden. J Am Coll Cardiol 2007;50:573–83.
48. Grines CL, Bonow RO, Casey DE Jr., et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. J Am Coll Cardiol 2007;49:734–9.
49. Schulz S, Schuster T, Mehilli J, et al. Stent thrombosis after drug-eluting stent implantation: incidence, timing, and relation to discontinuation of clopidogrel therapy over a 4 year period. Eur Heart J 2009;30:2714–21.
50. Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. Circulation 2006;113:2803–9.
51. Kuchulakanti PK, Chu WW, Torguson R, et al. Correlates and long-term outcomes of angiographically proven stent thrombosis with sirolimus- and paclitaxel-eluting stents. Circulation 2006;113:1108–13.
52. Tsai TT, Nallamothu BK, Bates ER. Letter to the editor regarding article "Correlates and long-term outcomes of angiographically proven stent thrombosis with sirolimus- and paclitaxel-eluting stents." Circulation 2006;114:e362, author reply e363.
53. Airoldi F, Colombo A, Morici N, et al. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. Circulation 2007;116:745–54.
54. Chacko R, Mulhearn M, Novack V, et al. Impact of target lesion and nontarget lesion cardiac events on 5-year clinical outcomes after sirolimus-eluting or bare-metal stenting. J Am Coll Cardiol Intv 2009;2:498–503.
55. Byrne RA, Schulz S, Mehilli J, et al. Rationale and design of a randomized, double-blind, placebo-controlled trial of 6 versus 12 months clopidogrel therapy after implantation of a drug-eluting stent: the Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE) study. Am Heart J 2009;157:620–4.e2.
56. Park SJ, Park DW, Kim YH, et al. Duration of dual antiplatelet therapy after implantation of drug-eluting stents. N Engl J Med 2010;362:1374–82.
57. Lau WC, Gurbel PA, Watkins PB, et al. Contribution of hepatic cytochrome P450 3A4 metabolic activity to the phenomenon of clopidogrel resistance. Circulation 2004;109:166–71.
58. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation 2003;107:2908–13.
59. Gori AM, Marcucci R, Migliorini A, et al. Incidence and clinical impact of dual nonresponsiveness to aspirin and clopidogrel in patients with drug-eluting stents. J Am Coll Cardiol 2008;52:734–9.
60. Lev EI, Patel RT, Maresh KJ, et al. Aspirin and clopidogrel drug response in patients undergoing percutaneous coronary intervention: the role of dual drug resistance. J Am Coll Cardiol 2006;47:27–33.
61. Simon T, Verstuyft C, Mary-Krause M, et al. Genetic determinants of response to clopidogrel and cardiovascular events. N Engl J Med 2009;360:363–75.
62. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med 2009;360:354–62.
63. Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. JAMA 2009;302:849–57.
64. Gurbel PA, Bliden KP, Hayes KM, Yoho JA, Herzog WR, Tantry US. The relation of dosing to clopidogrel responsiveness and the incidence of high post-treatment platelet aggregation in patients undergoing coronary stenting. J Am Coll Cardiol 2005;45:1392–6.
65. Mega JL, Close SL, Wiviott SD, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. Circulation 2009; 119:2553–60.
66. Jeong YH, Lee SW, Choi BR, et al. Randomized comparison of adjunctive cilostazol versus high maintenance dose clopidogrel in patients with high post-treatment platelet reactivity: results of the ACCEL-RESISTANCE (Adjunctive Cilostazol Versus High Maintenance Dose Clopidogrel in Patients With Clopidogrel Resistance) randomized study. J Am Coll Cardiol 2009;53:1101–9.
67. Gilard M, Arnaud B, Cornily JC, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. J Am Coll Cardiol 2008;51:256–60.
68. Kreutz RP, Stanek EJ, Aubert R, et al. Impact of proton pump inhibitors on the effectiveness of clopidogrel after coronary stent placement: the Clopidogrel Medco Outcomes Study. Paper presented at: the Society for Cardiovascular Angiography and Interventions (SCAI) 2009 Scientific Sessions; May 6, 2009; Las Vegas, NV.
69. O'Donoghue M, Wiviott SD. Clopidogrel response variability and future therapies: clopidogrel: does one size fit all? Circulation 2006; 114:e600–6.
70. Siller-Matula JM, Lang I, Christ G, Jilma B. Calcium-channel blockers reduce the antiplatelet effect of clopidogrel. J Am Coll Cardiol 2008;52:1557–63.
71. Sibbing D, von Beckerath N, Morath T, et al. Oral anticoagulation with coumarin derivatives and antiplatelet effects of clopidogrel. Eur Heart J 2010;31:1205–11.
72. O'Donoghue ML, Braunwald E, Antman EM, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. Lancet 2009;374:989–97.
73. Bhatt DL, Cryer B, Contant CF, et al. The COGENT trial. Late breaking clinical trial abstract. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 24, 2009; San Francisco, CA.

74. Kimura T, Morimoto T, Nakagawa Y, et al. Antiplatelet therapy and stent thrombosis after sirolimus-eluting stent implantation. Circulation 2009;119:987–95.
75. Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. JAMA 2007;297:159–68.
76. Tanzilli G, Greco C, Pelliccia F, et al. Effectiveness of two-year clopidogrel + aspirin in abolishing the risk of very late thrombosis after drug-eluting stent implantation (from the TYCOON [two-year ClOpidOgrel need] study). Am J Cardiol 2009;104:1357–61.
77. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.
78. Chen KY, Rha SW, Li YJ, et al. Triple versus dual antiplatelet therapy in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Circulation 2009;119:3207–14.
79. van der Giessen WJ, Lincoff AM, Schwartz RS, et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. Circulation 1996;94:1690–7.
80. John MC, Wessely R, Kastrati A, et al. Differential healing responses in polymer- and nonpolymer-based sirolimus-eluting stents. J Am Coll Cardiol Intv 2008;1:535–44.
81. Wilson GJ, Nkazawa G, Schwartz RS, et al. Comparison of inflammatory response after implantation of sirolimus and paclitaxel-eluting stents in porcine coronary arteries. Circulation 2009;120:141–9.
82. Byrne RA, Joner M, Kastrati A. Polymer coatings and delayed arterial healing following drug-eluting stent implantation. Minerva Cardioangiol 2009;57:567–84.
83. Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? Circulation 2004;109:701–5.
84. Finn AV, Nakazawa G, Joner M, et al. Vascular responses to drug eluting stents: importance of delayed healing. Arterioscler Thromb Vasc Biol 2007;27:1500–10.
85. Windecker S, Serruys PW, Wandel S, et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet 2008;372:1163–73.
86. Serruys PW, Ormiston JA, Onuma Y, et al. A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. Lancet 2009;373:897–910.
87. Onuma Y, Serruys PW, the Absorb Investigators. ABSORB trial: three year clinical results of the evaluation of the bioabsorbable everolimus-eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions (abstr). Circulation 2009;120:S951.

Key Words: acute myocardial infarction ■ bare-metal stent ■ drug-eluting stent ■ dual antiplatelet therapy ■ percutaneous coronary intervention ■ stent thrombosis.

PART III

Individualised Patient Assessment

Chapter 3

Individualized assessment for percutaneous or surgical revascularization

Topol's Textbook of Interventional Cardiology (6th Edition).
In press.

Scot Garg, Patrick W. Serruys

KEY POINTS

- Changes in the demographic of patients presenting in need of revascularization, advances in percutaneous and surgical revascularization techniques, and results from contemporary studies of percutaneous versus surgical revascularization have all made it imperative that patients are assessed as individuals prior to selection of treatment strategy.
- Coronary revascularization must be appropriately tailored taking into account a patient's co-morbidities, coronary anatomy and personal preferences.
- Risk stratification plays an important role in the assessment of patients undergoing revascularization.
- Risk models can be used to assist physicians in risk stratifying patients in need of revascularization. They can be broadly divided into those assessing patients on the basis of their clinical co-morbidities, their coronary anatomy, or a combination of the two.
- The increasingly active involvement of patient's in the decision making process has ensured that the final verdict regarding the modality of revascularization is made only after appropriate discussions have taken place between all interested parties.

INTRODUCTION

Revascularization of patients with coronary artery disease (CAD) has progressed exponentially since Andreas Grüntzig performed the first balloon angioplasty in 1977.[1] These developments which have been fuelled by new technology have blurred the boundary between what is considered exclusively surgical disease, and what can be treated percutaneously. Consequently, there is a greater need than ever to tailor revascularization appropriately, taking into considering a patient's co-morbidities, coronary anatomy and personal preferences. This chapter will explore the increasing requirement for a more individualized assessment of patients undergoing revascularization, and then review the risk models currently available to assist in this stratification process. Finally, risk stratification from an individual patient's perspective will be discussed.

SECTION I: THE NEED FOR INDIVIDUALIZED PATIENT ASSESSMENT

Three major confounding factors have made it imperative that patients are assessed as individuals prior to the selection of revascularization strategy.

PATIENT CO-MORBIDITIES

The demographics of patients presenting to tertiary care services in need of revascularization are changing. This has been largely the consequence of increased longevity of the general population, a lower threshold to investigate patients presenting with symptoms suggestive of obstructive coronary

disease, and increased resources making revascularization via by percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) more accessible. Together with increased age, patients in need of revascularization are now more likely to have co-morbidities such as diabetes, hypertension, and hyerlipidaemia.[2-3] These factors are all implicated in accelerating the progression of CAD, and consequently patients are more likely to present with more extensive CAD. The Arterial Revascularization Therapies Studies (ARTS) Part I and II were separated by a time period of 5-years and despite both studies having the same inclusion criteria, patients in ARTS-II had a significantly greater incidence of risk factors, and overall increased disease complexity (**Table 1-1**).[4]

Patient co-morbidities must be taken into consideration when assessing patients for revascularization as they have the potential to significantly influence patient outcomes, moreover they may have a different impact depending on the underlying revascularization strategy selected. Of note, Legrand *et al* demonstrated that patient age was a significant independent predictor of major adverse cardiovascular and cerebrovascular (MACCE) events in patients enrolled in the ARTS-I and II studies who were treated with CABG, but not PCI.[5] In a collaborative patient level analysis of ten randomized

Table 1-1: The changing baseline demographics of patients enrolled in drug-eluting stent trials

	All Comers Studies		Complex Disease Studies		
	SIRTAX[8]	**LEADERS[9]**	**ARTS-I[10]**	**ARTS-II[11]**	**SYNTAX[12]**
Year(s) of enrolment	2003-2004	2006-2007	1997-1998	2003	2005-2007
Stent Type	DES	DES	BMS	DES	DES
Demographics					
Age, years (mean±SD)	62±11	65±11	61±10	63±10	65±10
Diabetes, %	20	24	19	26	26
Hypertension, %	61	73	45	67	69
Hypercholesterolemia, %	59	67	58	74	78
Previous myocardial infarction, %	29	33	44	34	32
Left ventricular function, % (mean±SD)	57±12	56±12	61±12	60±12	59±13
Lesion Characteristics (per patient)					
Multi-vessel disease, %	59	23	96	100	92
Bifurcation lesions, %	8	22	35	34	72
Total occlusions, %	19	12	3	17	24
SYNTAX Score (mean±SD)	12±7	14±9	-	21±10	28±12
Mean number of diseased lesions	1.4	1.5	2.8	3.6	3.6*
Procedural Characteristics (per patient)					
Mean number of stents	1.2±0.5	1.3±0.7†	2.8±1.3	3.7±1.5	4.6±2.3
Total stent length, mm (mean±SD)	25.9±15.5	24.7±15.5†	47.6±21.7	72.5±32.1	86.1±47.9

*Treated lesions

† Per lesion; SD, standard deviation; DES, drug-eluting stent; BMS, bare-metal stent

trials of patients with multi-vessel disease (MVD) treated with PCI (using BMS) and CABG Hlatky *et al* demonstrated comparable rates of the 5-year mortality amongst both treatment groups in patients without diabetes.[6] Importantly, amongst diabetics, mortality was significantly higher in patients treated with PCI, even after multi-variate adjustment (**Figure 1-1**). The clear importance of patient co-morbidities is highlighted by their central presence in risk models used in contemporary practice to assist in decision making; which are discussed in Section II.

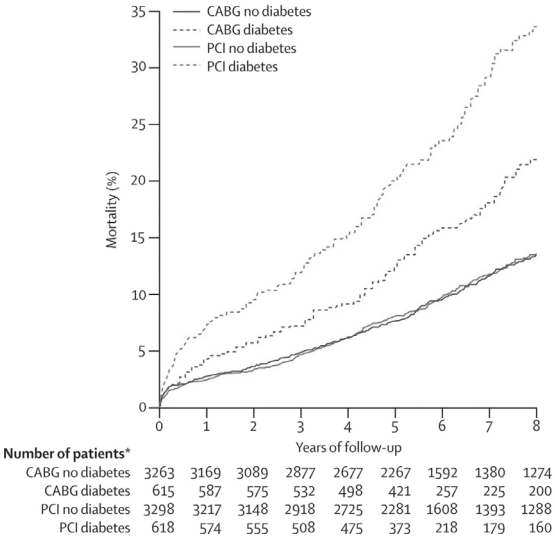


Figure 1-1: Cumulative survival curve of long-term mortality stratified according to diabetic status amongst patients with multi-vessel disease who were randomized to treatment with percutaneous coronary intervention or coronary artery bypass graft surgery. The importance of diabetic status on outcomes are highlighted not only by the higher mortality amongst diabetics compared to non-diabetics, but also by the greater impact diabetic status had on patients treated with PCI compared to CABG. Reprinted with permission from Hlatky MA, Boothroyd DB, Bravata DM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet.* 2009;373(9670):1190-1197.

TECHNOLOGICAL ADVANCES

The introduction in 2002 of drug eluting stents (DES) revolutionized the practice of interventional cardiology which was driven primarily through their dramatic reduction in rates of repeat revascularization.[7] The impressive results seen with the use of DES promptly resulted in an expansion in the indications for PCI, such that bifurcation lesions, chronic total occlusions and MVD were increasingly treated with PCI, where previously these lesion subsets were deemed more appropriate for surgical revascularization. Evidence of this expansion can be seen in the changing baseline lesion

characteristics of patients enrolled in 'all-comers' PCI studies such as SIRTAX (Sirolimus-eluting and Paclitaxel-eluting stents for coronary revascularization trial),[8] LEADERS (Limus Eluted from A Durable versus ERodable Stent coating study)[9] and in studies of complex (triple vessel disease [3VD], and/or left main [LM]) CAD such as ARTS-I,[10] ARTS-II[11] and the SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study (**Table 1-1**).[12] Further evidence in support of this change come from assessments of 'real-world' clinical practice which indicate that approximately one-third of patients with complex disease are now treated with PCI.[13] Coupled with this expanding use of PCI which was driven largely through the beneficial effects of DES, the introduction of lower profile balloons and new guide-wires, are other advances which include new adjunctive pharmacological therapies and the increasing availability of percutaneous extracorporeal circulatory support (**Figure 1-2**).[14-15] From a technical point of view therefore the majority of coro-

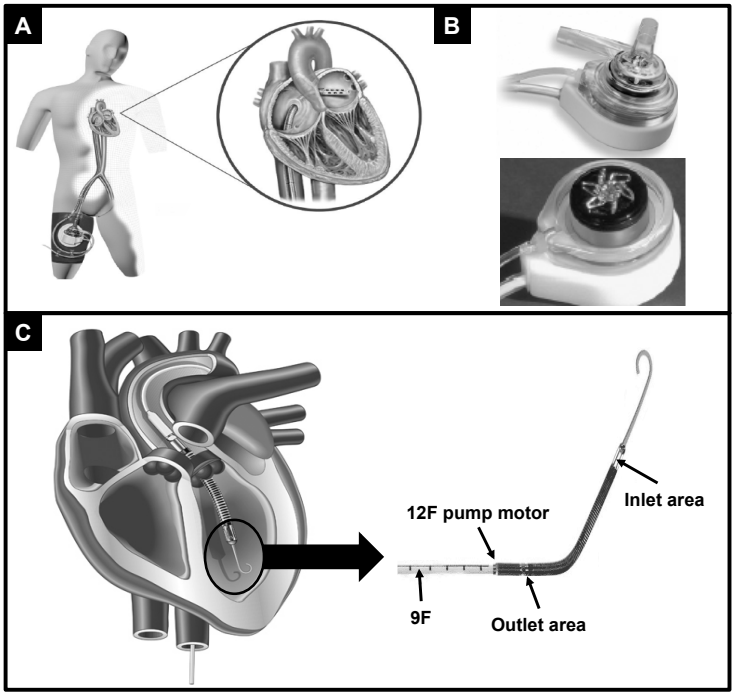


Figure 1-2: Devices that are increasingly available to provide assistance during high-risk PCI include percutaneous extra-corporeal circulatory support devices such as: (A, B) the TandemHeart® and (C) the Impella device. (A) The TandemHeart® removes oxygenated blood from the left atrium and returns this blood into the peripheral arterial circulation; with the (B) aid of a centrifugal pump. Reprinted from *EuroIntervention*, with permission from Europa (modified).[78] (C) The Impella left ventricular assist device is a miniaturized rotary blood pump, which is placed retrograde across the aortic valve, and aspirates (inlet area) up to 2.5l/min of blood from the left ventricular cavity, and subsequently expels (outlet area) this blood into the ascending aorta. Reprinted with permission from Valgimigli M, Steendijk P, Serruys PW, et al. Use of Impella Recover(R) LP 2.5 left ventricular assist device during high-risk percutaneous coronary interventions; clinical, haemodynamic and biochemical findings. *EuroIntervention* 2006;2(1):91-100.

nary lesions can now be addressed with PCI, however, this approach may not always be appropriate, necessitating the need for individual patient selection.

CLINICAL TRIAL RESULTS

Randomized trials comparing CABG and PCI have been centered on two major patient groups: those with isolated proximal left anterior descending artery lesions, and those with complex disease namely 3VD and/or LM disease. Taking the results of these studies at face-value, and irrespective of which patient group has been assessed, results at short- and long-term follow-up suggest that there are no differences in the hard clinical outcomes of death, and MI between patients treated with

Table 1-2: A summary of meta-analyses reporting long-term outcomes in patients with isolated proximal LAD disease or multi-vessel disease randomized to percutaneous or surgical revascularization.

Study [Ref]	No. of patients (PCI/CABG)	POBA/ BMS/ DES (%)	Follow-up (months)	Death (PCI vs. CABG)	MI (PCI vs. CABG)	Stroke (PCI vs. CABG)	Repeat revascularization (PCI vs. CABG)	MACCE (PCI vs. CABG)
Isolated Proximal LAD								
Aziz *et al*[16]	1952 (1300/652)	0/91/9	34	2.9% vs. 3.4%	2% vs. 1.1%	2.4% vs. 3.5%	14.3% vs. 4.4%*	21.4% vs. 11.1%*
Kapoor *et al*[17]	1210 (633/577)	22/59/19	60	9.4% vs. 7.2%	NA	NA	33.5% vs. 7.3%*	NA
Multi-vessel disease								
Bravata *et al*[20]	9963 (5019/4944)	56/42/2	60	9.3% vs. 11.3%	0.6% vs. 1.2%*	11.9% vs. 10.9%	46.1% vs. 40.1% vs. 9.8%*¶	-
Daemen *et al*[19]	3051 (1518/1533)	4/96/0	60	8.5% vs. 8.2%	2.5% vs. 2.9%	6.6% vs. 6.1%	25.0% vs. 6.3%*	34.2% vs. 19.6%*
Hlatky *et al*[6]	7812 (3923/3889)	63/37/0	5.9	10.0% vs. 8.4%	16.7% vs. 15.4%†	-	24.5% vs. 9.9%* †	36.4% vs. 20.1%*

*p<0.001
†composite with death
¶ Balloon angioplasty vs. PCI vs. CABG
PCI, percutaneous coronary intervention
CABG, coronary artery bypass grafting
MI, myocardial infarction
NA, not available
MACCE, major adverse cardiovascular and cerebrovascular events (a composite of death, stroke, MI, and repeat revascularization)
POBA, balloon angioplasty; BMS, bare metal stent; DES, drug eluting stent.

PCI or CABG (**Table 1-2**).[6,16-20] Undisputedly CABG has been associated with a clear and consistent significant reduction in rates of repeat revascularization.

Importantly, these studies all have several notable limitations which restrict the ability to extrapolate their results to routine clinical practice, and subsequently this reinforces the need to assess patients individually before selecting revascularization therapy.

a. The inclusion criteria have commonly excluded (through patient assessment) patients with impaired left ventricular function, LM disease, and multiple co-morbidities. Moreover, although these studies have been assessing patients with MVD, this extent of CAD was actually seen in only around one third of patients. Overall, only approximately 5-10% of all potential patients were enrolled, and therefore the comparable outcomes observed in these studies, and subsequent meta-analyses, can only be applied to a fraction of those patients in need of revascularization. It must be appreciated however that this patient selection was necessary to enable ethical randomization, (i.e. to ensure that patients were suitable for both PCI and CABG) however paradoxically by eliminating those patients at highest risk, it comes as no surprise that subsequent mortality was comparable. Of note, clinical outcomes have rarely been reported, other than in the Bypass Angioplasty Revascularization Investigation (BARI) study[21-22] and SYNTAX study[12] of the sizeable proportion of patients with complex disease who were screened, but not enrolled in the randomized arm of the study.
b. Clinical results have been presented for all patients en masse irrespective of their disease severity. There is a wide variation in the complexity of disease, and not all 3VD disease is the same, as highlighted by the important results of the SYNTAX study[12] which are discussed below.

Overall considering these limitations, these early randomized trials of PCI versus CABG indicate somewhat paradoxically that if patients are selected appropriately, comparable outcomes are achievable irrespective of the modality of revascularization eventually selected. Moreover in this group of patients with comparable outcomes, patient choice plays an important factor in determining the overall treatment strategy, as discussed further in Section III.

SYNTAX TRIAL

The SYNTAX trial, which currently represents the largest assessment of treatment with PCI or CABG in patients with complex disease, represents an important study which clearly indicates the importance, and potential benefits of assessing patients at an individual level.

The study aimed to supply evidence to support the already established, but non-evidence based, practice of performing PCI in patients with complex disease,[13] and also sought to identify which patients should only be treated with CABG. The study design attempted to address the limitations of the earlier trials described above, and in doing so it was anticipated that the results would be more relevant to everyday clinicians. Specifically:

Table 1-3: The SYNTAX score algorithm

1. Arterial Dominance
2. Arterial segments involved per lesion
3. Diameter stenosis
Total occlusion Significant lesions (50-99%)
Adverse Lesion Characteristics
4.. Total occlusion
i. Number of segments involved
ii Age of the total occlusion (>3 months)
iii. Blunt Stump
iv. Bridging collaterals
v. First segment beyond the occlusion visible by antegrade or retrograde filling
vi. Side branch involvement
5. Trifurcation
i. Number of segments diseased
6. Bifurcation
i. Medina Type
ii. Angulation between the distal main vessel and the side branch <70º
7. Aorto-ostial lesion
8. Severe tortuosity
9. Length >20mm
10. Heavy calcification
10. Thrombus
12. Diffuse disease/small vessels
i. Number of segments with diffuse disease/small vessels

The angiographic components of the SYNTAX score. The characteristics above are scored for each lesion greater than 50% diameter stenosis, and added to together to provide the total SYNTAX score. Full definitions of all variables are published[38-39] and available online (www.syntaxscore.com).

- To ensure results were applicable to routine practice the study was designed as 'an all-comers' trial such that there were no specific inclusion criteria, other than the need to have 3VD or LMS disease (in isolation or with CAD). Exclusion criteria were minimal and limited to prior revascularization, recent MI, or those requiring concomitant cardiac surgery.[23] In contrast to the earlier studies 70.9% of eligible patients were enrolled.
- The previously indicated problem of reporting outcomes from all patients with complex CAD together, irrespective of disease severity, was addressed in the SYNTAX study through the utilization of the newly developed SYNTAX score (SXscore)(**Table 1-3),** which enabled CAD complexity to be quantified.
- To ensure assessment of patients on an individual level, all patients eligible for enrollment were discussed at a 'Heart-Team' conference where an interventional cardiologist and cardiac surgeon carried out a careful and through review of the patient in terms their anginal status, co-morbidities, and coronary anatomy, using the respective Braunwald score, euroSCORE and SXscore (discussed in Section II). The consensus reached from this meeting was subsequently used to

allocate the patient into one of the three arms of the trial. In total 3075 patients were enrolled into:

1. Randomized group (1800 patients [58.5%]: 897 CABG, 903 PCI) – these patients had CAD which was suitable for treatment with PCI or CABG. The mean SXscore of this group was 26.1 and 28.8 in patients treated with CABG and PCI respectively.
2. CABG registry (1077 patients [35.0%]) – these patients had CAD that was considered unsuitable for PCI, clearly reflected in the high mean SXscore for this group of 37.8.
3. PCI registry (198 patients [6.4%]) – these patients were deemed unsuitable for CABG. The commonest reason for this decision was the presence of multiple co-morbidities[24] reflected in the mean euroSCORE of patients in this group which was 2 points higher than the mean in randomized group (5.8 vs. 3.8).

Overall the study failed to meet the pre-specified primary endpoint of non-inferiority in terms of 12-month major adverse cardio- and cerebrovascular events (MACCE), a composite of death, stroke, MI and repeat revascularization (17.8% vs. 12.4%, p=0.002). This was driven by significantly lower rates of repeat revascularization with CABG (13.5% vs. 5.9%, p<0.0001). Moreover, consistent with prior studies of MVD, there were no significant differences in the overall safety endpoints of death, MI or death/stroke/MI out to 12-months follow-up. Results at two-year follow-up, which are considered hypothesis generating in view of the failure to reach the primary endpoint, are somewhat similar to earlier results with comparable rates of death (PCI 6.2% vs. CABG 4.9%, p=0.24) and the composite of death/stroke and MI (10.8% vs. 9.6%, p=0.44), whilst significantly higher rates of repeat revascularization (17.4% vs. 8.6%, p<0.001) and overall MACCE (23.4% vs. 16.3%, p<0.001) were seen with PCI.[25]

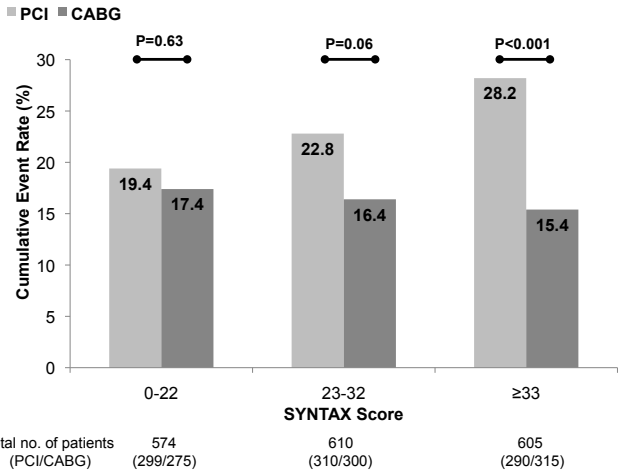


Figure 1-3: Two year rates of major adverse cardiovascular and cerebrovascular events (a composite of death, stroke, myocardial infarction and repeat revascularization) amongst the 1800 patients randomized to PCI or CABG in the SYNTAX study, stratified according to SYNTAX score. Of note, clinical outcomes were comparable between PCI and CABG in those with a SXscore of 0-22, trended in favor of CABG in those with a SXscore of 23-32, and were significantly lower with CABG in those with a SXscore ≥33.[25]

As indicated earlier analysis of all patients irrespective of disease severity does not provide adequate information for clinicians, who day-to-day are faced with patients with a wide variation of CAD complexity. To address this limitation of earlier studies, patient outcomes in the SYNTAX study were stratified according to terciles of the SXscore. As shown in **Figure 1-3**, clinical outcomes between patients treated with PCI and CABG were similar in those in the low SXscore group, trended in favor of CABG in the intermediate group, and were significantly lower in the CABG group amongst patients in the

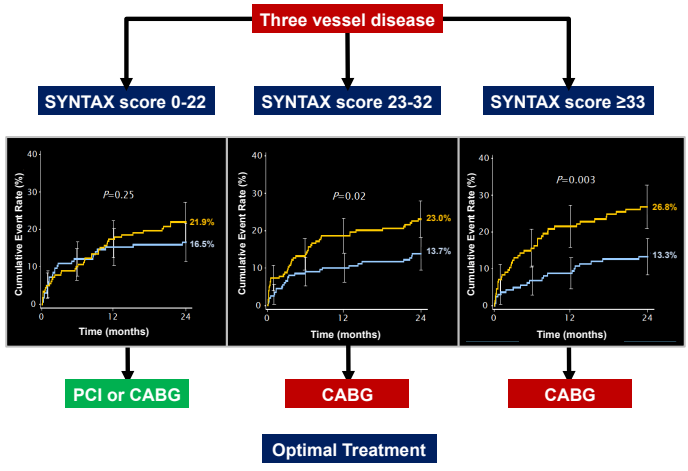
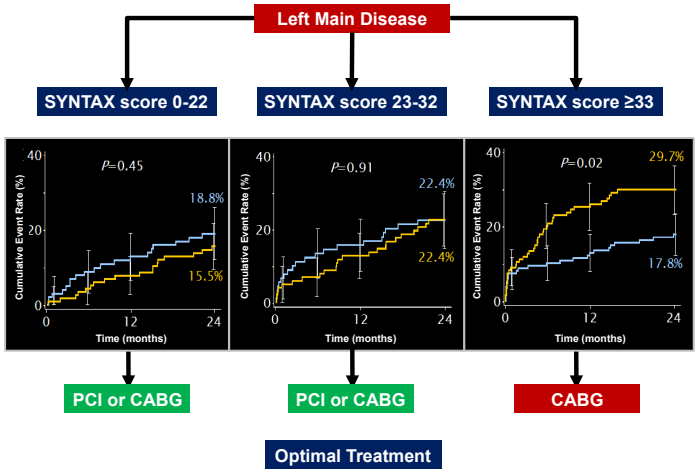


Figure 1-4: The evidence supporting the use of the SYNTAX score as a tool to assist in revascularization decisions. (Above) In patients with three-vessel disease, the rate of major adverse cardiovascular and cerebrovascular (MACCE, a composite of death, stroke, myocardial infarction and repeat revascularization) at 2-year follow-up was only comparable between patients treated with PCI (yellow) and CABG (blue) for SYNTAX scores of 0-22; for all other SYNTAX scores outcomes were significant better following CABG.[26] (Below) In patients with left main disease clinical outcomes were comparable between patients treated by PCI or CABG for all SYNTAX scores, apart from those above 32, when outcomes were significantly better with CABG.[27]



highest SXscore group. The intermediate group was further sub-divided into a 3VD cohort, where outcomes were lower with CABG, and into a LM cohort, where outcomes were comparable between PCI and CABG (**Figure 1-4**).[26-27]

These results reiterate the importance of assessing patients when selecting revascularization strategy. The SYNTAX study was able to identify those patients in whom either PCI or CABG was appropriate, and perhaps more importantly the group of patients in whom CABG was the optimal treatment. Considering the distribution of CAD in the SYNTAX study, overall one-third of patients with 3VD/LM disease were deemed to have CAD that could be treated safely and effectively with PCI or CABG, whilst in remaining two-thirds, CABG remained the standard of care. Whilst these results were consistent with what was already practiced;[13] the validation of the SXscore importantly facilitates a more objective assessment of patients by physicians as discussed in Section II.

SECTION II: INDIVIDUAL ASSESSMENT – FROM A PHYSICIAN'S PERSPECTI VE

There is no disputing the need and potential benefits of selecting revascularization strategy following an individualized patient assessment or risk stratification. Risk stratification is performed routinely and subconsciously by physicians in everyday clinical practice and is in essence behind all clinical decisions made by a physician. Stratification of risk is vital when assessing patients for revascularization as this treatment is only considered appropriate when, "*the expected benefits, in terms of survival or health outcomes (symptoms, functional status, and/or quality of life) exceed the expected negative consequences of the procedure*".[28] Section I has already discussed the factors which have increased the importance of this risk stratification in contemporary practice. Section II will describe the currently available methods of risk stratifying patients.

QUALITATIVE VS. QUANTITATIVE RISK ASSESSMENT

Qualitative risk stratification is subjective and relies on a clinician's experience, however advantageously for an individual's perspective this assessment has the greatest sensitivity as all factors relevant to assessing risk in that particular individual can be considered, rather than the select list of variables included in a risk model. Moreover, this subjective qualitative assessment also allows risk to be calculated and tailored to the expertise of the physician performing the procedure, as opposed to a clinician in another region who may use different techniques, and have different equipment available. Finally this assessment does not require a calculator or computer, and can be 'computed' sub-consciously very quickly. The major disadvantages of this method of risk assessment are its dependence on an operator's prior experience, and its high inter-observer variability.

Quantitative risk stratification can be performed using a variety of risk models which incorporate clinical variables which have been sourced from large patient databases.[29-36] These risk models largely incorporate objective variables ensuring adequate reproducibility of the score; however

those models such as the American College of Cardiology/American Heart Association (ACC/AHA) lesion score[37] or the SYNTAX score[38] which include angiographic variables continue to have documented intra- and inter-observer variability.[39-40] In addition to their role in the risk stratification of individual patients, these quantitative risk models have increasing use in the wider context of overall healthcare. They can provide a vital measure of overall patient care, and can help identify future directions to further improve outcomes. Clinical governance and the increasing requirement to publically report clinical performance (and complications) have also propelled the need to risk stratify patients thereby allowing a useful comparison of performance to be made between clinicians (and institutions) and the standards dictated by regulatory authorities.[41] In addition calculation of risk using accepted risk models can aid clinicians who are faced with an increasing need to be able to justify their clinical decisions to peers, regulatory bodies, and patients.

In comparison to the qualitative risk models, the use of a finite number of variables results in these model lacking the sensitivity to accurately predict risk in an individual, such that they are more apt at predicting risk for a population of patients with similar co-morbidities. The number of variables included in the model must strike a balance between sufficient numbers to enable a meaningful prediction of risk to be calculated; however the number must not be excessive so as to prevent use in routine practice. In addition, a minimal number of variables reduces the chances of colinearity between independent variables, which can result in redundant information being collected,[34] whilst also increasing the chances of 'over-fitting' the model, and thereby reducing the overall accuracy of the results.[42]

The applicability of a risk model to contemporary practice must also take into consideration the time when the model was developed. Risk models rely on large patient databases to derive appropriate weighting factors for variables in the model to enable the final calculation of risk. It follows that they are developed using retrospective information which may no longer be relevant in the era when the model is being used. The European System for Cardiac Operative Risk Evaluation (euroSCORE) for example was developed in 1999, however there have been calls for its recalibration as repeated evaluations indicate that it over-estimates risk by a factor of 2-3, which has largely been attributed to improvements in surgical techniques, and lower peri-operative mortality in the decade following its construction.[43-44] The Society of Thoracic Surgeons (STS) score is also derived from a large patient database, however unlike the euroSCORE, the STS calculator is being periodically recalibrated to ensures its results are applicable to contemporary practice.[45]

RISK MODELS IN CONTEMPORARY PRACTICE

Numerous risk models are available to assist clinicians in stratifying risk amongst patients undergoing revascularization. Some models are appropriate for patients prior to the selection of revascularization strategy, whilst some have only been validated in patients undergoing one form of treatment. Nevertheless the various models can largely be categorized according to the variables (clinical, angiographic or combination of both) which are used in the overall estimation of risk. **Table 1-4**

Table 1-4. Summary of contemporary and newly developed risk models for assessment of risk in patients undergoing revascularization.

Risk Model	Number of variables used to calculate score		Validated in PCI / CABG	
	Clinical	Angiographic	PCI	CABG
euroSCORE [12,29-31,46-53]	17	0	+	+
Mayo Clinic Risk Score [32,54,66]	17	0	+	+
ACEF [34]	3	0	-	+
National Cardiovascular Database Registry risk model[35]	8	0	+	-
AHA/ACC Lesion classification [37,55-58]	0	11 (per lesion)	+	-
SYNTAX score [4,12,26-27,38-39,48,53,57-58,60-65]	0	11 (per lesion)	+	+
Society of Thoracic Surgery score [36,45,54,67]	40	2	-	+
Global Risk Classification [68]	17	11 (per lesion)	+	+
Clinical SYNTAX score [69]	3	11 (per lesion)	+	-

PCI, percutaneous coronary intervention
CABG, coronary artery bypass grafting surgery
ACEF, age, creatinine and ejection fraction
AHA/ACC, American Heart Association/American College of Cardiology

summarizes the different risk models used in contemporary practice, and they are described in more detail below.

CLINICAL BASED SCORES

These risk scores only incorporate clinical variables, and do not require any data from the angiogram. They offer the advantage of being able to be computed relatively quickly, usually at the bedside, and principally include variables which are not subject to user interpretation, thereby ensuring excellent reproducibility.

euroSCORE

The additive euroSCORE[30] is a clinical risk score calculated using 17 different clinical variables (**Table 1-5**), which has been used since 1999 to predict in-hospital, and long-term mortality in patients undergoing cardiac surgery.[30,46-47] Early validation studies however suggested that it under-estimated risk in those at highest risk, resulting in the development of the logistic euroSCORE, which uses the same clinical variables, however it requires the use of an on-line calculator (available at www.euroscore.org) to quantify risk.[31]

In addition to its assessment and validation in patients undergoing surgical revascularization, the euroSCORE has also been evaluated in numerous studies of patients undergoing PCI,[12,48-52] the majority of which specifically enrolled patients with LM disease.[12,48-51] Of note, all studies, irrespective of disease severity, have been demonstrated the euroSCORE to be an independent predictor of mortality[49,52] and/or MACCE at follow-up ranging from 1- to 3-years.[12,48-51] Importantly those studies

Table 1-5. The components of the euroSCORE, and relevant weighting factors of the additive and logistic euroSCOREs.[30-31]

Patient	Characteristics	Additive	Logistic β coefficient
Age	Per 5 years or part thereof over the age of 60 years	1	0.07
Gender	Female	1	0.33
Chronic Pulmonary Disease	Long-term use of bronchodilators or steroids for respiratory disease	1	0.49
Peripheral arteriopathy	*Claudication, carotid stenosis>50%, previous or planned intervention on the abdominal aorta, limb arteries or carotids	2	0.66
Neurological dysfunction	Severely affected mobility or day to day function	2	0.84
Previous cardiac surgery	Previous opening of the pericardium	3	1.00
Serum creatinine	Pre-operatively greater than 200micromol/l	2	0.65
Active endocarditis	Antibiotic therapy at time of surgery	3	1.10
Critical preoperative state	*Preoperative cardiac arrest, ventilation, renal failure, inotropic support, intra-aortic balloon pump use, ventricular arrhythmia	3	0.91
Cardiac related factors			
Unstable angina	Rest pain requiring iv nitrates	2	0.57
Left ventricular function	Moderate (30-50%)	1	0.42
	Poor (<30%)	3	1.09
Recent MI	Within 90 days	2	0.55
Pulmonary hypertension	Systolic pulmonary pressure>60mmHg	2	0.77
Operation related factors			
Emergency	Operation performed before the start of next working day	2	0.71
Other than isolated CABG	Major cardiac procedure other than or in addition to CABG	2	0.54
Surgery on thoracic aorta		3	1.16
Post infarct septal rupture		4	1.46
Constant β_0			-4.79

*Any of the following
The logistic euroSCORE can be calculated at www.euroscore.org.

which also included a surgical control group, such as the SYNTAX study, the MAIN-COMPARE study, and the registry by Rodés-Cabau *et al*, also demonstrated that the euroSCORE was an independent predictor of MACCE in surgical patients.[48,50,53]

Specifically in the SYNTAX study, which represents the only randomized study assessing the euroSCORE, the additive euroSCORE was shown to be an independent predictor of MACCE at 1-year follow-up irrespective of the method of revascularization (OR: 1.21; 95% CI [1.12-1.32], p<0.001) in 705 patients undergoing LM revascularisation.[48] Similarly at intermediate follow-up of 23-months, Rodés-Cabau *et al* identified a euroSCORE ≥9 as the best predictor of MACCE after PCI and CABG

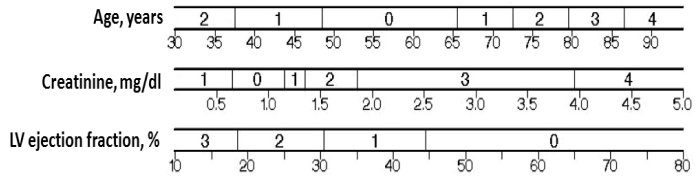
amongst 249 octogenarians with LM disease.[50] In the MAIN-COMPARE registry which enrolled over 1500 patients with LM disease followed up for a median of 3.1 years, the euroSCORE has been identified as an independent predictor of death/MI/stroke irrespective of revascularization strategy.[53] In addition in the same registry a euroSCORE ≥6 has been shown to be an independent predictor of mortality following either PCI or CABG.[49]

The ability of the euroSCORE to identify patients at high risk of adverse events is not confined to those with LM disease. Romagnoli *et al* have previously reported that the euroSCORE is an independent predictor of in-hospital mortality amongst over 1100 patients, 70% of whom had single vessel disease. Moreover, the C-statistic for the prediction of in-hospital mortality using the euroSCORE in this population was 0.91.[52]

In summary, whilst acknowledging that most of these studies have been non-randomized observational studies, the findings do suggest that the euroSCORE is a valuable tool in the individual assessment of risk prior to the selection of revascularization strategy. Furthermore these data also indicate that the euroSCORE has little utility in helping determine treatment strategy, as the risk of adverse events from a high euroSCORE is similarly high following either PCI or CABG.

Table 1-6. The Mayo Clinic Risk Score [32]

Variable	Points
Age, years	See below
Creatinine, mg/dl	See below
Left ventricular ejection fraction %	See below
Pre-procedural shock	9
Myocardial infarction < 24 hours	4
Congestive heart failure on presentation (without acute MI or shock)	3
Peripheral vascular disease	2
Mayo Clinic Risk Score	Sum of the. above



The Mayo Clinic Risk Score.[32] Congestive heart failure (CHF) is not entered in patients presenting with myocardial infarction (MI) or shock. If creatinine is unavailable: 1 point is added if the patient is male or has CHF. If ejection fraction is unavailable: 1 point is added if the patient has CHF. For all other variables, if a risk factor is unknown, no points are added.

Mayo Clinic Risk Score (MCRS)

The MCRS represents a clinical based risk score, incorporating seven variables (**Table 1-6**), which was initially developed to predict in –hospital mortality in patients undergoing PCI, however subsequent validation has also been performed in patients undergoing CABG.[32,54] In PCI patients the score was initially validated in 7,457 patients from the Mayo clinic database with resulting C-statistics of 0.74 and 0.89 for the prediction of MACE and procedural death, respectively.[32] A subsequent larger external validation performed in over 300,000 patients from the National Cardiovascular Data Registry demonstrated a good predictive ability of MCRS, with a C-statistic of 0.885 for the prediction of in-hospital mortality.[33] In patients undergoing CABG, a strong association has been demonstrated between the MCRS and mortality, however the overall performance has been shown to be inferior to the Society of Thoracic Surgery (STS) score.[54]

Table 1-7: The National Cardiovascular Database

Variable	Scoring Response Categories			
Age	<60	≥60, <70	≥70, <80	≥80
Weighted score	0	4	8	14
Cardiogenic shock	No	Yes		
Weighted score	0	25		
Prior CHF	No	Yes		
Weighted score	0	5		
Peripheral vascular disease	No	Yes		
Weighted score	0	5		
Chronic lung disease	No	Yes		
Weighted score	0	4		
GFR (ml/min)	<30	30-60	60-90	>90
Weighted score	18	10	6	0
NYHA Class IV	No	Yes		
Weighted score	0	4		
PCI Status (STEMI)	Elective	Urgent	Emergent	Salvage
Weighted score	12	15	20	38
PCI Status (no STEMI)	Elective	Urgent	Emergent	Salvage
Weighted score	0	8	20	42

Registry risk model.[35]

CHF, congestive cardiac failure; GFR, glomerular filtration rate; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

The risk of in-hospital mortality is derived using **Figure 1-5**

These results suggest that the MCRS can be used to assess risk in patients undergoing revascularisation; however validated outcomes are limited to only in-hospital mortality. Additional studies assessing the impact of the MCRS in patients randomised to PCI and CABG remain outstanding.

Age, Creatinine, Ejection Fraction (ACEF) Score

The ACEF score represents a newly developed risk model which uses just three clinical variables: patient age, ejection fraction (%) and serum creatinine to predict in-hospital mortality in patients undergoing elective CABG.[34] The three variables are combined using a simple formula [patient age/ejection fraction (%)] + [1 if creatinine >2mg/dl]. The only published data thus far comes from a single institution and includes the initial data set of 4557 patients, and a subsequent validation series of 4091 patients. Nevertheless results demonstrated a similar accuracy and calibration for the prediction of in-hospital mortality with the ACEF score when compared with other more complicated surgical risk scores such as the euroSCORE and the Cleveland Clinic Score.

The current data, although limited to a single centre, indicates a role for the ACEF score in the assessment of risk in patients undergoing CABG; however the precise role of the ACEF score in assessing patients undergoing revascularization (PCI or CABG) will only be defined following its evaluation in patients undergoing PCI.

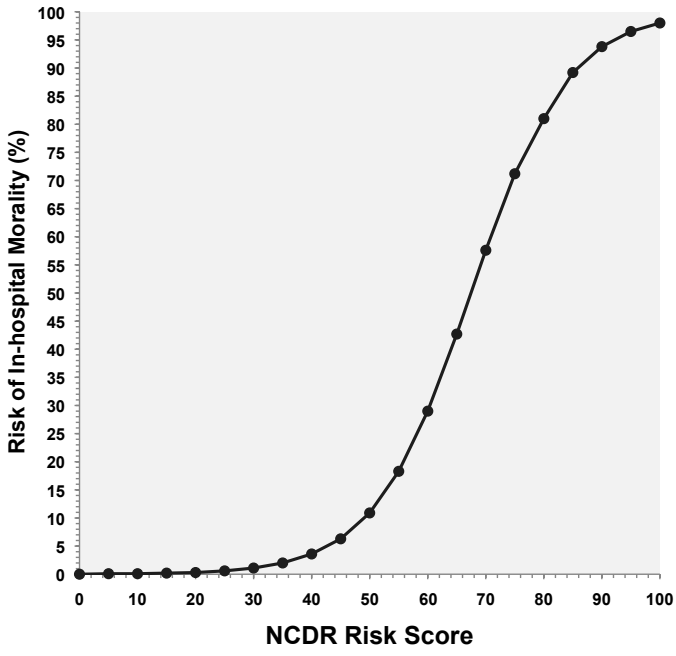


Figure 1-5: The predicted risk of in-hospital mortality using the National Cardiovascular Database Registry risk score described in Table 1-7.[35]

National Cardiovascular Database Registry (NCDR) CathPCI Risk Prediction Score

The NCDR CathPCI risk prediction score is the most contemporary clinical based risk model currently available. It incorporates information from eight clinical variables (**Table 1-7**) which are assigned appropriate weighted values, and then added together to give a final score which can be translated into a risk of in-hospital mortality (**Figure 1-5)**.[35] The score was developed using data from over 180,000 patients from the voluntary US NCDR database, and validated in over 400,000 patients from the same database who underwent PCI between March 2006 and March 2007. Of note, the C-statistic for the prediction of in-hospital mortality was consistently above 0.90 for in-hospital mortality, whilst a lower, but nevertheless adequate C-statistic of 0.83 was seen for 30-day mortality.

There are as yet no data on the use of this model in patients undergoing CABG, however it worth acknowledging that a number of variables used in the NCDR model are also used in the euroSCORE. Moreover, the large numbers of patients which have been used to validate the NCDR model, and the high discriminatory ability certainly indicate that it may become an important risk tool for patients undergoing revascularization in due course.

ANGIOGRAPHIC-BASED SCORES

Two major angiographic based scores have been developed, both of which are independent of patient clinical variables, being calculated using only angiographic data. As alluded to earlier, this introduces a subjective element to the assessment of risk,[39-40] and consequently introduces a degree of intra- and inter-observer variability, which is notably absent from the clinical scores described above. Finally these scores can only be computed after diagnostic coronary angiography has been performed, thereby moving assessment further down the treatment pathway.

ACC/AHA Lesion classification

The ACC/AHA lesion classification which was initially devised in 1986 and modified in 1990, uses 11 angiographic variables to categorize lesions into four groups: Type A, B1, B2 and C. Historical studies prior to the arrival of DES indicated that that ACC/AHA lesion classification did have a prognostic impact on early and late outcomes.[37,55] In contemporary practice evaluation of the ACC/AHA lesion classification is limited to retrospective registries, the largest of which is the German Cypher registry, which enrolled over 6,700 patients with approximately 8,000 lesions. At 6-month follow-up no definite relationship was identified between clinical outcomes and ACC/AHA lesion class.[56] These results are at variance to the positive relationship identified between ACC/AHA lesion class and clinical outcomes in smaller studies of patients with more complex disease.[57-58]

Specifically Valgimigli *et al* reported that a higher ACC/AHA lesion score (derived by assigning 1, 2, 3 and 4 points to Type A, B1, B2 and C lesions respectively) correlated with poor clinical outcomes amongst 306 patients with three vessel disease undergoing PCI with DES.[57] More recently Capodanno *et al* demonstrated that the ACC/AHA lesion score predicted both cardiac death (p=0.001) and MACE (p=0.02) at 1-year follow-up amongst 255 patients with LM undergoing PCI with DES.[57]

Table 1-8: A summary of the results of the most prominent studies which have assessed the impact of the SYNTAX score on clinical outcomes in patients undergoing PCI.

Study Name	No. of patients (FUP, mths)	MACE, % (Tercile 1 vs. 2 vs. 3)	Death, % (Tercile 1 vs. 2 vs. 3)	MI, % (Tercile 1 vs. 2 vs. 3)	Repeat revascularization, % (Tercile 1 vs. 2 vs. 3)	Independent predictor	
						Mortality	MACE
All-Comers Population							
LEADERS[61]	1397 (12)	7.8 vs. 8.9 vs. 15.4*	1.5 vs. 2.1 vs. 5.6*	4.3 vs. 4.9 vs. 5.9	4.7 vs. 6.1 vs. 8.7†¶	+	+
SIRTAX[63]	848 (60)	12.5 vs. 21.2 vs. 24.2*	6.3 vs. 8.1 vs. 11.8	3.1vs. 8.7vs. 8.1†	9.4 vs. 15.7 vs. 15.7†¶	-	+
Complex disease							
ARTS-II[4]	607 (60)	19.9 vs. 29.9 vs. 32.9*	2.4 vs. 7.5 vs. 6.5	3.3 vs. 7.0 vs. 7.0	13.9 vs. 22.6 vs. 24.6†‡	NA	+
SYNTAX[12]	903 (12)	13.6 vs. 16.7 vs. 23.4*	2.0 vs. 3.3 vs. 8.0*	2.7 vs. 4.9 vs. 7.0	11.5 vs. 12.1 vs. 16.8	NA	NA
Left Main Disease							
SYNTAX LM cohort[59]	357 (12)	7.7 vs. 12.6 vs. 25.4*	0.9 vs. 1.0 vs. 9.7*	1.7 vs. 2.9 vs. 7.5	7.7 vs. 9.7 vs. 17.2†	NA	+
CUSTOMIZE registry[58]	255 (12)	7.4 vs. 21.4 vs. 20.4	2.5 vs. 1.1 vs. 13.1§	NA	NA	+	+
MAIN-COMPARE[53]	819 (36)	4.6 vs. 9.4 vs. 11.4†‖	NA	NA	NA	-	-
Rotterdam registry [62]	148 (48)	46.2 vs. 55.1 vs. 69.6†	NA	NA	NA	+	-

†<0.05
*<0.01
¶Clinically indicate-target lesion revascularization,
‡All revascularization
§Cardiac death
‖MACE defined as death/M/stroke
NA, not reported
FUP, follow-up
Mths, months

Of note, in this study the ACC/AHA lesion score was also found to be an independent predictor of cardiac death, but not MACE.

SYNTAX Score

The SXscore represents a comprehensive angiographic scoring system which allows the complexity of CAD to be quantified.[38-39] Both lesion location and adverse lesion characteristics are used in calculation which can be performed using either a downloadable calculator or the SXscore website (www.syntaxscore.com)(**Table 1-3**). The score, which uses several historical anatomical scores as its base, was initially devised specifically for the SYNTAX trial as a means to 'force' the cardiologist and cardiac surgeon to study the coronary angiogram in detail. At that time, it was also hypothesized that the SXscore may also correlate with clinical outcomes.[38]

The score was first used prospectively in the SYNTAX trial, and has since been calculated in a number of different clinical trials both in elective and acute patients, with simple or complex disease, followed-up for between 1- and 5-years.[4,12,53,57-63] The main results from these studies at maximum follow-up are shown in **Table 1-8.** In all studies irrespective of follow-up duration, a higher SXscore tercile has consistently been associated with the poorest outcomes,[4,12,53,57-63] moreover several studies also identified the SXscore to be an independent predictor of MACE[4,57-61] and/or mortality[58,61-62] in patients undergoing PCI. Overall these results support the role of the SXscore in risk stratifying patients following diagnostic coronary angiography.

Importantly prospective data from the SYNTAX trial, and retrospective analysis of the CUSTOMIZE registry, both of which included a surgical control arm, have also provided evidence which supports the use of the SXscore in helping determine revascularization strategy. This expanded role stems from the identification of the SXscore as an independent predictor of MACCE for patients undergoing PCI, whilst no similar relationship has been demonstrated in patients treated with CABG. In the SYNTAX study the rate of MACCE amongst patients with 3VD/LM disease undergoing PCI was 19.4%, 22.8% and 28.2% for SXscore terciles low, intermediate and high, which contrasts with respective rates amongst CABG patients of 17.4%, 16.4% and 15.4%. This flat relationship amongst CABG patients is somewhat expected as bypass anastomoses are inserted distal to underlying complex disease. In practice these results suggest patients with a high SXscore have significantly better outcomes, and a lower risk of events following CABG compared to those having PCI. In patients with a low SXscore both treatment modalities offer comparable outcomes, whilst in the intermediate group, CABG offers superior outcomes in patients with 3VD, whilst comparable outcomes are seen in LM patients (**Figures 1-3 & 1-4**).[26-27] A similar relationship was seen in the CUSTOMIZE registry where rates of MACE amongst LM patients treated with PCI and CABG for those with a SXscore ≤34 were 8.1% and 6.2% (p=0.46) respectively, compared to 32.7% and 8.5% (p<0.001) for those with SXscore >34.

The absence of any relationship between the SXscore and events rates amongst surgical patients is further supported by Lemesle *et al* who reported outcomes amongst 320 patients undergoing CABG stratified according to SXscore tercile. At 1-year follow-up rates of death/stroke/MI 9.4%, 7.5%, and 10.4% in patients in respective low, intermediate and high SXscore terciles (p=0.75).[64] In contrast, Birim *et al* identified the SXscore to be an independent predictor of 1-year MACCE amongst a cohort of 148 patients undergoing CABG.[65] The small sample size and retrospective design may have influenced the results, which have not yet been repeated, or fully explained.

A positive correlation has been reported between the SXscore and the ACC/AHA lesion score, however more detailed analysis indicates that the SXscore has a superior discriminative ability for both cardiac death (SX score 0.83 vs. 0.76 ACC/AHA)[58] and MACCE (SXscore 0.73 vs. ACC/AHA 0.56).[57]

In summary, in the short period of time since its introduction the SXscore has been evaluated in a number of different studies which all suggest that it has a role to play in risk stratifying patients undergoing revascularization. In addition, results from those studies which have included a surgi-

cal treatment arm, have provided evidence to indicate the SXscore also has a utility in assisting in important revascularization decisions in those patients with CAD.

COMBINED RISK SCORES

The previous discussion has reviewed risk models which rely on either clinical or angiographic variables. There is no disputing that for a complete individualized patient assessment both factors must be taken into consideration. Moreover current evidence indicates that clinical- and angiographic-based risk models may be better suited to predict different patient outcomes. Clinical based scores appear to be better at predicting clinical end points such as death or MI, whilst angiographic-based scores appear to be superior for the prediction of angiographic success, and the risk of repeat revascularization. Of note, Peterson *et al* observed only a minimal improvement in the ability of the NCDR CathPCI risk score to predict in-hospital mortality following the inclusion of angiographic variables.[35] These findings are in line with previous reports which demonstrated that the MCRS was superior to the ACC/AHA lesion classification in the prediction of death/stroke/MI/emergent CABG, but inferior for the prediction of angiographic failure.[66]

These differential outcomes according to the variables assessed in the risk model have raised interest in combined risk models, which assess risk by considering both clinical and angiographic variables. In view of this several combined clinical and angiographic risk scores have been developed. Other than the Society of Thoracic Surgery score (STS), the newer combined scores have yet to be validated in large patients populations, such that outcome data are currently confined to small, retrospective studies, with limited follow-up. The most prominent combined risk scores include:

Society of Thoracic Surgery (STS) Score

The STS score predicts the risk of operative mortality and morbidity after cardiac surgery, and is calculated by means of an online calculator that requests information on forty clinical and two

		SYNTAX Score Tercile		
		Low	**Intermediate**	**High**
euroSCORE	**Low**	Low	Low	Intermediate
	Medium	Low	Low	Intermediate
	High	Intermediate	Intermediate	High

- Global Risk Classification (GRC) is derived using the above matrix
- The GRC divides patients into Low, Intermediate and High risk groups as shown.

Figure 1-6: The Global Risk Classification matrix:[68]

angiographic variables (presence of LM lesion and number of vessels diseased).[36,45] As alluded to earlier, and unlike the euroSCORE, the STS score undergoes periodic re-calibration, which is vital to ensure that its results remain applicable to contemporary practice. In comparison with other clinical based models in patients undergoing CABG, the STS score has been shown to be superior to both the MCRS,[54] and the euroSCORE.[67] Importantly, however there has been no evaluation of the STS score in patients undergoing PCI or any comparison between the STS score and angiographic-based scores. Consequently the role of the STS score in the assessment of patients undergoing revascularization is confined to those in whom surgical revascularization has already been selected.

euroSCORE-SYNTAX

The euroSCORE and the SXscore are the most extensively studied risk models in patients undergoing revascularization. Moreover, combining both scores should offer the potential to harness the positive aspects of each, namely the ability of the euroSCORE to identify patients at high risk of adverse events irrespective of treatment modality, and the ability of the SXscore to assist in establishing optimal revascularization strategy.

Whilst the principal behind combining both scores is simple, the method of actually combining both into an effective risk model has been harder to establish. In the SYNTAX study simply sub-dividing patients in SXscore tertiles by a euroSCORE above or below the median failed to demonstrate a consistent and understandable relationship. This may in part have been due to the small numbers of patients in each sub-group.

A more recent suggestion, which appears to hold promise, has been described by Capodanno *et al*, who developed a Global Risk Classification (GRC). The GRC categories patients into low, medium and high risk using a matrix which incorporates a patient's euroSCORE, which is sub-divided into the

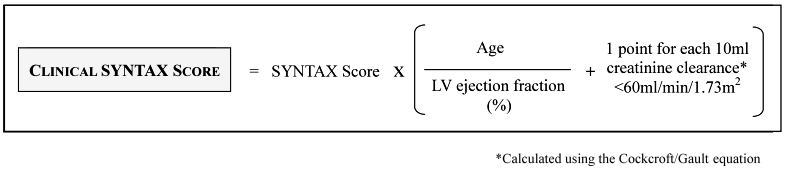


Figure 1-7: The Clinical SYNTAX score formula[69]

historically defined groups of low (0-2), intermediate (3-5) and high risk (≥6), and their SXscore, which is divided into low, intermediate and high terciles (**Figure 1-6**).[68] The GRC has so far only been applied to a population of 255 patients undergoing LM revascularization, for which SXscores were calculated retrospectively. At 2-year follow-up the rates of cardiac death in patients in low, intermediate and high SXscores terciles were 3.9%, 5.4% and 21.9%, whilst rates of 1.6%, 16.0% and 31.4% were seen in low, intermediate and high GRC groups. Additional results indicate that the GRC had a greater discriminatory ability when compared with other risk scores, including the euroSCORE and the SXscore,

for the prediction of in-hospital and 2-year mortality. Overall the study reiterated the importance of considering both clinical and angiographic variables in the assessment of overall risk, and provided a combined scoring system which requires additional validation in a large patient group.

Clinical SYNTAX Score (CSS)

The Clinical SYNTAX score (CSS) was borne out of the need to include a clinical component to the angiographic SXscore.[69] The CSS score incorporates, as its clinical component, the ACEF score[34] which has been modified by replacing serum creatinine (which originally received one point if it was >2mg/dl), with a weighted score linked to the creatinine clearance. This modification was implemented to improve the discrimination of risk, which was previously observed when a similar modification was incorporated into the euroSCORE.[70] The CSS is calculated by multiplying the SXscore with this modified ACEF score (**Figure 1-7**). Currently the CSS has only been evaluated in patients enrolled with complex disease who were enrolled in the ARTS-II study. Nevertheless at 5-year follow-up, amongst patients with triple vessel disease, the CSS was shown to have a superior discriminative ability compared to the SXscore and ACEF in the prediction of both mortality (CSS 0.80 vs. SXscore 0.70 vs. ACEF 0.73) and MACCE (CSS 0.67 vs. SXscore 0.64 vs. ACEF 0.59).[69] Further evaluation is necessary to validate this score in a larger, more diverse patient population.

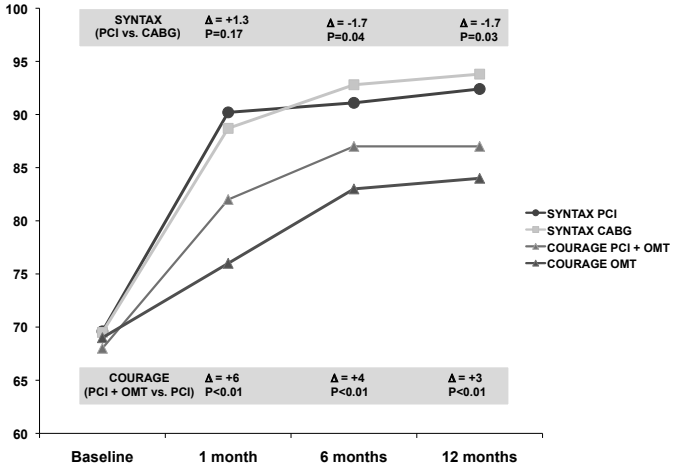


Figure 1-8: The change in Seattle Angina Questionnaire angina frequency during follow-up of the SYNTAX study and the COURAGE study.[74,76] All therapies lead to a reduction in angina frequency; however the improvement is greatest following surgical revascularization. Importantly the difference between PCI and CABG in the SYNTAX study is not considered clinically significant; moreover it is considerably less than the difference between PCI and optimal medical therapy (OMT) and OMT alone in the COURAGE study.

SECTION III: INDIVIDUAL ASSESSMENT – FROM A PATIENT'S PERSPECTIVE

The above discussions have focused entirely on the factors physicians must take into account when making revascularization decisions. Importantly however, in the era of increased patient choice and transparency, and a greater patient involvement in decision making, it is vital to also consider aspects from a patient's perspective through the assessment of health related quality of life (QoL). This patient oriented approach is all the more important given the comparable rates of mortality and MI that have been reported amongst patients with complex disease treated with PCI or CABG at both short-, and long-term follow-up (**Table 1-2**).[4,6,12,19,25,71]

Unfortunately data on this key topic are limited to only a handful of studies which have assessed PCI in patients receiving DES. Of note, early studies comparing PCI (with BMS) and CABG have indicated a trend towards improved QoL outcomes with CABG; however these results have largely driven by higher rates of repeat revascularization with BMS, a phenomenon addressed following the introduction of DES.[7] For example the SOS (Stent or Surgery) study reported favorable health related QoL with CABG compared to PCI in terms of reduced angina frequency and physical limitation at 6-months, with the superior reduction in angina frequency maintained out to 12-months.[72] Similarly at 12-months follow-up in the MASS II study, patients treated with CABG had a greater improvement in health related QoL compared to those treated with PCI and medical therapy.[73]

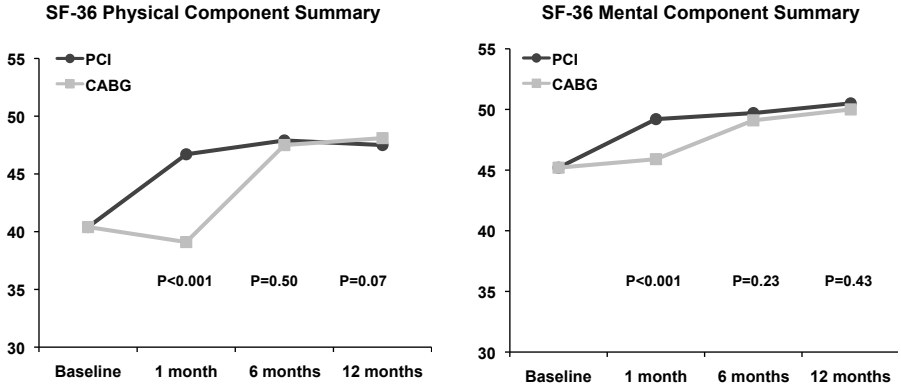


Figure 1-9: The temporal change in the SF-36 physical and mental component during follow-up after revascularization with either PCI or CABG in the SYNTAX study. Importantly at 1-month a significantly better outcome for both parameters was noted in those treated with PCI, however by 12-months this difference had eroded such that both treatments were comparable.[74]

Data on QoL from patients treated with DES and CABG are limited to the 12-month results from the SYNTAX study and 3-year results from the ARTS-II study.[74-75] Encouragingly results from the SYNTAX study indicate that despite recruitment of a very complex patient population, treatment with PCI or CABG does lead to a significant improvement in QoL compared to baseline. Moreover, consistent

with earlier studies the greatest improvement in QoL is seen in those treated with CABG compared to PCI. It is noteworthy that the difference in the Seattle Angina Questionnaire angina frequency between both groups, which was 1.7 at 6- and 12-months is less than that deemed to be clinically relevant, and also less than that observed in other studies such as SoS (3-point difference at 12-months), and COURAGE (3-6 point difference)(**Figure 1-8**).[76] Similarly, data from the ARTS-II study indicates the absence of any significant difference in angina status between patients treated with DES and CABG from as early as 1-month after the index procedure through to 3-year follow-up; of note, treatment with BMS lead to consistently higher rates of angina.[75]

Although these results appear to indicate that QoL after revascularization with PCI or CABG is largely comparable, it must be stressed that these results are based on study populations, and as with the risk models discussed previously, individual patients will have may have different concerns, not captured in these evaluations of QoL. For example some patients may be more willing to accept the increased chances of a repeat procedure with PCI as this treatment allows them to return to normal activity promptly after the procedure, conversely others may be content with the longer convalesce from CABG, as this offers a suitable trade off with the subsequently lower risk of repeat revascularization.[77] Interestingly, in the SYNTAX study physical limitations, QoL and treatment satisfaction were all significantly better with PCI compared to CABG at 1-month, however by 6-months these differences were comparable (**Figure 1-9**).

Clearly an individual patient's views on these issues cannot be captured in a questionnaire, but through a frank discussion between patient, cardiologist and cardiac surgeon. Therefore in patients where PCI or CABG is an equally valid revascularization technique, the thoughts, and concerns of individual patients must also be considered before deciding on the optimal revascularization strategy.

CONCLUSIONS

The face of revascularization is changing as result of a greater numbers of patients with co-morbidities presenting with more extensive coronary artery disease in need of revascularization. Concurrent with this have been the advances in PCI and surgical technology, which have lead to a blurring of the classical divisions between which patients and coronary lesions are suitable exclusively for PCI or CABG. This welcome change has increased the importance of assessing patients as individuals taking into consideration their co-morbidities, angiographic findings, and ultimately where appropriate, their personal preferences prior to establishing a treatment strategy. To aid physicians in quantifying this risk numerous risk models have been developed, each incorporating different clinical and angiographic parameters. The importance of these models in contemporary practice is in part emphasized by their inclusion for the first time in society guidelines on myocardial revascularization.[79,80] Unfortunately, however, no validation has been performed of all models in the same patient population, and thereby no one model can be recommended above another. Nevertheless, the evidence indicates that risk stratification, irrespective of how it is performed, plays an important role in the assessment of patients undergoing revascularization.

LIST OF REFERENCES

1. Gruntzig A. Transluminal dilatation of coronary-artery stenosis. *Lancet.* 1978;1(8058):263.
2. Hilliard AA, From AM, Lennon RJ, Singh M, Lerman A, Gersh BJ, Holmes DR, Jr., Rihal CS, Prasad A. Percutaneous revascularization for stable coronary artery disease temporal trends and impact of drug-eluting stents. *JACC Cardiovasc Interv.* 2010;3(2):172-179.
3. Vranckx P, Boersma E, Garg S, Valgimigli M, Van Es GA, Goedhart D, Serruys PW. Cardiovascular Risk profile of patients included in stent trials: A meta-analysis of individual patient data from randomized clinical trials. Insights from 33 prospective stent trials in Europe. *EuroIntervention.* In press.
4. Serruys PW, Onuma Y, Garg S, Vranckx P, De Bruyne B, Morice MC, Colombo A, Macaya C, Richardt G, Fajadet J, Hamm C, Schuijer M, Rademaker T, Wittebols K, Stoll HP. 5-Year Clinical Outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the Sirolimus-Eluting Stent in the Treatment of Patients With Multivessel De Novo Coronary Artery Lesions. *J Am Coll Cardiol.* 2010;55:1093-1101.
5. LeGrand V, Garg S, Serruys PW, Virtanen K, Szurawitzki G, Voudris V, Fontanelli A, Endersen K, Kranjec I, Rademaker T, Stefanidis C, Wittebols K. Influence of Age on the Clinical Outcomes of Coronary Revascularization for the Treatment of patients with Multivessel de novo Coronary Artery Lesions. Sirolimus-Eluting Stent vs. Coronary Artery Bypass Surgery and Bare Metal Stent: Insight from the Multicenter Randomized Arterial Revascularization Therapy Study Part I (ARTS-I) and Part II (ARTS-II). *Eurointervention.* 2010.
6. Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, Carrie D, Clayton TC, Danchin N, Flather M, Hamm CW, Hueb WA, Kahler J, Kelsey SF, King SB, Kosinski AS, Lopes N, McDonald KM, Rodriguez A, Serruys P, Sigwart U, Stables RH, Owens DK, Pocock SJ. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet.* 2009;373(9670):1190-1197.
7. Garg S, Serruys PW. Coronary stents - Current Status. *J Am Coll Cardiol.*2010; 56(10 Suppl):S1-S42.
8. Windecker S, Remondino A, Eberli FR, Juni P, Raber L, Wenaweser P, Togni M, Billinger M, Tuller D, Seiler C, Roffi M, Corti R, Sutsch G, Maier W, Luscher T, Hess OM, Egger M, Meier B. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. *N Engl J Med.* 2005;353(7):653-662.
9. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Juni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet.* 2008;372(9644):1163-1173.
10. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schonberger JP, Buller N, Bonser R, van den Brand MJ, van Herwerden LA, Morel MA, van Hout BA. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med.* 2001;344(15):1117-1124.
11. Serruys PW, Ong ATL, Morice M-C, De Bruyne B, Colombo A, Macaya C, Richardt G, Fajadet J, Hamm C, Dawkins K, O'Malley AJ, Bressers M, Dennis D, Investigators obotAI. Arterial Revascularisation Therapies Study Part II - Sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. *EuroIntervention.* 2005;1(2):147-156.
12. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med.* 2009;360(10):961-972.
13. Kappetein AP, Dawkins KD, Mohr FW, Morice MC, Mack MJ, Russell ME, Pomar J, Serruys PW. Current

percutaneous coronary intervention and coronary artery bypass grafting practices for three-vessel and left main coronary artery disease. Insights from the SYNTAX run-in phase. *Eur J Cardiothorac Surg.* 2006;29(4):486-491.

14. Sjauw KD, Konorza T, Erbel R, Danna PL, Viecca M, Minden HH, Butter C, Engstrom T, Hassager C, Machado FP, Pedrazzini G, Wagner DR, Schamberger R, Kerber S, Mathey DG, Schofer J, Engstrom AE, Henriques JP. Supported high-risk percutaneous coronary intervention with the Impella 2.5 device the Europella registry. *J Am Coll Cardiol.* 2009;54(25):2430-2434.

15. Vranckx P, Schultz CJ, Valgimigli M, Eindhoven JA, Kappetein AP, Regar ES, Van Domburg R, Serruys PW. Assisted circulation using the TandemHeart during very high-risk PCI of the unprotected left main coronary artery in patients declined for CABG. *Catheter Cardiovasc Interv.* 2009;74(2):302-310.

16. Aziz O, Rao C, Panesar SS, Jones C, Morris S, Darzi A, Athanasiou T. Meta-analysis of minimally invasive internal thoracic artery bypass versus percutaneous revascularisation for isolated lesions of the left anterior descending artery. *BMJ.* 2007;334(7594):617-.

17. Kapoor JR, Gienger AL, Ardehali R, Varghese R, Perez MV, Sundaram V, McDonald KM, Owens DK, Hlatky MA, Bravata DM. Isolated Disease of the Proximal Left Anterior Descending Artery: Comparing the Effectiveness of Percutaneous Coronary Interventions and Coronary Artery Bypass Surgery. *J Am Coll Cardiol Intv.* 2008;1(5):483-491.

18. Thiele H, Neumann-Schniedewind P, Jacobs S, Boudriot E, Walther T, Mohr FW, Schuler G, Falk V. Randomized comparison of minimally invasive direct coronary artery bypass surgery versus sirolimus-eluting stenting in isolated proximal left anterior descending coronary artery stenosis. *J Am Coll Cardiol.* 2009;53(25):2324-2331.

19. Daemen J, Boersma E, Flather M, Booth J, Stables R, Rodriguez A, Rodriguez-Granillo G, Hueb WA, Lemos PA, Serruys PW. Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. *Circulation.* 2008;118(11):1146-1154.

20. Bravata DM, Gienger AL, McDonald KM, Sundaram V, Perez MV, Varghese R, Kapoor JR, Ardehali R, Owens DK, Hlatky MA. Systematic Review: The Comparative Effectiveness of Percutaneous Coronary Interventions and Coronary Artery Bypass Graft Surgery. *Annals of Internal Medicine.* 2007;147(10):703.

21. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. *N Engl J Med.* 1996;335(4):217-225.

22. The final 10-year follow-up results from the BARI randomized trial. *J Am Coll Cardiol.* 2007;49(15):1600-1606.

23. Ong AT, Serruys PW, Mohr FW, Morice MC, Kappetein AP, Holmes DR, Jr., Mack MJ, van den Brand M, Morel MA, van Es GA, Kleijne J, Koglin J, Russell ME. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. *Am Heart J.* 2006;151(6):1194-1204.

24. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Supplementary appendix - Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease *N Engl J Med.* 2009;360(10):961-972 DOI: 910.1056/NEJMoa0804626.

25. Kappetein AP. Optimal revascularization strategy in patients with three-vessel disease and/or left main disease. The 2-year Outcomes of the SYNTAX Trial. Presentation at the ESC Congress, Barcelona, 2nd September 2009. Available online www.syntaxscore.com.

26. Morice MC. Multivessel Disease Lessons From SYNTAX (Early Results and 2 Year Follow-Up): Interventional

Perspectives. Presentation at Transcatheter Cardiovascular Therapeutics, San Francisco, 21st September 2009.

27. Serruys PW. Left Main Lessons from SYNTAX (Early Results and 2 Year Follow-up): Interventional Perspectives. Presentation Transcatheter Cardiovascular Therapeutics, 21st September 2009. [Available online: www.tctmd.com/txshow.aspx?tid=9390768&id=83938&trid=938634.].

28. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization: a report by the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol.* 2009;53(6):530-553.

29. Roques F, Nashef SA, Michel P, Gauducheau E, de Vincentiis C, Baudet E, Cortina J, David M, Faichney A, Gabrielle F, Gams E, Harjula A, Jones MT, Pintor PP, Salamon R, Thulin L. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. *Eur J Cardiothorac Surg.* 1999;15(6):816-822; discussion 822-813.

30. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg.* 1999;16(1):9-13.

31. Roques F, Michel P, Goldstone AR, Nashef SAM. The logistic EuroSCORE. *Eur Heart J.* 2003;24(9):882-.

32. Singh M, Rihal CS, Lennon RJ, Spertus J, Rumsfeld JS, Holmes DR. Bedside Estimation of Risk From Percutaneous Coronary Intervention: The New Mayo Clinic Risk Scores. *Mayo Clinic Proceedings.* 2007;82(6):701-708.

33. Singh M, Peterson ED, Milford-Beland S, Rumsfeld JS, Spertus JA. Validation of the mayo clinic risk score for in-hospital mortality after percutaneous coronary interventions using the national cardiovascular data registry. *Circ Cardiovasc Interv.* 2008;1(1):36-44.

34. Ranucci M, Castelvecchio S, Menicanti L, Frigiola A, Pelissero G. Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony. *Circulation.* 2009;119(24):3053-3061.

35. Peterson ED, Dai D, DeLong ER, Brennan JM, Singh M, Rao SV, Shaw RE, Roe MT, Ho KKL, Klein LW, Krone RJ, Weintraub WS, Brindis RG, Rumsfeld JS, Spertus JA. Contemporary Mortality Risk Prediction for Percutaneous Coronary Intervention: Results From 588,398 Procedures in the National Cardiovascular Data Registry. *J Am Coll Cardiol.* 2010;55(18):1923-1932.

36. Shroyer AL, Coombs LP, Peterson ED, Eiken MC, DeLong ER, Chen A, Ferguson TB, Jr., Grover FL, Edwards FH. The Society of Thoracic Surgeons: 30-day operative mortality and morbidity risk models. *Ann Thorac Surg.* 2003;75(6):1856-1864; discussion 1864-1855.

37. Ryan TJ, Bauman WB, Kennedy JW, Kereiakes DJ, King SB, 3rd, McCallister BD, Smith SC, Jr., Ullyot DJ. Guidelines for percutaneous transluminal coronary angioplasty. A report of the American Heart Association/American College of Cardiology Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Percutaneous Transluminal Coronary Angioplasty). *Circulation.* 1993;88(6):2987-3007.

38. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Van Dyck N, Russell ME, Mohr FW, Serruys PW. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention.* 2005;1(2):219-227.

39. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, Van Dyck N, Mack M, Holmes D,

Feldman T, Morice MC, Colombo A, Bass E, Leadley K, Dawkins KD, van Es GA, Morel MA, Mohr FW. Assessment of the SYNTAX score in the Syntax study. *Eurointervention.* 2009;5(1):50-56.

40. Garg S, Girasis C, Sarno G, Goedhart D, Morel MA, Garcia-Garcia HM, Bressers M, Es GA, Serruys PW. The SYNTAX score revisited: A reassessment of the SYNTAX score reproducibility. *Catheter Cardiovasc Interv.* 2010;75(6):946-952.

41. Califf RM, Peterson ED, Gibbons RJ, Garson A, Jr., Brindis RG, Beller GA, Smith SC, Jr. Integrating quality into the cycle of therapeutic development. *J Am Coll Cardiol.* 2002;40(11):1895-1901.

42. Concato J, Feinstein AR, Holford TR. The risk of determining risk with multivariable models. *Ann Intern Med.* 1993;118(3):201-210.

43. Choong CK, Sergeant P, Nashef SA, Smith JA, Bridgewater B. The EuroSCORE risk stratification system in the current era: how accurate is it and what should be done if it is inaccurate? *Eur J Cardiothorac Surg.* 2009;35(1):59-61.

44. Bhatti F, Grayson AD, Grotte G, Fabri BM, Au J, Jones M, Bridgewater B. The logistic EuroSCORE in cardiac surgery: how well does it predict operative risk? *Heart.* 2006;92(12):1817-1820.

45. Shahian DM, O'Brien SM, Filardo G, Ferraris VA, Haan CK, Rich JB, Normand SL, DeLong ER, Shewan CM, Dokholyan RS, Peterson ED, Edwards FH, Anderson RP. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 1--coronary artery bypass grafting surgery. *Ann Thorac Surg.* 2009;88(1 Suppl):S2-22.

46. Toumpoulis IK, Anagnostopoulos CE, DeRose JJ, Swistel DG. European system for cardiac operative risk evaluation predicts long-term survival in patients with coronary artery bypass grafting. *Eur J Cardiothorac Surg.* 2004;25(1):51-58.

47. De Maria R, Mazzoni M, Parolini M, Gregori D, Bortone F, Arena V, Parodi O. Predictive value of EuroSCORE on long term outcome in cardiac surgery patients: a single institution study. *Heart.* 2005;91(6):779-784.

48. Morice MC, Serruys PW, Kappetein AP, Feldman T, Stahle E, Colombo A, Mack M, Holmes Jr DR, Torracca L, Van Es GA, Leadley K, Dawkins KD, Mohr FW. Outcomes in Patients with De Novo Left Main Disease Treated With Either Percutaneous Coronary Intervention using TAXUS Express2 Paclitaxel-Eluting Stent or Coronary Artery Bypass Graft Treatment in the SYNTAX Trial. *Circulation.* 2010; 121(24):2645-2653.

49. Min SY, Park DW, Yun SC, Kim YH, Lee JY, Kang SJ, Lee SW, Lee CW, Kim JJ, Park SW, Park SJ. Major predictors of long-term clinical outcomes after coronary revascularization in patients with unprotected left main coronary disease: analysis from the MAIN-COMPARE study. *Circ Cardiovasc Interv.* 2010;3(2):127-133.

50. Rodes-Cabau J, Deblois J, Bertrand OF, Mohammadi S, Courtis J, Larose E, Dagenais F, Dery JP, Mathieu P, Rousseau M, Barbeau G, Baillot R, Gleeton O, Perron J, Nguyen CM, Roy L, Doyle D, De Larochelliere R, Bogaty P, Voisine P. Nonrandomized comparison of coronary artery bypass surgery and percutaneous coronary intervention for the treatment of unprotected left main coronary artery disease in octogenarians. *Circulation.* 2008;118(23):2374-2381.

51. Kim YH, Ahn JM, Park DW, Lee BK, Lee CW, Hong MK, Kim JJ, Park SW, Park SJ. EuroSCORE as a predictor of death and myocardial infarction after unprotected left main coronary stenting. *Am J Cardiol.* 2006;98(12):1567-1570.

52. Romagnoli E, Burzotta F, Trani C, Siviglia M, Biondi-Zoccai GG, Niccoli G, Leone AM, Porto I, Mazzari MA, Mongiardo R, Rebuzzi AG, Schiavoni G, Crea F. EuroSCORE as predictor of in-hospital mortality after percutaneous coronary intervention. *Heart.* 2009;95(1):43-48.

53. Kim Y-H, Park D-W, Kim W-J, Lee J-Y, Yun S-C, Kang S-J, Lee S-W, Lee CW, Park S-W, Park S-J. Validation of SYNTAX

(Synergy between PCI with Taxus and Cardiac Surgery) Score for Prediction of Outcomes After Unprotected Left Main Coronary Revascularization. *J Am Coll Cardiol Intv.* 2010;3(6):612-623

54. Singh M, Gersh BJ, Li S, Rumsfeld JS, Spertus JA, O'Brien SM, Suri RM, Peterson ED. Mayo Clinic Risk Score for percutaneous coronary intervention predicts in-hospital mortality in patients undergoing coronary artery bypass graft surgery. *Circulation.* 2008;117(3):356-362.

55. Kastrati A, Schomig A, Elezi S, Dirschinger J, Mehilli J, Schuhlen H, Blasini R, Neumann FJ. Prognostic value of the modified american college of Cardiology/American heart association stenosis morphology classification for long-term angiographic and clinical outcome after coronary stent placement. *Circulation.* 1999;100(12):1285-1290.

56. Khattab AA, Hamm CW, Senges J, Toelg R, Geist V, Bonzel T, Kelm M, Levenson B, Nienaber CA, Pfannebecker T, Sabin G, Schneider S, Tebbe U, Richardt G. Prognostic value of the modified American College of Cardiology/American Heart Association lesion morphology classification for clinical outcome after sirolimus-eluting stent placement (results of the prospective multicenter German Cypher Registry). *Am J Cardiol.* 2008;101(4):477-482.

57. Valgimigli M, Serruys PW, Tsuchida K, Vaina S, Morel MA, van den Brand MJ, Colombo A, Morice MC, Dawkins K, de Bruyne B, Kornowski R, de Servi S, Guagliumi G, Jukema JW, Mohr FW, Kappetein AP, Wittebols K, Stoll HP, Boersma E, Parrinello G. Cyphering the complexity of coronary artery disease using the syntax score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. *Am J Cardiol.* 2007;99(8):1072-1081.

58. Capodanno D, Di Salvo ME, Cincotta G, Miano M, Tamburino C, Tamburino C. Usefulness of the SYNTAX Score for Predicting Clinical Outcome After Percutaneous Coronary Intervention of Unprotected Left Main Coronary Artery Disease. *Circ Cardiovasc Intervent.* 2009;2(4):302-308.

59. Morice MC, Serruys PW, Kappetein AP, Feldman T, Stahle E, Colombo A, Mack M, Holmes Jr DR, Torracca L, Van Es GA, Leadley K, Dawkins KD, Mohr FW. Outcomes in Patients with De Novo Left Main Disease Treated With Either Percutaneous Coronary Intervention using TAXUS Express2 Paclitaxel-Eluting Stent or Coronary Artery Bypass Graft Treatment in the SYNTAX Trial. *Circulation.* 2010;121(24):2645-2653.

60. Capodanno D, Capranzano P, Di Salvo ME, Caggegi A, Tomasello D, Cincotta G, Miano M, Patane M, Tamburino C, Tolaro S, Patane L, Calafiore AM. Usefulness of SYNTAX score to select patients with left main coronary artery disease to be treated with coronary artery bypass graft. *J Am Coll Cardiol Intv.* 2009;2(8):731-738.

61. Wykrzykowska J, Garg S, Girasis C, de Vries T, Morel MA, van Es GA, Buszman P, Linke A, Ischinger T, Klauss V, Corti R, Eberli F, Wijns W, Morice MC, di Mario C, van Geuns RJ, Juni P, Windecker S, Serruys PW. Value of the Syntax Score (SX) for Risk Assessment in the "All-comers" Population of the Randomized Multicenter Leaders Trial. *J Am Coll Cardiol.* 2010;56(4):272-277.

62. Onuma Y, Girasis C, Piazza N, Garcia-Garcia HM, Kukreja N, Garg S, Eindhoven J, Cheng J-M, Valgimigli M, Van Domburg R, Serruys PW. Long-term clinical results following stenting of the Left Main Stem - Insights from RESEARCH and T-SEARCH Registries. *J Am Coll Cardiol Intv.*2010;3(6):584-594

63. Girasis C, Garg S, Raber L, Sarno G, Morel MA, Garcia Garcia HM, Serruys P, Windecker S. Prediction of 5-year clinical outcomes using the SYNTAX score in patients undergoing PCI from the Sirolimus eluting stent compared with paclitaxel eluting stent for coronary revascularisation (SIRTAX) trial. Abstract at American College of Cardiology meeting, March 14-16th 2010, Atlanta GA.

64. Lemesle G, Bonello L, de Labriolle A, Steinberg DH, Roy P, Pinto Slottow TL, Torguson R, Kaneshige K, Xue Z, Suddath WO, Satler LF, Kent KM, Lindsay J, Pichard AD, Waksman R. Prognostic value of the Syntax score in

patients undergoing coronary artery bypass grafting for three-vessel coronary artery disease. *Catheter Cardiovasc Interv.* 2009;73(5):612-617.

65. Birim O, van Gameren M, Bogers AJ, Serruys PW, Mohr FW, Kappetein AP. Complexity of coronary vasculature predicts outcome of surgery for left main disease. *The Annals of thoracic surgery.* 2009;87(4):1097-1104; discussion 1104-1095.

66. Singh M, Rihal CS, Lennon RJ, Garratt KN, Holmes DR, Jr. Comparison of Mayo Clinic risk score and American College of Cardiology/American Heart Association lesion classification in the prediction of adverse cardiovascular outcome following percutaneous coronary interventions. *J Am Coll Cardiol.* 2004;44(2):357-361.

67. Ad N, Barnett SD, Speir AM. The performance of the EuroSCORE and the Society of Thoracic Surgeons mortality risk score: the gender factor. *Interact Cardiovasc Thorac Surg.* 2007;6(2):192-195.

68. Capodanno D, Miano M, Cincotta G, Caggegi A, Ruperto C, Bucalo R, Sanfilippo A, Capranzano P, Tamburino C. EuroSCORE refines the predictive ability of SYNTAX score in patients undergoing left main percutaneous coronary intervention. *Am Heart J.* 2010; 159(1):103-109.

69. Garg S, Sarno G, Garcia Garcia HM, Girasis C, Wykrzykowska J, Dawkins KD, Serruys PW. A New Tool for the Risk Stratification of Patients With Complex Coronary Artery Disease: The Clinical Syntax Score. *Circ Cardiovasc Interv.*2010; 3(4):317-326

70. Walter J, Mortasawi A, Arnrich B, Albert A, Frerichs I, Rosendahl U, Ennker J. Creatinine clearance versus serum creatinine as a risk factor in cardiac surgery. *BMC Surg.* 2003;3:4.

71. Serruys PW, Ong AT, van Herwerden LA, Sousa JE, Jatene A, Bonnier JJ, Schonberger JP, Buller N, Bonser R, Disco C, Backx B, Hugenholtz PG, Firth BG, Unger F. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. *J Am Coll Cardiol.* 2005;46(4):575-581.

72. Zhang Z, Mahoney EM, Stables RH, Booth J, Nugara F, Spertus JA, Weintraub WS. Disease-specific health status after stent-assisted percutaneous coronary intervention and coronary artery bypass surgery: one-year results from the Stent or Surgery trial. *Circulation.* 2003;108(14):1694-1700.

73. Favarato ME, Hueb W, Boden WE, Lopes N, Nogueira CR, Takiuti M, Gois AF, Borges JC, Favarato D, Aldrighi JM, Oliveira SA, Ramires JA. Quality of life in patients with symptomatic multivessel coronary artery disease: a comparative post hoc analyses of medical, angioplasty or surgical strategies-MASS II trial. *Int J Cardiol.* 2007;116(3):364-370.

74. Cohen DJ, Van Hout BA, Serruys PW, Mohr FW, Macaya C, Rodriguez E, Den Heijer P, Vrakking MM, Wang K, Mahoney EM, Audi S, Leadley K, Dawkins KD, Kappetein AP, on behalf of the SYNTAX trial investigators. Health-Related Quality of Life after Percutaneous Coronary Intervention with Drug-Eluting Stents vs. Coronary-Artery Bypass Grafting in Patients with Severe Coronary Artery Disease: One-Year Results from the SYNTAX Trial. *Submitted*.

75. van Domburg R, Daemen J, Morice M, de Bruyne B, Colombo A, Macaya C, Richardt G, Fajadet J, Hamm C, Van Es GA, Wittebols K, Macours N, Stoll HP, Serruys PW. Short- and long-term health related quality-of-life and anginal status of the Arterial Revascularisation Therapies Study part II, ARTS-II; sirolimus-eluting stents for the treatment of patients with multivessel coronary artery disease. *EuroIntervention.* 2010;5:962-967.

76. Weintraub WS, Spertus JA, Kolm P, Maron DJ, Zhang Z, Jurkovitz C, Zhang W, Hartigan PM, Lewis C, Veledar E, Bowen J, Dunbar SB, Deaton C, Kaufman S, O'Rourke RA, Goeree R, Barnett PG, Teo KK, Boden WE, Mancini GB. Effect of PCI on quality of life in patients with stable coronary disease. *N Engl J Med.* 2008;359(7):677-687.

77. Federspiel J, Stearns S, Van Domburg R, Sheridan B, Lund J, Serruys P. Risk-Benefit Trade-offs in Revascularization Choices. *EuroIntervention.*2010 online first

78. Vranckx P, Meliga E, De Jaegere PP, Van den Ent M, Regar ES, Serruys PW. The TandemHeart, percutaneous transseptal left ventricular assist device: a safeguard in high-risk percutaneous coronary interventions. The six-year Rotterdam experience. *EuroIntervention.* 2008;4(3):331-337.

79. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D, Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas PE, Widimsky P, Alfieri O, Dunning J, Elia S, Kappetein P, Lockowandt U, Sarris G, Vouhe P, von Segesser L, Agewall S, Aladashvili A, Alexopoulos D, Antunes MJ, Atalar E, Brutel de la Riviere A, Doganov A, Eha J, Fajadet J, Ferreira R, Garot J, Halcox J, Hasin Y, Janssens S, Kervinen K, Laufer G, Legrand V, Nashef SA, Neumann FJ, Niemela K, Nihoyannopoulos P, Noc M, Piek JJ, Pirk J, Rozenman Y, Sabate M, Starc R, Thielmann M, Wheatley DJ, Windecker S, Zembala M. Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2010;31:2501-2555.

80. Guidelines on myocardial revascularization. *Eur J Cardiothorac Surg.* 2010;38 Suppl:S1-S52.

PART IV

Tools For Risk Assessment in Patients Treated by PCI

Chapter 4.1

Coronary angioplasty: Do we need to EuroSCORE?

Nat Rev Cardiol 2009; 6(4):267-268

Scot Garg, Patrick W. Serruys

Interventional Cardiology

Coronary angioplasty: do we need to EuroSCORE?

Scot Garg and Patrick Serruys*

An effective risk score for patients undergoing coronary angioplasty is yet to be established. In this article we discuss the merits of using the EuroSCORE risk model for assessing these patients, and propose a potential modification to the system.

Percutaneous coronary intervention (PCI) is increasingly being used in the management of complicated cases of coronary artery disease, some of which would previously have only been treatable with surgery. In 1995 cardiac surgeons developed the EuroSCORE risk model (Table 1) to predict postoperative mortality among patients undergoing open-heart surgery. Romagnoli *et al*. have now assessed whether this widely-used and validated scoring system for cardiac surgery is applicable to patients receiving PCI.[1]

The paper by Romagnoli *et al.* is relevant to current practice because as yet no effective and robust risk model for PCI has been established, despite the undeniable importance of risk stratifying these patients. In the short-term, a risk model provides clinicians with additional information to help establish the most appropriate treatment strategy for each individual, and also enables patients to make a better-informed decision about their treatment. In the long-term, risk models can be used to measure the success of treatment and to help improve standards of care. In terms of clinical governance, and the public reporting of an individual consultant's performance, the risk stratification of patients is imperative to ensure clinicians receive a fair evaluation. The use of risk models has become more important with the increasing need for clinicians to justify clinical decisions to their peers and patients alike.

The main finding from the prospective study by Romagnoli *et al* in 1,173 consecutive patients treated with PCI in a single centre is that the EuroSCORE system was an independent predictor of in-hospital mortality (P = 0.002). The model had an area under the receiver-operating characteristics curve of 0.91 (95% CI 0.86–0.97) for identifying patients at risk of death during their index hospitalization. Given that the EuroSCORE system does not consider coronary anatomy, it is not surprising that the model did not effectively determine procedural success (area under the receiver-operating characteristics curve 0.56, 95% CI 0.47–0.64). This finding is important when assessing the usefulness of the study in real terms. The major limitation of the EuroSCORE and other scoring systems is that they determine the risk of the procedure, but not the potential benefits to the patient, or the chances of procedural success.

There is an overlap of risk factors in patients undergoing cardiac surgery and those receiving PCI; therefore, risk models, such as the EuroSCORE system or the Mayo Clinic risk score (MCRS)[2] that only consider patient characteristics, can be applied to individuals having either treatment. Although this application of risk models might seem practical, there is a danger that these scoring systems will become too generalized and consequently not very useful.

There has been a trend towards the development of simple scoring systems for coro-

Patient Characteristics		Score
Age	Per 5 years or part thereof over the age of 60 years	1
Gender	Female	1
Chronic Pulmonary Disease	Long-term use of bronchodilators or steroids for respiratory disease	1
Peripheral arteriopathy	*Claudication, carotid stenosis>50%, previous or planned intervention on the abdominal aorta, limb arteries or carotids	2
Neurological dysfunction	Severely affected mobility or day to day function	2
Previous cardiac surgery	Previous opening of the pericardium	3
Serum creatinine	Pre-operatively greater than 200micromol/l	2
Active endocarditis	Antibiotic therapy at time of surgery	3
Critical preoperative state	*Preoperative cardiac arrest, ventilation, renal failure, inotropic support, intra-aortic balloon pump use, ventricular arrhythmia	3
Cardiac related factors		
Unstable angina	Rest pain requiring iv nitrates	2
Left ventricular function	Moderate (30-50%) Poor (<30%)	1 3
Recent MI	Within 90 days	2
Pulmonary hypertension	Systolic pulmonary pressure>60mmHg	2
Operation related factors		
Emergency	Operation performed before the start of next working day	2
Other than isolated CABG	Major cardiac procedure other than or in addition to CABG	2
Surgery on thoracic aorta		3
Post infarct septal rupture		4

*Any of the following MI, myocardial infarction. CABG, coronary artery bypass grafting

Table 1. The various factors required to calculate the EuroSCORE. The additive score is simply an addition of each factor to give a predicted mortality (%) from cardiac surgery. The logistic EuroSCORE uses the same parameters but requires a more complex calculation, and was developed because the additive score tended to under estimate risk in those deemed at the highest risk.[6]

-nary artery disease, but we should question whether this is the ideal approach, given the complexities of the condition being assessed.

One of the initial 'selling points' of the EuroSCORE model was its simple calculation, but now—with the abundance of computers available in the clinical setting—is this simplicity still needed? In the paper by Romagnoli *et al.*, patients were stratified as being low-risk (EuroSCORE 0–2), medium-risk (EuroSCORE 3–5), or high-risk (EuroSCORE ≥6), but this categorization is imprecise and there is an inherent risk in over-simplifying risk assessment.

As mentioned, the EuroSCORE model and other currently-available scoring systems do not incorporate an assessment of the coronary anatomy. Surely the central aim of any complete patient risk model is to improve patient care and provide optimum treatment at the lowest risk If so, intuition tells us that this goal cannot be achieved without considering both patient and disease characteristics. For example, irrespective of patient factors, chronic total occlusions have long been associated with a lower chance of procedural success, and a higher risk of complications when compared with less complex lesion.[3] Unsur-

prisingly, therefore, the addition of lesion characteristics to the MCRS resulted in better prediction of procedural success than the use of the MCRS alone.[4] Interventional cardiologists subconsciously risk score coronary lesions, on the basis of their personal experience, because they have developed a 'feel' for what they can and cannot treat. Clearly, this system is open to interpretation and is certainly not a substitute for a robust risk model. The categorization of patients into single, double, or triple-vessel disease carries the same problems.

In 2005 a new angiographic scoring system —the SYNTAX score—was devised by Sianos *et al.*[5] This score does not take patient characteristics into account, and relies solely on coronary anatomy and lesion characteristics, enabling complex anatomy to be quantified, and results in a score that can be used to aid treatment decisions. The prospective value of the SYNTAX score is yet to be established, but initial results are promising.

We propose that some form of combination score is required—the EuroSCORE component assessing mortality risk and the SYNTAX score indicating disease complexity. Such a model could be used by a heart team—comprising a cardiologist and a cardiac surgeon—to best advise each individual patient about their optimum management strategy.

References

1. Romagnoli E, Burzotta F, Trani C, et al. EuroSCORE as predictor of in-hospital mortality after percutaneous coronary intervention. *Heart* 2009;95(1): 43-48.

2. Singh M, Rihal CS, Lennon RJ, Spertus J, Rumsfeld JS, Holmes DR. Bedside Estimation of Risk From Percutaneous Coronary Intervention: The New Mayo Clinic Risk Scores. *Mayo Clinic Proceedings.* 2007;82(6): 701-708.

3. Hoye A, van Domburg RT, Sonnenschein K, Serruys PW. Percutaneous coronary intervention for chronic total occlusions: the Thoraxcenter experience 1992-2002. *Eur Heart J.* 2005;26(24): 2630-2636.

4. Singh M, Rihal CS, Lennon RJ, Garratt KN, Holmes DR, Jr. Comparison of Mayo Clinic risk score and American College of Cardiology/American Heart Association lesion classification in the prediction of adverse cardiovascular outcome following percutaneous coronary interventions. *J Am Coll Cardiol.* 2004;44(2): 357-361.

5. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention.* 2005;1(2): 219-227.

6. Roques F, Michel P, Goldstone AR, Nashef SAM. The logistic EuroSCORE. *Eur Heart J.* 2003;24(9): 882-.

Chapter 4.2

Assessment of the SYNTAX score in the SYNTAX study

EuroIntervention 2009; 5(1):50-56

Patrick W. Serruys, Yoshi Onuma, Scot Garg , Giovanna Sarno, Marcel Van de Brand, Arie-Pieter Kappetein, Nic Van Dyck, Michael Mack, David Holmes Jr, Ted Feldman, Marie-Claude Morice, Antonio Colombo, Eric Bass, Katrin Leadley, Keith Dawkins, Gerrit-Anne van Es, Marie-Angèle Morel, Fredrich Mohr

EuroIntervention

Assessment of the SYNTAX score in the Syntax study

Patrick W. Serruys[1]*, MD, PhD; Yoshinobu Onuma[1], MD; Scot Garg[1], MD, MRCP; Giovanna Sarno[1], MD, PhD; Marcel van den Brand[2], MD, PhD; Arie-Pieter Kappetein[3], MD, PhD; Nic Van Dyck[4], RN; Michael Mack[5], MD; David Holmes[6], MD; Ted Feldman[7], MD; Marie-Claude Morice[8], MD; Antonio Colombo[9], MD; Eric Bass[10], BA; Katrin Leadley[10], MD; Keith D. Dawkins[10], MD; Gerrit-Anne van Es[11], PhD; Marie-Angèle M. Morel[11], BSc; Friedrich W. Mohr[12], MD

1.Department of Interventional Cardiology, Erasmus Medical Center, Thoraxcenter Rotterdam, The Netherlands; 2. Ouderkerk aan den IJssel, The Netherlands; 3. Department of Cardiothoracic Surgery, Erasmus Medical Center, Thoraxcenter, Rotterdam, The Netherlands; 4. Boston Scientific Corporation, Maastricht, The Netherlands; 5. Medical City Dallas Hospital, Dallas, TX, USA; 6. The Mayo Clinic, Rochester, MN, USA; 7. Evanston Hospital, Evanston, IL, USA; 8. Institut Cardiovasculaire Paris Sud, Massy, France; 9. San Raffaele Hospital, Milano, Italy; 10. Boston Scientific Corporation, Natick, MA, USA; 11. Cardialysis BV, Rotterdam, The Netherlands; 12. Herzzentrum, Leipzig, Germany

N. Van Dyck, E. Bass, K. Leadley and K. Dawkins are employees of Boston Scientific. GA. van Es, MA. Morel are employees of Cardialysis. The remaining authors have no disclosure to declare related to this investigation.

Guest Editor: Valentin Fuster, MD, PhD. Zena and Michael A. Wiener Cardiovascular Institute, The Marie-Josee and Henry R. Kravis Cardiovascular Health Center, The Mount Sinai School of Medicine, New York, NY, USA.

KEYWORDS
SYNTAX score, SYNTAX study, complex lesions, percutaneous coronary intervention, coronary artery bypass surgery

Abstract

Aims: The SYNTAX™ score has been designed to better anticipate the risks of percutaneous or surgical revascularisation, taking into account the functional impact of the coronary circulation with all its anatomic components including the presence of bifurcations, total occlusions, thrombus, calcification, and small vessels. The purpose of this paper is to describe the baseline assessment of the SYNTAX™ score in the Syntax randomised trial, the corelab reproducibility, the potential difference in score assessment between the investigator and the corelab, and to ascertain the impact on one-year outcome after either percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) in patients with complex coronary artery disease.

Methods and results: To assess the reliability of Syntax™ scoring, 100 diagnostic angiograms from the Syntax trial were randomly selected and assessed independently by two observers. Intra-observer variability was assessed by analysing 91 sets of angiograms after an interval of at least eight weeks by one of the observers. Clinical outcomes in the randomised cohort of the Syntax trial up to one year are presented with stratification by tertile group of the SYNTAX™ score. The weighted kappa value for the inter-observer reproducibility on the global score was 0.45, while the intra-observer weighted kappa value was 0.59. The SYNTAX™ score as calculated by investigators consistently underscored the corelab score by 3.4 points. When the Syntax randomised cohort was stratified by tertiles of the SYNTAX™ score, there were similar or non-significantly different MACCE rates in those with low or intermediate scores; however in the top tertile the MACCE rate was greater in those receiving PCI compared to CABG.

Conclusions: The SYNTAX™ score is a visual coronary score with an acceptable corelab reproducibility that has an impact on the one-year outcome of those having PCI, whereas it has no effect on the one-year outcome following surgical revascularisation. The SYNTAX™ score tool is likely to be useful in a wide range of patients with complex coronary disease.

Introduction

In previously published randomised trials including 2 and 3-vessel disease, patient selection or exclusion criteria resulted in only 2-12% of the patients screened being randomised[1]. During the initial debate on the design of the Syntax study, it was argued that despite the fact that patients with two or three vessel disease have been included in previous randomised trials, in the "real world" surgeons were often confronted with more complex anatomy and comorbidities. Therefore, the all-comer approach became the cornerstone of the Syntax trial, reducing exclusion criteria to a minimum (previous intervention, acute myocardial infarction and concomitant cardiac surgery)[2].

The anatomic heterogeneity in the patients enrolled in previous randomised trials renders their interpretation difficult. For example, a patient with 3-vessel disease and multiple lesions in each vascular territory (including long lesion, bifurcation and total chronic occlusion) was pooled together with a patient with three focal lesions in the mid-portions of each coronary artery. Both were conventionally named "3-vessel disease", despite the fact that the first patient represents a greater therapeutic challenge for the interventional cardiologist, and has a completely different prognosis compared to the second patient regardless of the revascularisation strategy. Thus the interpretation of the results of previously conducted randomised trials is severely limited by the absence of grading of the severity of coronary artery disease, and by the lack of comparison of lesion complexity based on pretreatment angiographic criteria[3].

In the Syntax trial, the decision to refer the patient for either surgery or percutaneous coronary intervention (PCI) was the result of a pretreatment consensus reached between the cardiac surgeon and the interventional cardiologist. In this so called "Heart-Team Conference" the surgeon and interventional cardiologist fully assessed anginal status, comorbidities, coronary anatomy and left ventricular function. Although other scoring systems, such as the Braunwald, NYHA or CCS classification could be used to assess angina status; whilst the EuroSCORE and Parsonnet score could be used to assess the patient history, comorbidities, pulmonary and cardiovascular function[4,5], there was no available comprehensive score to describe – in detail – the coronary anatomy. Therefore, the SYNTAX™ score has been designed to better anticipate the risks of percutaneous or surgical revascularisation, taking into account the functional impact of the coronary circulation with all its anatomic components, including bifurcations, total occlusions, thrombus, calcification, small vessels etc. The SYNTAX™ score was not initially devised to predict short or long term prognosis, but was a score designed to allow a detailed objective assessment, and therefore comparison of the coronary anatomy between one patient and another. During the heart-team conference, the calculation of the SYNTAX™ score became pivotal in the selection of the revascularisation strategy. As a result of the heart-team conference the population was subdivided into three groups: patients judged to be only eligible for cardiac surgery, patients eligible for PCI, and patients potentially amenable to both types of revascularisation. In designing the SYNTAX™ score, the authors' selected six pre-existing classifications or scores to create a complex algorithm, mixing anatomical and functional characteristics that might increase the risk and complexity of percutaneous or surgical treatment. (see appendix – online as supplementary data at www.eurointervention.org) At the time of the design, it was not known whether the complexity of the coronary anatomy, as described by the score, would have an impact on the outcome of surgery. The purpose of the present paper is to describe the baseline assessment of the SYNTAX™ score, the corelab reproducibility, the potential difference in the score assessment between the investigator and the corelab, and to ascertain the impact of the score on the short- and long-term outcome of PCI and coronary artery bypass graft surgery (CABG). At the time it was designed it was anticipated that the prospective, blind, raw SYNTAX™ score would be retrospectively weighted, based on the short- and long-term outcomes of the Syntax trial.

Methods

The Syntax trial

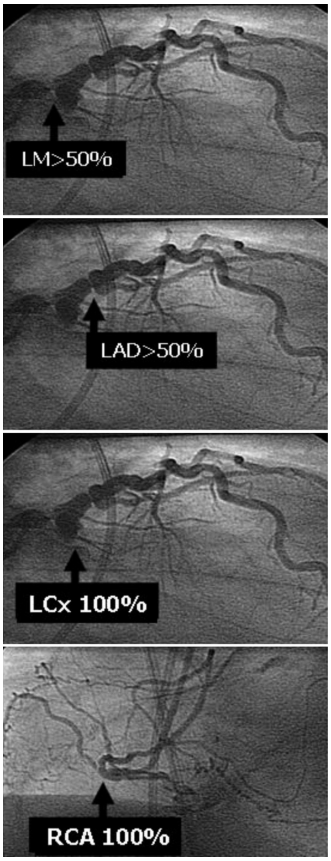
The design of the Syntax trial has been described in detail elsewhere[6]. Between March 2005 and April 2007, 4337 patients were screened leading to randomisation of 1,800 patients with LM and/or 3VD to CABG (n=897) or PCI with TAXUS Express2 (n=903) at one of 23 sites in the US (n=245) and 62 sites in Europe (n=1555). Almost 30% of screened patients were found to be amenable for only one treatment option and were enrolled in either the CABG (n=1077) or PCI (n=198) nested registries, while 9.4% of patients were not willing to participate or had a treatment preference.

Assessment of coronary angiograms

To assess the reliability of Syntax scoring, we randomly selected 100 diagnostic angiograms from the Syntax trial. All the angiographic variables pertinent to calculating the SYNTAX™ score were obtained by reviewing the diagnostic angiograms acquired before the procedure. Those films were assessed independently by two corelab technicians who were blinded to the clinical baseline characteristics, procedural data and clinical outcomes. In case of disagreement, the opinion of the third observer, a supervising cardiologist, was obtained and the final decision was made by consensus. To assess intra-observer variability, 91 sets of angiograms were analysed at least eight weeks later by one additional observer who remained blinded to the results of the first analysis.

SYNTAX™ score and angiographic analysis

Each coronary lesion producing >50% luminal obstruction lumen in vessels ≥1.5 mm was separately scored and summated to provide the overall SYNTAX™ score which was calculated using dedicated software that integrates (a) the number of lesions with their specific weighting factors based on the amount of myocardium distal to the lesion according to the score of Leaman et al[7], and (b) the morphologic features of each single lesion, as reported in the appendix. An example of SYNTAX™ score calculation in one subject is shown in Figure 1.



Lesion 1
Segment 5: 5x2 . . 10
+Bifurcation type 1,0,0 1
+Heavy calcification 2
Lesion 1 score:. 13

Lesion 2
Segment 6: 3.5x2 7
+Bifurcation type 1,0,0 1
+Angulation <70 1
+Heavy calcification 2
Lesion 2 score:. 11

Lesion 3
Segment 11: 1.5x5 . . . . . 7.5
Age of T.O is unknown 1
+Blunt stump. 1
+Side-branch 1
+Heavy calcification 2
Lesion 3 score:. 12.5

Lesion 4
Segment 1: 1x5 5
Age of T.O is unknown 1
+Blunt stump. 1
+Side branch 1
First segment visualised by contrast 4 2
+Heavy calcification 2
Lesion 4 score:. 12

Total score: 48.5

Figure 1. An example of Syntax scoring.

Statistical analysis

The degree of agreement was measured as a weighted kappa statistics that reflect the agreement between two or more observations using weight to quantify the relative difference between categories[8,12]. It is usual to consider kappa values greater than 0.75 to represent excellent agreement beyond chance; values below 0.40 to represent a poor agreement beyond chance, and values between 0.40 and 0.75 to represent fair to good agreement beyond chance. The reproducibility of Syntax scoring was evaluated by calculating the intra-observer and inter-observer variability, which was defined as the difference between the corresponding measurements expressed as a percent of their mean. All variables were expressed as mean±standard deviation or median and range. A 2-tailed P value of <0.05 was considered to indicate statistical significance. The incidence of events over time was studied with the use of the Kaplan-Meier method, whilst log-rank tests were applied to evaluate differences between the treatment groups. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored.

Results

Corelab reproducibility

At the corelab, the value of the first measurement was, on average, 30.3 versus 29.2 for the second measurement, with an SD of 11.5 and 11.3, respectively. The mean of the differences (measure of precision) was 2.1 with a SD of 9.1 (measure of accuracy), which reflects the core laboratory inter-observer variability. As shown in Table 1, the weighted kappa value for the observations of the global score was 0.45, while the weighted kappa value for the number of lesions was 0.59. The values of weighted kappa was 0.82 for the diagnosis of total occlusions, 0.41 for bifurcation lesions and 0.63 for ostial lesions. Inconsistency in the scoring was mainly due to the presence of lesions in small vessels and at bifurcations. The weighted kappa for tertile partitioning of Syntax score (0-22, 23-32, 33-) was 0.52.

Table 2 represents the weighted kappa values for intra-observer reproducibility. The weighted kappa value for the global score was 0.59, while the weighted kappa value for the number of lesions, total occlusions and bifurcation lesions was 0.71, 0.85 and 0.68, respectively. The weighted kappa for tertile partitioning of Syntax™ score (0-22, 23-32, 33-) was 0.61.

Table 1. Inter-observer reproducibility.

		Total SYNTAX™ score in classes of 10 Observer 2							
Observer 1	Frequency	0-10	11-20	21-30	31-40	41-50	51-60	61-70	Total
	0-10	3	0	0	0	0	0	0	3
	11-20	0	9	2	2	0	0	0	13
	21-30	0	6	18	11	1	1	0	37
	31-40	0	1	14	9	1	2	0	27
	41-50	0	1	2	7	4	1	0	15
	51-60	0	0	1	1	1	0	0	3
	61-70	0	0	0	0	0	0	2	2
	Total	3	17	37	30	7	4	2	100

K=0.45 (SE 0.072). The inter-observer difference in SYNTAX™ score calculation at the corelab when the scores are sub-divided into categories of 10 points (0-10, 11-20).

Table 2. Intra-observer reproducibility.

	Total SYNTAX™ score in classes of 10							
Frequency	0-10	11-20	21-30	31-40	41-50	51-60	71-80	Total
0-10	0	1	0	0	0	0	0	1
11-20	2	24	11	2	0	0	0	39
21-30	0	6	19	4	0	0	0	29
31-40	0	1	4	5	2	0	0	12
41-50	0	1	1	1	3	2	0	8
51-60	0	0	0	0	0	1	0	1
71-80	0	0	0	0	0	0	1	1
Total	2	33	35	12	5	3	1	91

K=0.59 (SE 0.069). The intra-observer difference in SYNTAX™ score calculation at the corelab when the scores are sub-divided into categories of 10 points (0-10, 11-20)

SYNTAX™ score – corelab scoring vs on-site scoring

Figure 2 shows the SYNTAX™ score in the CABG registry, the randomised cohorts and the PCI registry; average values as well as ranges are shown for the corelab and the site. The following observations can be made from these data: 1) the CABG registry has the highest score (37.8±13.3), the second highest group is the PCI registry with an average score of 31.6±12.3, whilst the randomised cohorts had intermediate scores of around 28-29, almost 10 points below the level of the CABG registry; 2) the investigators consistently underscored the corelab score by 3.4 points; 3) as expected by design, the score in the two randomised cohorts are comparable, (29.1±9.1 for CABG vs. 28.4± for PCI cohort, p=0.19).

SYNTAX™ score according to treatment groups

Figure 3 shows the distribution of the SYNTAX™ score in the PCI registry, the CABG registry and the cohort randomised to surgery or PCI. The score distribution in these different subgroups is more or less Gaussian. The Gaussian curves of the SYNTAX™ score for patients randomised to CABG and PCI are almost superimposable. The distribution of the score for the PCI registry is shifted rightward

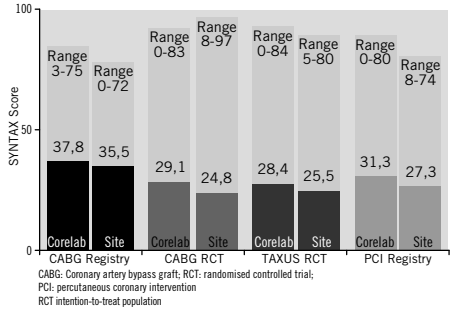


Figure 2. Bar graph of raw SYNTAX™ scores in each cohort of the Syntax trial: a comparison between Corelab assessment and site reporting. CABG: coronary artery bypass graft; RCT: randomised controlled trial; PCI: percutaneous coronary intervention.

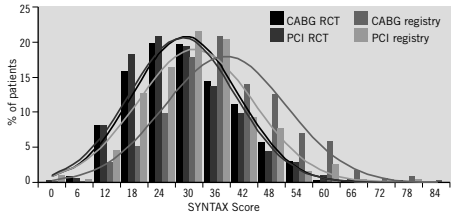


Figure 3. SYNTAX™ score distribution in the registries and in the randomised cohorts.

with a mean value of 31.6±12.3, and the distribution of the SYNTAX™ score in the CABG registry is shifted even further to the right with a peak value of 37.8±33.3. When the scores of the randomised patients were divided into tertiles, the upper boundary of the lowest tertile is 22, the second tertile ranges from 23 to 32, and the lower boundary for the highest tertile is equal or greater than 33.

SYNTAX™ score and outcome at one year

As previously reported[6] – and demonstrated in Figure 4A and 4B – there was no difference in outcome amongst patients randomised to surgery between those who had low, intermediate or high scores; the major adverse cardiovascular and cerebrovascular event (MACCE) rates at one year was 14.4%, 11.7% and 10.7% for low, intermediate and high scores respectively (p=0.38). In those randomised to PCI there is a significant separation (log rank p value 0.007) of the cumulative event rate curves between patients with low, intermediate and high scores; with respective MACCE rates at 12 months of 13.5%, 16.6%, and 23.3%.

These data would suggest that patients with a low SYNTAX™ score, regardless of the presence of left main stem or 3-vessel disease, have comparable outcomes after revascularisation with PCI or CABG (Figure 5A-C); furthermore, the MACCE rate in this SYNTAX™ score cohort is not influenced by diabetic status[9]. Therefore, the selected revascularisation strategy in this group of patients will depend on individual patient characteristics, patient preference and the physician choice.

Patients with 3-vessel disease and intermediate SYNTAX™ scores had, irrespective of their diabetic status, a higher MACCE rate

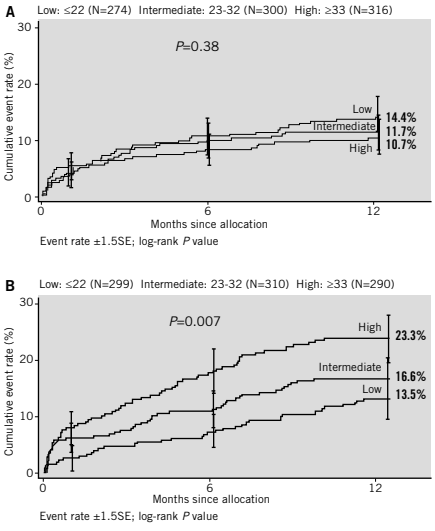


Figure 4A. Kaplan-Meier estimates of MACCE rate up to 12 months in the cohort randomised to CABG treatment stratified by tertile of SYNTAX™ score. There are no statistically significant differences between the 3 curves (p=0,38). Figure 4B. Kaplan-Meier estimates of MACCE rate to 12 months in the cohort randomised to PCI treatment stratified by tertile of SYNTAX™ score. Each curve separates at 12 months with statistical significance by log-rank test (p=0.007).

following PCI than after bypass surgery[6,9]. Ultimately, the final selection of treatment in this group will depend on patient characteristics and comorbidity; however, PCI remains a valid option for those patients with left main disease who do not have diabetes. (Figure 5 B and 6) The MACCE rate in patients with high scores (≥33), with or without diabetes, is significantly higher in patients having PCI compared to CABG, and therefore it is inferred that PCI typically is limited by a higher repeat revascularisation rate and might be considered as surgical candidates.(Figure 5C)

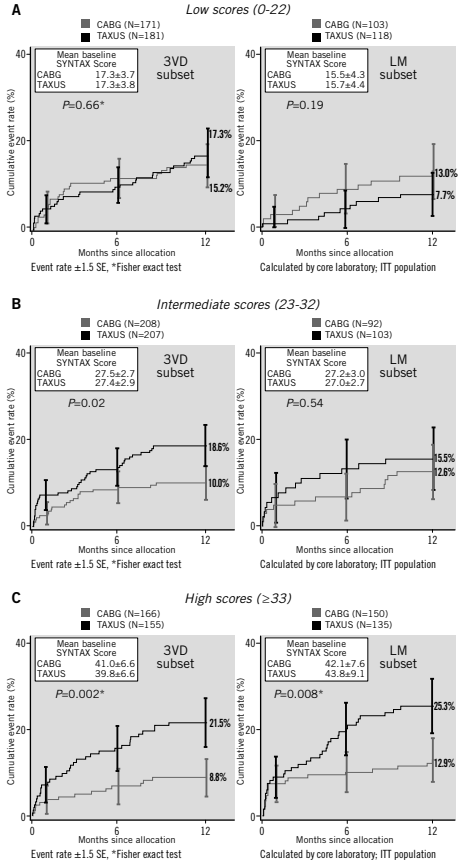


Figure 5A-C show side-by side Kaplan-Meier curves for patients either with left main or in patients with 3-vessel disease, according to the tertiles of the SYNTAX™ score in the overall population.

Discussion

The present report underscores the important prognostic value of the SYNTAX™ score. When the general principles of analysis (i.e. the heart-team decision, SYNTAX™ score, and diabetic status) are applied to the entire enrolled population (n=3,075), it appears that numerically one-third of all the patients could reasonably be treated by PCI, whilst two-thirds of the patients might be referred to surgery, with the caveat that the present assessment is based on the result of one-year outcome. It has been repeatedly demonstrated that Kaplan Meier curves related to the outcome of surgery or PCI diverge with time, and based on the 5-year outcome the current partition in surgical and PCI candidates might be reviewed more conservatively in the near future[3,10,11]. This conclusion is based on the prospective, and thus blind and unbiased, evaluation of the SYNTAX™ score prior to randomisation by a blinded corelab who were unaware of the clinical status of the patient.

Overall, in the registries and in the randomised cohorts, the evaluation of the score by the corelab was somewhat more stringent, and the score was numerically higher than those calculated by the participating site. The critical question remains as to whether this potentially powerful prognostic index, at least for PCI, is a reproducible parameter. As with any visual and categorical parameter, reproducibility should be assessed by Kappa statistics. In the present study, the Kappa parameters for inter- and intra-observer reproducibility of the global SYNTAX™ score were superior to 0.40 but inferior to 0.70, which indicate fair to good agreement[8]; obviously there is room for improvement. The reproducibility of the score in the future will likely improve with the quality of angiography,

the standardisation of the angiographic views acquired during diagnostic imaging, the provision of a SYNTAX™ score tutorial with examples based on real images, operator training, the use of objectively quantified parameters (e.g. stenosis, severity and length), consensus between highly qualified observers (technician or interventional cardiologist) and user-friendly software facilitating on-line correction. In addition, taking into account the fact that angiograms performed in the SYNTAX trial and registry may have been of higher quality than in the routine clinical practice, it would be very important to evaluate the reproducibility of SYNTAX score in a "real world" practice.

Kappa statistics are a generally accepted method of evaluating agreement between observers and are most useful when observations are frequent and have a Gaussian distribution (Figure 3). It is well known that visual estimates of lesion characteristics are less accurate in comparison to quantitatively derived parameters, as has been demonstrated in previously conducted variability and quality control studies. Beauman and Vogel[12] compared visual estimations of lesion severity, to quantitative analyses of percent diameter stenosis of coronary and phantom obstructions. Quantitatively assessed coronary arteries comprising a 50% diameter stenosis and 50% phantom stenosis recordings were visually scored in ranges from 15 to 80 percent, and 30 to 95 percent respectively. Determination of the reference diameter showed that only 41% of the estimations were within 10 % of the range of the quantitatively derived diameter.

Another study in 50 lesions[13] reported an inter-observer agreement of 73% for stenosis length (defined as the length of that portion of the stenosis that had a >30% reduction in luminal diameter using the adjacent normal vessel diameter as a 'yardstick' or unit) and 64% for lesion eccentricity (defined as asymmetrically positioning in one or more views), resulting in kappa values of respectively 0.38 and 0.25. The Cardialysis corelab in 1993 reported[14] the level of agreement in inter-observer observation made on 151 lesions: 79 % for lesion eccentricity, 71% for branch point involvement, 86% for location in a bend, 98% for presence of thrombus, 90% for presence of calcification and 75 % for the lesion type according to the ACC / AHA classification. These results were largely confirmed in a second evaluation reported in 1996[15]. Another study of 403 coronary lesions using the kappa statistics showed an excellent agreement for type C lesions (k=0.85); good agreement for TIMI flow (k=0.73), ABC classification (k=0.48), angulation (k=0.48) and side branch (k=0.40); and poor agreement for eccentricity, tortuosity, lesion calcification, and in the distinction of discrete, diffuse and tubular lesion length. The SYNTAX™ score analysed in its constituent components largely confirmed the results previously reported.

An issue of essential relevance, which contributes to the poor agreement within and between investigators, is a clear description of the definitions of lesion characteristics being assessed. Length of lesion can be interpreted, for example, as the length of plaque related to the pre-defined size of the catheter on the image. An alternative definition is the length where the lumen diameter has a stenosis > 70%, or >50%, or >30%. This can then be expressed in absolute diameters, or in terms of normal lumen diameter ratio. Lesion length can also be defined as the calliper measurement of the distance from the proximal to the distal shoulder of the lesion in the projection that best elongates the stenosis. For the SYNTAX™ score <10 and >20 mm were deliberately chosen as cut-off points for lesion length because these leave the least room for variation in interpretation.

A panel assessment gives a substantial improvement in inter- and intra-observer agreement. It is clear that the weighted sum of several simultaneous observations eliminates the most extreme disagreements, whereas the assessor working in isolation can develop his own interpretation and thus deviate from the original definitions. Serial observations as in pre-readings, with knowledge of the results of the first observer's judgement, may result in higher kappa values for qualitatively assessed lesion characteristics. The mechanism of improved agreement in case of pre-reading, however, differs from improved agreement following panel assessment. In serial readings, the first assessment is dominant and respected by the second reviewer, who tends to comply, resulting in an improved outcome. So far the assessment of the SYNTAX™ score, as a prognostic index, has been only reported in the ARTS-II registry. Valgimigli et al[16] specifically divided the population with 3-vessel disease in tertiles according to SYNTAX™ score and reported the outcome separately. It is noticeable that the MACCE rate in the highest tertile of the ARTS-II trial (SYNTAX™ score >26) at one year is 21.5%, which is identical to the MACCE rate observed in the highest tertile of the Syntax trial (SYNTAX™ score ≥33) in the subgroup of the 3-vessel disease (Figure 5C).

In the Syntax study, and in the subgroups of patients with 3-vessel disease and/or left main disease, the prognostic value of the SYNTAX™ score is even more significant. Irrespective of their diabetic status, the one-year outcome of all patients with left main and/ or 3-vessel disease with a SYNTAX™ score less than 22 was comparable between those randomised to PCI or surgery[6]. Patients with 3-vessel disease with intermediate or high scores, with or without diabetes, had significantly lower repeat revascularisation rates with surgical revascularisation than with percutaneous treatment. However, non-diabetic patients with an intermediate score and a left-main lesion (isolated or not) have an excellent outcome with PCI when compared to surgery. The take-home message is that in an all-comer population of left-main and 3-vessel disease, numerically one-third of these patients could be legitimately treated by PCI and that two thirds of patients might be referred to surgery. This initial assessment will have to be re-evaluated after medium-term follow-up out to five years. In addition, the cut-off of low, intermediate and high Syntax score classification should be further standardised and re-evaluated in the other cohort to establish robustness of this scoring system in prediction of outcomes. Finally, we should emphasise that the analysis of the outcome was related to the raw data of the score which was based on an arbitrary ranking of the complexity of the lesions. The impact of certain anatomic parameters (tortuosity, ostial lesion etc.) on predicted outcome may have been overestimated or underestimated and should be re-evaluated on the basis of the actual outcome at one year. The process of simplifying and weighting the SYNTAX™ score will be a retrospective exercise, based on complex statistical analysis, and will again need to be prospectively tested on a

different patient population. It might be more straight-forward to combine a prognostic index of mortality such as the EuroSCORE, with the descriptive coronary score of the Syntax trial, to provide more accurate risk assessment on the outcome.

The data presented in this report are the result of post-hoc subgroup analyses. It was based on a tertile division of the entire study population with the partitioning criteria being subsequently applied to subgroups of patients with either main stem or 3-vessel disease. None of the subgroup analyses (with SYNTAX™ score tertile defined a posteriori) were prespecified or statistically powered. It should be emphasised that the global hierarchical statistical hypothesis of non-inferiority of PCI as compared to surgery for treatment of left main and/ or 3-vessel disease was not confirmed; therefore, the observational data provided in the present report are hypothesis generating, and should be further validated in order to be formally incorporated in guidelines on appropriateness of revascularisation for left main or 3-vessel disease[17].

References

1. Hoffman SN, TenBrook JA, Wolf MP, Pauker SG, Salem DN, Wong JB. A meta-analysis of randomized controlled trials comparing coronary artery bypass graft with percutaneous transluminal coronary angioplasty: one- to eight-year outcomes. *J Am Coll Cardiol* 2003; 41(8):1293-1304.

2. Ong AT, Serruys PW, Mohr FW, Morice MC, Kappetein AP, Holmes DR, Jr., Mack MJ, van den Brand M, Morel MA, van Es GA, Kleijne J, Koglin J, Russell ME. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. *Am Heart J* 2006; 151(6):1194-1204.

3. Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, Carrié D, Clayton TC, Danchin N, Flather M, Hueb WA, Kahler J, Kelsey SF, King SB, Kosinski AS, Lopes N, McDonald KM, Rodriguez A, Serruys P, Sigwart U, Stables RH, Owens DK, Pocock SJ. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet.* 2009;373:1190-7.

4. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg* 1999;16(1):9-13.

5. Parsonnet V, Dean D, Bernstein AD. A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. *Circulation* 1989; 79(6 Pt 2):I3-12.

6. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Percutaneous Coronary Intervention versus Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease. *N Engl J Med.* 2009;360:961-72.

7. Leaman DM, Brower RW, Meester GT, Serruys P, van den Brand M. Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. *Circulation* 1981; 63:285-299.

8. Fleiss J. Statistical methods for rates and proportions. 2nd edition : John Wiley & Sons Inc.; 1981.

9. Banning AP, Westaby S, Mohr FW, Kappetein AP, Morice M-C, Berti S, Glauber M, Kellett MA, Kramer RS, Leadley K, Dawkins KD, Serruys PW. Comparison of Cardiac Surgery and Paclitaxel-Eluting Stents in Non-Diabetic and Diabetic Patients with Left main or Three-Vessel Coronary Artery Disease. *Lancet* 2009; in-press.

10. Serruys PW, Ong AT, van Herwerden LA, Sousa JE, Jatene A, Bonnier JJ, Schonberger JP, Buller N, Bonser R, Disco C, Backx B, Hugenholtz PG, Firth BG, Unger F. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. *JACC* 2005;46:575-581.

11. Serruys PW, Daemen J, Morice MC, De Bruyne B, Colombo A, Macaya C, Richardt G, Fajadet J, Hamm C, Dawkins KD, Vranckx P, Bressers M, van Domburg R, Schuijer M, Wittebols K, Pieters M, Stoll HP, on behalf of the ARTS II Investigators. Three-year follow-up of the ARTS-II - sirolimus-eluting stents for the treatment of patients with multivessel coronary aretery disease. *EuroIntervention* 2007;3:450-459.

12. Beauman GJ, Vogel RA. Accuracy of individual and panel visual interpretations of coronary arteriograms: implications for clinical decisions. *JACC* 1990; 16:108-113.

13. Ellis S, Alderman EL, Cain K, Wright A, Bourassa M, Fisher L. Morphology of left anterior descending coronary territory lesions as a predictor of anterior myocardial infarction: a CASS Registry Study. *JACC* 1989; 13(7):1481-1491.

14. Hermans WR, Foley DP, Rensing BJ, Rutsch W, Heyndrickx GR, Danchin N, Mast G, Hanet C, Lablanche JM, Rafflenbeul W, et al. Usefulness of quantitative and qualitative angiographic lesion morphology, and clinical characteristics in predicting major adverse cardiac events during and after native coronary balloon angioplasty. CARPORT and MERCATOR Study Groups. *Am J Cardiol.* 1993; 72(1):14-20.

15. Herrman JP, Azar A, Umans VA, Boersma E, von Es GA, Serruys PW. Inter- and intra-observer variability in the qualitative categorization of coronary angiograms. *Int J Card Imaging* 1996;12(1):21-30.

16. Valgimigli M, Serruys PW, Tsuchida K, Vaina S, Morel MA, van den Brand MJ, Colombo A, Morice MC, Dawkins K, de Bruyne B, Kornowski R, de Servi S, Guagliumi G, Jukema JW, Mohr FW, Kappetein AP, Wittebols K, Stoll HP, Boersma E, Parrinello G. Cyphering the complexity of coronary artery disease using the SYNTAX™ score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. *Am J Cardiol.* 2007; 99(8):1072-1081.

17. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization: a report by the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 2009; 53(6):530-553.

Appendix

Pre-existing classifications

The SYNTAX score has been developed based on the following:

1. The AHA classification of the coronary tree segments modified for the ARTS study
2. The Leaman score
3. The ACC/AHA lesions classification system
4. The total occlusion classification system
5. The Medina classification bifurcation lesions
6. Consultation of experts

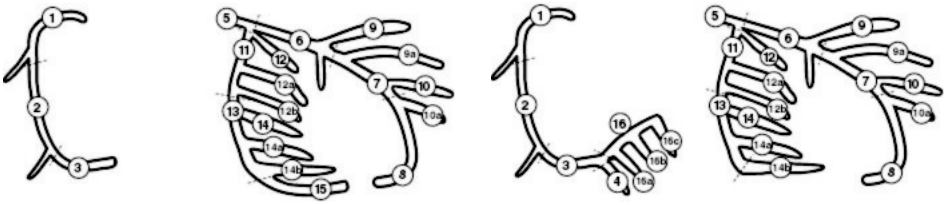
Each of these classifications has focused on the specific functional and anatomical parameters of the lesion. Thus it was necessary to develop a global classification system that would take into account all the variables.

Definition of the coronary tree segments

The definition of the coronary tree segments is based on the classification proposed by the AHA and modified for the ARTS I and II trials[1,2]. This system divided the arterial tree into 16 segments (Figure 1) and this has been adopted in the SYNTAX score.

Leaman score[3]

The ìLeaman scoreî is based on the severity of luminal diameter narrowing and weighed according to the usual blood flow to the left ventricle in each vessel or vessel segment. In a right dominant system, the right coronary artery (RCA) supplies approximately 16%, and the left coronary artery (LCA) 84% of the flow to the left ventricle (LV). This 84% is normally directed for 66% to the left anterior descending artery (LAD), and for 33% into the left circumflex coronary artery (LCX). Thus, the Left Main (LM) supplies approximately five times, the LAD approximately 3.5 times (84/16 x 0.66), and the circumflex 1.5 times as much blood as the RCA to the LV. In a left dominant system the RCA does not contribute to the blood supply of the ventricle. Thus the LM supplies 100% of the flow to the LV. The RCA contribution of blood flow to the LV is now supplied by the LCX. Hence the LAD provides 58% (weighing factor 3.5) and the LCX 42% (weighing factor 2.5) of the total flow to the LV. Using the same principle of relative blood supply to the LV, all coronary segments have been given a weighing factor, Table 1. The contribution of each coronary segment to the blood flow to the LV is used as a multiplication factor for the calculation of the Leaman score and as such has been transferred to the SYNTAX score.



Left *Right*

Figure 1.

1. *RCA proximal: From the ostium to one half the distance to the acute margin of the heart.*
2. *RCA mid: From the end of first segment to acute margin of heart.*
3. *RCA distal: From the acute margin of the heart to the origin of the posterior descending artery.*
4. *Posterior descending artery: Running in the posterior interventricular groove.*
16. *Posterolateral branch from RCA: Posterolateral branch originating from the distal coronary artery distal to the crux.*
16a. *Posterolateral branch from RCA: First posterolateral branch from segment 16.*
16b. *Posterolateral branch from RCA: Second posterolateral branch from segment 16.*
16c. *Posterolateral branch from RCA: Third posterolateral branch from segment 16.*
5. *Left main: From the ostium of the LCA through bifurcation into left anterior descending and left circumflex branches.*
6. *LAD proximal: Proximal to and including first major septal branch.*
7. *LAD mid: LAD immediately distal to origin of first septal branch and extending to the point where LAD forms an angle (RAO view). If this angle is not identifiable this segment ends at one half the distance from the first septal to the apex of the heart.*
8. *LAD apical: Terminal portion of LAD, beginning at the end of previous segment and extending to or beyond the apex.*
9. *First diagonal: The first diagonal originating from segment 6 or 7.*
9a. *First diagonal a: Additional first diagonal originating from segment 6 or 7, before segment 8.*
10. *Second diagonal: Originating from segment 8 or the transition between segment 7 and 8.*
10a. *Second diagonal a: Additional second diagonal originating from segment 8.*
11. *Proximal circumflex artery: Main stem of circumflex from its origin of left main and including origin of first obtuse marginal branch.*
12. *Intermediate/anterolateral artery: Branch from trifurcating left main other than proximal LAD or LCX. It belongs to the circumflex territory.*
12a. *Obtuse marginal a: First side branch of circumflex running in general to the area of obtuse margin of the heart.*
12b. *Obtuse marginal b: Second additional branch of circumflex running in the same direction as 12.*
13. *Distal circumflex artery: The stem of the circumflex distal to the origin of the most distal obtuse marginal branch, and running along the posterior left atrioventricular groove. Calibre may be small or artery absent.*
14. *Left posterolateral: Running to the posterolateral surface of the left ventricle. May be absent or a division of obtuse marginal branch.*
14a. *Left posterolateral a: Distal from 14 and running in the same direction.*
14b. *Left posterolateral b: Distal from 14 and 14 a and running in the same direction.*
15. *Posterior descending: Most distal part of dominant left circumflex when present. It gives origin to septal branches. When this artery is present, segment 4 is usually absent.*

Table 1. Segment weighing factors.

Segment No		Right dominance	Left dominance
1	RCA proximal	1	0
2	RCA mid	1	0
3	RCA distal	1	0
4	Posterior descending artery	1	n.a.
16	Posterolateral branch from RCA	0.5	n.a.
16a	Posterolateral branch from RCA	0.5	n.a.
16b	Posterolateral branch from RCA	0.5	n.a.
16c	Posterolateral branch from RCA	0.5	n.a.
5	Left Main	5	6
6	LAD proximal	3.5	3.5
7	LAD mid	2.5	2.5
8	LAD apical	1	1
9	First diagonal	1	1
9a	First diagonala	1	1
10	Second diagonal	0.5	0.5
10a	Second diagonala	0.5	0.5
11	Proximal circumflex artery	1.5	2.5
12	Intermediate/ anterolateral artery	1	1
12a	Obtuse marginala	1	1
12b	Obtuse marginalb	1	1
13	Distal circumflex artery	0.5	1.5
14	Left posterolateral	0.5	1
14a	Left posterolaterala	0.5	1
14b	Left posterolateralb	0.5	1
15	Posterior descending	n.a.	1

Table 2. Lesions adverse characteristic scoring.

Diameter reduction (*)		
– Total occlusion		x5
– Significant lesion (50-99%)		x2
Total occlusion (TO)		
– Age >3months or unknown		+1
– Blunt stump		+1
– Bridging		+1
– First segment visible beyond TO (**)+1/ per non-visible segment		
– Side branch (SB)	– Yes, SB <1.5 mm	+1
	– Yes, SB ≥1.5 mm	+1
Trifurcations		
– 1 diseased segment		+3
– 2 diseased segments		+4
– 3 diseased segments		+5
– 4 diseased segments		+6
Bifurcations		
– Type 100, 010, 110		+1
– Type 111, 101, 011, 001		+2
– Angulation <70°		+1
Aorto-ostial stenosis		+1
Severe tortuosity		+2
Length > 20 mm		+1
Heavy calcification		+2
Thrombus		+1
"Diffuse disease"/small vessels		+1/ per segment number

x: multiplication; +: addition; (*) In the SYNTAX algorithm there is no question for % luminal diameter reduction. The lesions are considered as significant (50-99% luminal diameter reduction) or occlusive (100%). (**) Please see figure 2

Lesion definition

A coronary lesion with a diameter stenosis>50% in a vessel ≥1.5 mm is significant, and must be scored. A lesion can involve one or more diseased segments. Less severe lesions should not be included in the SYNTAX score. The percent diameter stenosis is not considered in the algorithm. Distinction has been made only between occlusive (100% diameter stenosis) and non occlusive (50-99% diameter stenosis) disease. A multiplication factor of 2 is used for non-occlusive lesions, and 5 for occlusive lesions reflecting the difficulty of percutaneous treatment, Table 1. Importantly, all other adverse lesion characteristics considered in the SYNTAX score have an additive value, Table 2.

Multiple stenoses

If serial stenoses are less than three reference vessel diameters apart, they should be scored as one lesion. However, stenoses at a greater distance from each other (more than three reference vessel diameters), are considered as separate lesions.

ACC/AHA lesion classification system[4,5]

This lesion classification system is based on parameters, such as length, eccentricity, angulation, calcification, involvement of side branches and thrombus. Lesions are classified as Type A, (high success and low risk), Type B (moderate success and moderate risk) or Type C (low success and high risk). The majority of these individual parameters have been incorporated in the SYNTAX score (Table 2). Although the ACC/AHA system takes into account total occlusions and bifurcation lesions, classifying them as a high-risk, this is not considered to be detailed enough to adequately quantify their complexity.

Total occlusion classification system[6]

A lesion is defined as a total occlusion when no intra-luminal antegrade flow (TIMI 0) is visible distal to the point of occlusion. Segments distal to the occlusion may be filled by bridging, ipsilateral or contra-lateral collaterals. Parameters suggested in this system such as an occlusion older than three months; the presence of a side branch at the site of the occlusion and its size; a blunt stump; the presence of bridging collaterals, and occlusion length have all been incorporated into the SYNTAX score, Table 2. The length of the obstructed segment is calculated by measuring the distance between the stump of the occlusion and the first segment beyond the occlusion, visualised by ante-grade or retrograde collateral flow, Figure 2. The age of the total occlusion is scored based on a history of previous myocardial infarction, worsening symptoms, or previous angiographic or electrocardiographic data. In cases where this information is absent the age of total occlusion is scored as unknown.

Trifurcation lesions

Trifurcation is the division of a main branch into three branches (with a minimal diameter of 1.5 mm). In a trifurcation, one, two, three or four of the involved segments can be significantly diseased. The most common example of a trifurcation is at the division of LM

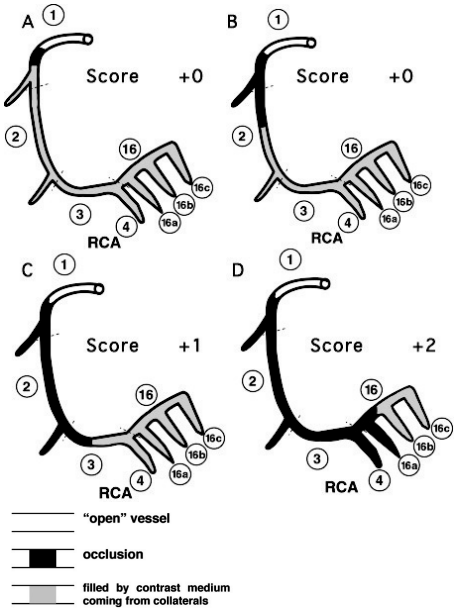


Figure 2. Total occlusion length assessment.

A) Total occlusion involving segments 1. Segments 1, 2, 3, 4, 16, 16a, 16b, 16c are filled by antegrade or retrograde collateral flow (visualised by contrast). No points are added to the score.

B) Total occlusion involving segments 1 and 2. Segments 2, 3, 4, 16, 16a, 16b, 16c are filled by antegrade or retrograde collateral flow (visualised by contrast). No points are added to the score.

C) Total occlusion involving segments 1, 2 and 3. Segments 3, 4, 16, 16a, 16b, 16c are filled by antegrade or retrograde collateral flow (visualised by contrast). One point is added to the score.

D) Total occlusion involving segments 1, 2, 3, 4, 16 and 16a Segments 16, 16b, 16c are visualised by antegrade or retrograde collateral flow (visualised by contrast). Two points are added to the score

into the LAD, LCX, and an intermediate branch. Trifurcations are only scored for the following segment junctions: 3/4/16/16a, 5/6/11/12, 11/12a/12b/13, 6/7/9/9a and 7/8/10/10a, Table 2.

Bifurcation lesions and the Medina classification system[7]

A bifurcation is defined as the division of a main, parent, branch into two daughter branches (each with a minimal diameter of 1.5mm). Bifurcation lesions may involve the proximal main vessel, the distal main vessel and the side branch and are classified according to the Medina classification. The smaller of the two daughter branches should be designated as the ìside branchî. In cases of a left main stem lesion, either the LCX or the LAD can be designated as the side branch, depending on their respective calibres. Only those lesions in direct contact with the bifurcation should be scored.

Bifurcation lesions not involving the ostium of the side branch are classified as type 1,0,0 if the lesion in the main vessel is proximal to the bifurcation; type 0,1,0 if the lesion is in the main branch is distal to the bifurcation, and type 1,1,0 if the lesion in the main branch lies both proximal and distal to the side branch. Bifurcation lesions involving the ostium of the side branch are classified as type 1,0,1 if the lesion in the main branch is proximal to the bifurcation; type 0,1,1 if the lesion in the main branch is distal to the bifurcation, and type 1,1,1 if the main branch lesion lies both proximal and distal to the side branch. As plaque shift can occur even when only the ostium of a side branch is narrowed, such a lesion is also considered as a bifurcation (type 0,0,1) (Figure 3). Bifurcations are only considered for the following segment junctions: 5/6/11, 6/7/9, 7/8/10, 11/13/12a, 13/14/14a and 3/4/16 and 13/14/15 in case of left dominance.

One lesion characteristic added to the bifurcation lesion classification is an angulation between the side branch and the distal main vessel of less than 70 degrees. Despite the fact that this represents a less technical challenge, it is regarded as an adverse lesion characteristic due to the fact that the smaller this angle is the more difficult it will be to cover the ostium of the side branch when stenting is necessary, Figure 4.

Aorto-ostial lesions

A lesion is classified as aorto-ostial when it is located immediately at the origin of the coronary arteries from the aorta. It applies only to segments 1 and 5. In case of an absent LM (double ostium of the Left Coronary Artery), segment 6 of the LAD and 11 of the LCX originate directly from the aorta, and consequently may also involve aorto-ostial lesions. An aorto-ostial location is regarded as an adverse characteristic because the treatment of such lesions is technically more challenging.

Diffuse disease/small vessels

This characteristic is present when at least 75% of the length of any segment(s) proximal to the lesion, at the site of the lesion or distal to the lesion has a vessel diameter of ≤2 mm.

Diffuse disease/small vessels is the last question of the algorithm and is the only non-lesion specific question. This question pertains to all the segments of that targeted vascular territory (either LAD and its

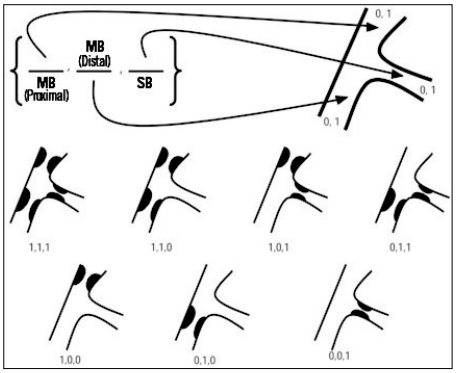


Figure 3. Bifurcation classification (according to MEDINA classification).

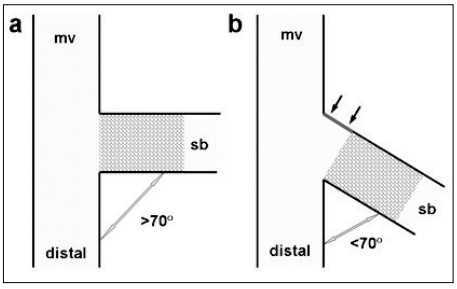


Figure 4. a) An example of a bifurcation lesion with a wide angle (>70 degrees) between the side branch and the distal main vessel. Although technical challenging sometimes, the stent can fully cover both the proximal and distal rims of the side branch ostium. b) An example of a bifurcation with a steep angle (<70 degrees) between the side branch and the distal main vessel. Side branch stenting might be technically less challenging compared to the previous anatomy but when the stent is placed to cover the distal rim of the ostium the proximal rim will remain uncovered (red line with arrows). If the stent is placed to cover the proximal rim it will protrude into the main vessel distally. mv denotes main vessel, sb denotes side branch

branches, or LCX and its branches, or RCA and its branches) provided this vascular territory exhibits at least one lesion. This question will appear only once per vascular territory after the assessor has described for the final time a stenotic lesion in that vascular territory. For example, if a patient has a lesion in the RCA located in segment 1 the assessor will be asked to characterise the diffuse/small appearance of all the segments of the RCA vascular territory (1, 2, 3, 4, 16, 16a, 16b, 16c). This will occur only after indicating that no other coronary lesions need to be scored within the RCA vascular territory.

The SYNTAX score algorithm (Table 3)

The SYNTAX score is calculated by a computer program consisting of sequential and interactive self-guided questions. The algorithm consists of twelve main questions. They can be divided in two groups: The first three determine the dominance, the total number of lesions and the vessel segments diseased per lesion and they appear once. The maximum number of lesions allowed is twelve and each lesion is characterised by a number, 1 to 12. Each lesion can involve one or more diseased segments. In this case each vessel segment involved contributes to the lesion scoring. There is no limit in the number of segments involved per lesion. The last nine questions refer to adverse lesion characteristics and are repeated for each lesion. The question referring to a total occlusion is the first one. If a total occlusion is scored, answers must be given to detailed sub-questions. The last of these sub-questions refers to the presence or absence of side branches and their size. If there are no side branches or if their diameter is <1.5 mm then the questions related to the trifurcation and bifurcation lesions will be automatically skipped since vessels <1.5 mm are not considered large enough for treatment either with PCI or CABG. If side branches with diameter ≥1.5 mm are involved then the lesion is considered as both total occlusion and bifurcation lesion and the algorithm will continue with

Table 3. The SYNTAX score algorithm.

1. Dominance	
2. Number of lesions	
3. Segments involved per lesion	
Lesion characteristics	
4. Total occlusion	i. Number of segments involved ii. Age of the total occlusion (>3 months) iii. Blunt stump iv. Bridging collaterals v. First segment beyond the occlusion visible by antegrade or retrograde filling vi. Side branch involvement
5. Trifurcation	i. Number of segments diseased
6. Bifurcation	i. Type ii. Angulation between the distal main vessel and the side branch <70°
7. Aorto-ostial lesion	
8. Severe tortuosity	
9. Length >20 mm	
10. Heavy calcification	
11. Thrombus	
12. Diffuse disease/ small vessels	i. Number of segments with diffuse disease/small vessels

The SYNTAX score is calculated by a computer program consisting of sequential and interactive self-guided questions. All the below mentioned definitions are projected in a side window when the signal (i) indicating information, available for each question, is pointed to with the cursor.

Definitions

Dominance. a) Right dominance: the posterior descending coronary artery is a branch of the right coronary artery (segment 4). b) Left dominance: the posterior descending artery is a branch of the left coronary artery (segment 15). Co-dominance does not exist as an option at the SYNTAX score.

Total occlusion. No intra-luminal antegrade flow (TIMI 0) beyond the point of occlusion.

Bridging collaterals. Small channels running in parallel to the vessel and connecting the proximal vessel to the distal vessel, and being responsible for the ipsilateral collateralisation.

Trifurcation. A division of a main branch into three branches. Trifurcations are only scored for the following segment junctions: 3/4/16/16a, 5/6/11/12, 11/12a/12b/13, 6/7/9/9a and 7/8/10/10a.

Bifurcation. A bifurcation is defined as the division of a main, parent, branch into two daughter branches (with a minimal diameter of 1.5mm). Bifurcations are only considered for the following segment junctions: 5/6/11, 6/7/9, 7/8/10, 11/13/12a, 13/14/14a and 3/4/16 and in case of left dominance 13/14/15.

Aorto ostial. A lesion is classified as aorto-ostial when it is located immediately at the origin of the coronary vessels from the aorta (applies only to segments 1, 5, 6 and 11).

Severe tortuosity. One or more bends of 90 o or more, or three or more bends of 45° to 90° proximal to the diseased segment.

Length >20 mm. Estimation of the length of that portion of the stenosis that has ≥50% reduction in luminal diameter in the projection where the lesion appears to be the longest. (In case of a bifurcation lesion at least one of the branches has a lesion length of >20 mm).

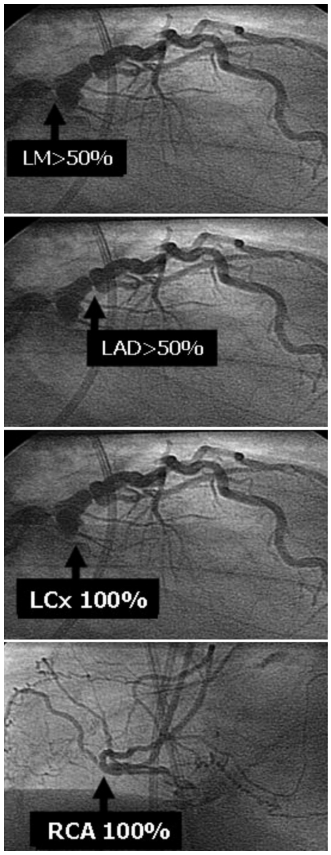
Heavy calcification. Multiple persisting opacifications of the coronary wall visible in more than one projection surrounding the complete lumen of the coronary artery at the site of the lesion.

Thrombus. Spherical, ovoid or irregular intraluminal filling defect or lucency surrounded on three sides by contrast medium seen just distal or within the coronary stenosis in multiple projections, or a visible embolisation of intraluminal material downstream.

Diffuse disease/small vessels. More than 75% of the length of any segment(s) proximal to the lesion, at the site of the lesion or distal to the lesion that has a vessel diameter of <2 mm.

all the questions. The same is the case for non-occlusive lesions. With the exception of the selection of the type in case of a bifurcation or a trifurcation lesion all the other questions of the algorithm can be answered by selecting “yes” or “no”.

An important characteristic of the SYNTAX score is that it is lesion based. For each lesion a separate score is calculated. The total SYNTAX score is derived from the summation of these individual scores. After the completion of the algorithm a report is automatically generated summarising all the adverse characteristics, and the individual scoring of each lesion as well as the total SYNTAX score. Two examples of the SYNTAX score calculation are presented in Figures 5 and 6. Both patients have significant stenosis in all three coronary arteries with four lesions each but the calculated SYNTAX score differs greatly (54.5 versus 19) reflecting the more complex pattern of coronary artery disease in the patient with the higher score.



Lesion 1
Segment 5: 5x2 . . 10
+Bifurcation
type 1,0,0 1
+Heavy
calcification 2
Lesion 1 score: . 13

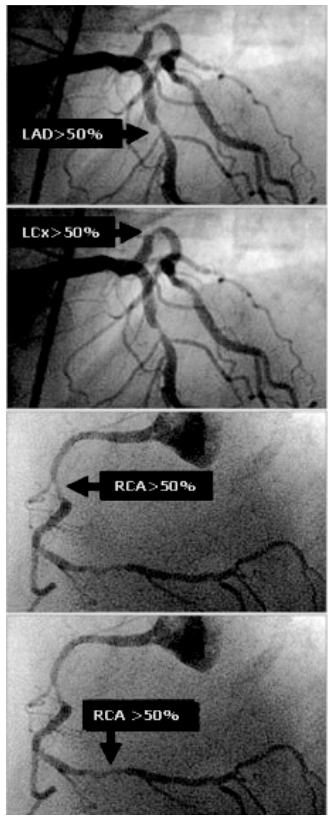
Lesion 2
Segment 6:
3.5x2 7
+Bifurcation
type 1,0,0 1
+Angulation
<70 1
+Heavy
calcification 2
Lesion 2
score:. 11

Lesion 3
Segment 11:
1.5x5 . . . . . 7.5
Age of T.O
is unknown 1
+Blunt stump. 1
+Side branch 1
+Heavy
calcification 2
Lesion 3
score:. 12.5

Lesion 4
Segment 1:
1x5 5
Age of T.O
is unknown 1
+Blunt stump. 1
+Side branch 1
First segment
visualised
by contrast 4 2
+Heavy
calcification 2
Lesion 4 score: . 12

Total score: 48.5

Figure 5. First example of the Syntax score calculation.



Lesion 1
Segment 6:
3.5x2 7
Lesion 1 score: . . 7

Lesion 2
Segment 11:
1.5x2 3
+Tortuosity. 2
Lesion 2 score: . . 5

Lesion 3
Segment 2:
1x2 2
Lesion 3 score: . . 2

Lesion 4
Segment 3:
1x2 2
+Tortuosity. 2
+Length 1
Lesion 4 score: . . 5

Total score:. 19

Figure 6. Second example of the Syntax score calculation.

References

1. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, McGoon DC, Murphy ML, Roe BB. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation* 1975; 51(4 Suppl):5-40.

2. Serruys PW, Unger F, van Hout BA, van den Brand MJ, van Herwerden LA, van Es GA, Bonnier JJ, Simon R, Cremer J, Colombo A, Santoli C, Vandormael M, Marshall PR, Madonna O, Firth BG, Breeman A, Morel MA, Hugenholtz PG. The ARTS study (Arterial Revascularization Therapies Study). *Semin Interv Cardiol* 1999; 4(4):209-219.

3. Leaman DM, Brower RW, Meester GT, Serruys P, van den Brand M. Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. *Circulation* 1981; 63(2):285-299.

4. Ryan TJ, Faxon DP, Gunnar RM, Kennedy JW, King SB, 3rd, Loop FD, Peterson KL, Reeves TJ, Williams DO, Winters WL, Jr., et al. Guidelines for

percutaneous transluminal coronary angioplasty. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). *Circulation* 1988; 78(2):486-502.

5. Smith SC, Jr., Dove JT, Jacobs AK, Kennedy JW, Kereiakes D, Kern MJ, Kuntz RE, Popma JJ, Schaff HV, Williams DO, Gibbons RJ, Alpert JP, Eagle KA, Faxon DP, Fuster V, Gardner TJ, Gregoratos G, Russell RO, Smith SC, Jr. ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines)-executive summary: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty) endorsed by the Society for Cardiac Angiography and Interventions. *Circulation* 2001; 103(24):3019-3041.

6. Hamburger JN, Serruys PW, Seabra-Gomes R, Simon R, Koolen JJ, Fleck E, Mathey D, Sievert H, Rutsch W, Buchwald A, Marco J, Al-Kasab SM, Pizulli L, Hamm C, Corcos T, Reifart N, Hanrath P, Taeymans Y. Recanalization of total coronary occlusions using a laser guidewire (the European TOTAL Surveillance Study). *The American journal of cardiology* 1997; 80(11):1419-1423.

7. Medina A, Suarez de Lezo J, Pan M. [A new classification of coronary bifurcation lesions]. Revista espanola de cardiologia 2006; 59(2):183.

Chapter 4.3

The SYNTAX Score revisited: A new assessment of the SYNTAX score reproducibility

Catheter Cardiovasc Interv 2010; 75(6): 946-952

Scot Garg , Chrysafios Girasis, Giovanna Sarno, Dick Goedhart, Marie-Angèle Morel, Marco Bressers, Hector M. Garcia-Garcia, Gerrit-Anne Van Es, Patrick W. Serruys

The SYNTAX Score Revisited: A Reassessment of the SYNTAX Score Reproducibility

Scot Garg,[1] MBChB, MRCP, Chrysafios Girasis,[1] MD, Giovanna Sarno,[1] MD, PhD, Dick Goedhart,[2] PhD, Marie-Angèle Morel,[2] BSc, Hector M. Garcia-Garcia,[2] MD, PhD, Marco Bressers,[2] MSc, Gerrit-Anne van Es,[2] PhD, and Patrick W. Serruys,[1*] MD, PhD, on behalf of the SYNTAX trial investigators

Objectives: To reassess the reproducibility of the SYNTAX score. Background: The SYNTAX score appears to have an important role to play in the evaluation of patients with complex coronary artery disease undergoing revascularisation. However, the calculation of the SYNTAX score relies on the subjective assessment of lesions using coronary angiography, and therefore is subject to intra-and inter-observer variability. Methods: The SYNTAX score was calculated in 100 patients randomly selected from the SYNTAX trial, on two occasions 8 weeks apart, by a team made up of three interventional cardiologists. The weighted kappa values were compared with values obtained 1 year previously, when core lab analysts assessed the intra-observer reproducibility amongst the same patient cohort. Results: The mean ± standard deviation difference in SYNTAX score was 2.1 ± 7.6. The respective weighted kappa values for the number of lesions, bifurcation lesions, ostial lesions, and total occlusions were 0.62, 0.36, 0.66, and 0.91 compared with 0.59, 0.41, 0.63, and 0.82 in the previous core lab assessment. The weighted kappa for the intra-observer reproducibility of the SYNTAX score grouped into deciles was 0.54, and according to the terciles ≤22, >22–≤32, >32 was 0.51 both indicating a moderate level of agreement beyond the level of chance. In the previous assessment, the comparative kappa values were 0.45 and 0.53. Conclusions: The SYNTAX score has moderate intra-observer reproducibility when assessed by a team of three interventional cardiologists, which is consistent with a prior evaluation performed by core lab analysts. The scoring of bifurcation lesions remains the main source of inconsistency. © 2010 Wiley-Liss, Inc.

Key words: SYNTAX score; intra-observer variability; SYNTAX trial

INTRODUCTION

Coronary artery bypass grafting (CABG) has historically been the preferred method of revascularisation in patients with complex coronary artery disease (CAD); however, recent evidence indicates that in specific groups of patients, percutaneous coronary intervention (PCI) can offer a safe and efficacious alternative treatment [1–4]. This expanding use of PCI [5] has consequently increased the importance of developing a systematic approach for risk stratifying these complex patients. The ability to objectively decide, which patients with complex CAD are suitable for PCI has gained new ground recently following the introduction of the SYNTAX score [6,7]. This lesion based scoring system cannot only quantify coronary anatomy, but studies also demonstrate that it has a role in the short and long term risk stratification of patients having percutaneous revascularisation [1,4,8–10].

The SYNTAX score is calculated using lesion assessment based on coronary angiography, however, this is subject to intra- and inter-observer variability [11–13], which may ultimately affect the overall reproducibility of the score. A poorly reproducible score will limit its clinical application, and in particular will make guideline recommendations based on specific scores of limited value. The aim of this study was to reassess the intra-observer SYNTAX score

[1]Department of Interventional Cardiology, Erasmus MC, Rotterdam, Netherlands
[2]Cardialysis BV, Rotterdam, The Netherlands

Conflicts of Interest: Nothing to report.

*Correspondence to: Patrick W. Serruys, MD, PhD, Ba583a, Thoraxcentre, Erasmus MC,'s-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl

Received 15 October 2009; Revision accepted 8 November 2009

DOI 10.1002/ccd.22372
Published online 9 February 2010 in Wiley InterScience (www.interscience.wiley.com)

reproducibility, and compare it to previously reported values, which were obtained from an assessment by core lab analysts (Cardialysis, Rotterdam, The Netherlands) of the same patients 1 year earlier [7].

METHODS

Study Population

The study population comprised of 100 coronary angiograms, which had been randomly selected from patients who had been enrolled in the SYTNAX trial [1]. These angiograms were exactly the same as those which had been assessed in a previous intra-observer reproducibility evaluation of the SYNTAX score, which is described in full elsewhere [7].

SYNTAX Score Calculation

The SYNTAX score for each patient was calculated prospectively by a team of three interventional cardiologists who scored all coronary lesions with a diameter stenosis $\geq$50%, in vessels $\geq$1.5 mm, using the SYNTAX score algorithm, which is described in full elsewhere [6,7] and is available on the SYNTAX score website (www.syntaxscore.com) [14]. All three investigators reviewed the coronary angiogram, and decided by consensus: (i) the number of significant lesions that were present, (ii) which coronary segments were involved, and (iii) the presence of any adverse lesion characteristics. Once agreement had been reached one investigator entered the data onto a dedicated software package. The investigators were blinded to the clinical baseline characteristics, procedural data, clinical outcomes, and previously calculated SYNTAX score. Furthermore, investigators continued to remain blinded to the calculated SYNTAX score even after the all lesion variables had been recorded.

Intra-Observer Reproducibility

To assess intra-observer reproducibility, the angiograms were reanalyzed by the same team of three interventional cardiologists 8 weeks after the first analysis. The investigators remained blinded to the results of the first analysis.

Statistics

The justification for a sample size of 100 coronary angiograms is provided elsewhere, [7] but in brief a power calculation revealed that a group size of 100 coronary angiograms would be more than sufficient to achieve a reasonable and precise kappa-value.

The extent of intra-observer agreement beyond the level of chance was measured as a percentage of the total agreement using the kappa statistic. This is routinely used to assess the level of agreement between two or more categorical observations in excess of a chance agreement [15]. The kappa value was calculated using the standard formula: [observed agreement − expected agreement]/[1 − expected agreement]. The qualitative classification of the kappa value used to interpret the degree of agreement beyond chance is shown in Table I [16]. The standard kappa does not take into account the degree of disagreement between observers and all disagreement is treated equally as total disagreement. Therefore, the Cicchetti-Allison method was used to calculate the weighted kappa to allow the relative differences between categorical variables to be appropriately quantified [17]. Those observations on the diagonal line in the table of round one *versus* round two measurements (a corresponding score in each round) were given a higher weight than observations further from the diagonal. In addition, the further the observation was away from the diagonal, the less weight it was given using a linear scale.

TABLE I. Quantitative Classification of Kappa Values as a Degree of Agreement Beyond the Level of Chance [16]

Kappa value	Degree of agreement beyond chance
0	None
0.0 < Kappa ≤ 0.2	Slight
0.2 < Kappa ≤ 0.4	Fair
0.4 < Kappa ≤ 0.6	Moderate
0.6 < Kappa ≤ 0.8	Substantial
0.8 < Kappa ≤ 1.0	Almost perfect

The weighted kappa statistic was calculated for as follows: (1) the total number lesions; (2) number of total occlusions; (3) number of bifurcation lesions; (4) number of ostial lesions; (5) total SYNTAX score in deciles (6) and SYNTAX score terciles ($\leq$22, >22–$\leq$32, >32).

All analyses were performed using SAS (Cary, NC) version 8.02 by a dedicated statistician.

RESULTS

In total 92 (92%) angiograms were included in the final analysis. Eight of the angiograms were excluded because they could not be viewed on two occasions as a result of technical problems with the angiogram disk.

Reproducibility Assessment

The results recorded during the two rounds of the study for the total number lesions; the number of total occlusions; the number of bifurcation lesions; the number of ostial lesions; the total SYNTAX score in deciles; and the SYNTAX score in terciles are shown in Tables II–VII, together with the corresponding kappa value for the degree of agreement between both

TABLE II. Total number of lesions recorded during both rounds of the study

Round Two Number of Lesions	Round One Number of Lesions						
	1	2	3	4	5	6	Total
1	6	1	0	0	0	0	7
2	2	7	4	2	0	0	15
3	0	0	19	10	0	0	29
4	0	0	10	9	6	0	25
5	0	0	1	1	7	5	14
6	0	0	0	0	2	0	2
Total	8	8	34	22	15	5	92
Weighted kappa 0.62							

Shaded boxes represent concordant scores.

TABLE IV. Number of Bifurcations Lesions Recorded During Both Rounds of the Study

Round Two Number of Bifurcation Lesions	Round One Number of Bifurcation Lesions				
	0	1	2	3	Total
0	14	8	2	1	25
1	9	27	9	1	46
2	0	8	10	1	19
3	1	0	1	0	2
Total	24	43	22	3	92
Weighted kappa 0.36					

Shaded boxes represent concordant scores.

measurements beyond the level of chance. Table VIII shows the comparison of kappa values between this assessment of SYNTAX score reproducibility, and the previous assessment performed in the same population in 2008 [7].

SYNTAX Score

Figure 1 shows the SYNTAX score calculated for each patient in both rounds of the study. The majority of the values lie close to the line of concordance; however, five main outliers (highlighted) are present.

The overall mean SYNTAX score was 24.3 (range 4–54) and 26.4 (range 8–58) for rounds one and two, respectively. The mean difference (measure of precision) was 2.1 with a standard deviation of 7.6 (measure of accuracy). In the previous assessment in 2008, the respective values for the mean score in round one, mean score in round two, mean ± standard deviation of the difference were 31.3, 29.2, and 2.1 ± 9.1, respectively [7].

DISCUSSION

The main finding from this study is that the SYNTAX score had moderate intra-observer reproducibility when assessed by a team of three interventional cardiologists, with the main source of inconsistency

TABLE III. Number of Total Occlusions Recorded During Both Rounds of the Study

Round Two Number of Total Occlusions	Round One Number of Total Occlusions				
	0	1	2	Total
0	59	2	0	61
1	1	21	0	22
2	0	2	7	9
Total	60	25	7	92
Weighted kappa 0.91				

Shaded boxes represent concordant scores.

TABLE V. Number of Ostial Lesions Recorded During Both Rounds of the Study

Round Two Number of Ostial Lesions	Round One Number of Ostial Lesions		
	0	1	Total
0	74	2	76
1	6	10	16
Total	80	12	92
Weighted kappa 0.66			

Shaded boxes represent concordant scores.

TABLE VI. Total SYNTAX Score (in deciles) Calculated During Both Rounds of the Study

Round Two SYNTAX Score (deciles)	Round One SYNTAX Score (deciles)							
		0-10	11-20	21-30	31-40	41-50	51-60	Total
	0-10	3	2	0	0	0	0	5
	11-20	1	16	10	1	2	0	30
	21-30	0	5	22	7	1	0	35
	31-40	0	1	4	9	2	1	17
	41-50	0	0	0	2	2	0	4
	51-60	0	0	0	0	0	1	1
	Total	4	24	36	19	7	2	92
	Weighted kappa 0.54							

Shaded boxes represent concordant scores.

stemming from the evaluation of bifurcation lesions. Furthermore, these results are consistent with a previous evaluation of the score's reproducibility as performed by core lab analysts.

The Rationale for Evaluating the SYNTAX Score Reproducibility

The ability to select patients with complex CAD [triple vessel disease/left main stem disease (LMS)] who are suitable for PCI has never been as important as in the current environment where increasing numbers of patients with multiple comorbidities are being investigated, and treated for CAD [18]. These patients frequently have complex CAD, and pose a challenging clinical problem particularly as technological advances have ensured that PCI can be used to treat the majority of coronary lesions; however, this is not always the most appropriate treatment. Furthermore, the final decision regarding the method of revascularisation is also no longer simply the outcome of a discussion between physician and surgeon. Patients are becoming increasingly involved in the decision making process, and, therefore, an adequate method of risk stratification is important to enable them to make the most appropriate decision for them, as an individual [19].

The recently developed SYNTAX score [6,7] appears to have an important role to play in the evaluation of these complex patients, thereby addressing an unmet clinical need. Prospective data from the SYNTAX trial and retrospective analysis of the CUSTOMIZE registry has indicated that the SYNTAX score can reliably identify those patients with complex CAD most appropriately managed with CABG as opposed to PCI [1,4]. Moreover, evidence from prospective and retrospective analyses performed in over 4,000 patients so far suggests that the SYNTAX score can also be used to predict short and long term clinical outcomes in those undergoing PCI [1,8–10].

On the background of this increasingly complex decision making process and the positive data from trials, which have assessed the SYNTAX score's performance, it is anticipated that the SYNTAX score will be used increasingly in day-to-day clinical practice, and may will eventually be incorporated into clinical practice guidelines. The likelihood of this happening, however, is highly dependent on the demonstration of an adequately reproducible score. Importantly, this serves to improve the confidence that individual clinicians have in using the score, and also increases the probability that clinicians will adhere to suggested recommendations based on specific scores values.

TABLE VII. SYNTAX Score According to Terciles Recorded During Both Rounds of the Study

Round Two SYNTAX Score (terciles)	Round One SYNTAX Score (terciles)			
		≤22	>22-≤32	>32	Total
	≤22	27	9	3	39
	>22-≤32	7	20	11	38
	>32	1	3	11	15
	Total	35	32	25	92
	Weighted kappa 0.51				

Shaded boxes represent concordant scores.

SYNTAX Score Reproducibility

In this study, the overall reproducibility of the SYNTAX score was moderate, with a kappa value of 0.54. To place this in the context of other subjective assessments, the interpretation of T wave changes on an exercise stress test; the assessment of regional wall

TABLE VIII. Comparison of Weighted Kappa Values From 2008 and 2009 Reproducibility Assessment

Parameter	Kappa value 2008 study [7]	Kappa value 2009 study
Total number of lesions	0.59	0.62
Number of total occlusions	0.82	0.91
Number of bifurcation lesions	0.41	0.36
Number of ostial lesions	0.63	0.66
SYNTAX score (deciles)	0.45	0.54
SYNTAX score (terciles)	0.53	0.51

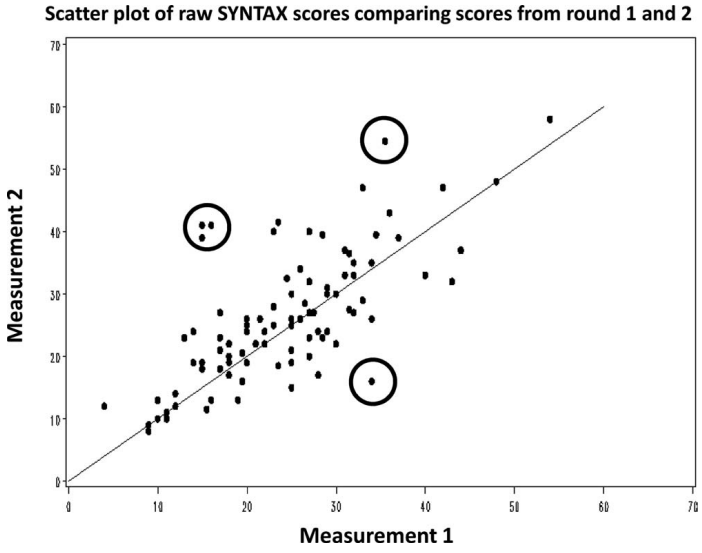


Fig. 1. Five main outliers are observed which on retrospective analysis are mainly caused by discrepancies in selecting the segments involved in bifurcation lesions, particular those involving the distal left main stem.

motion abnormalities on echocardiography; and the previous intra-observer reproducibility of the SYNTAX score have been shown to have kappa values of 0.25, 0.41, and 0.45, respectively [7,20,21].

One of the major factors influencing the SYNTAX score's reproducibility is the use of diagnostic coronary angiography to assess lesion characteristics; however, this currently represents the "gold-standard" investigation for patients with suspected CAD, and is unlikely to change in the near future. It is well known that coronary angiography is subject to intra- and inter-observer variability [22] with assessment being influenced by amongst other things the quality of the diagnostic pictures, the angiographic views that are selected, lesion eccentricity, operator experience and interpretation [11–13]. Moreover, previous studies have indicated that the assessment of lesion severity based on visual estimation is inferior when compared with quantitatively derived parameters. For example, Beauman and Vogel [12] demonstrated that the visual estimation of a 50% phantom stenosis by a group of observers ranged between 30 and 95%.

Bifurcation lesions were the lesion type with the lowest reproducibility, which is consistent with the previous study [7]. Of note discrepancies in the scoring of bifurcation lesions, and in particular those involving the distal LMS, were the main culprits in the five cases with the greatest difference between round one and round two scores (range: 19–26). This inconsistency reiterates the difficulty in evaluating whether lesions involving the distal LMS extend into the ostium of the left anterior descending (LAD)/circumflex (Cx) coronary artery. Vessel foreshortening and overlap make visualization and accurate lesion assessment in this region difficult, particularly when using only coronary angiography for assessment. In fact studies demonstrate that LMS lesions are subject to the greatest degree of intra- and inter-observer variability on coronary angiography, when compared with lesions located elsewhere in the coronary tree [23,24]. In practice a suspicious lesion in this area warrants further evaluation with intra-vascular ultrasound, coronary CT, and/or functional assessment with fractional flow reserve [23,25,26]. In this study, lesion assessment was confined only to coronary angiography, however, the reproducibility in the assessment of bifurcation lesions may well have improved if additional imaging had been available as it is in clinical practice.

Importantly, the difference in SYNTAX score between a lesion involving only the distal LMS, as

compared with a distal LMS lesion extending into the ostium of the LAD/Cx is sufficiently large enough to move a patient from a low tercile score where PCI is a viable option, to the highest tercile where CABG is the standard of care. This serves to reinforce the importance of appropriate evaluation of lesions, particularly those suspected of involving the distal LMS.

Limitations

Although the kappa value is currently the accepted standard measure of intra-observer reproducibility, it is not without its limitations. By definition, it represents agreement beyond the level of chance, however, the actual level of chance agreement is variable and affected by the prevalence of the disease being studied [27]. The SYNTAX study was a multi-centre trial that enrolled patients in many different countries, and as such there is likely to be a genetic and geographic variation in the prevalence of CAD seen amongst the trial population. Nevertheless, this is not particularly relevant for the purposes of this study as investigators were blinded to clinical data. Conversely, an important factor which may have directly affected the level of chance agreement (and the resulting kappa) by acting as a surrogate for prevalence was the differences noted amongst the study population in both the quality of the diagnostic angiogram, and the angiographic views recorded. It follows that the probability of chance agreement is likely to be somewhat higher in those cases with a good quality angiogram with ample views, when compared with angiograms of poorer quality and limited views. Therefore, in those situations where the prevalence is skewed, for example as a result of an angiogram of excellent quality, a low kappa value can result from genuine poor agreement, or as a consequence of a high probability of chance agreement [28]. Unfortunately, neither the diagnostic quality nor the number of views taken per angiogram were formally assessed in this study. The effect of the angiograms' quality on the prevalence of disease can effectively be eliminated by using 100 blinded assessors scoring the same angiogram. Overall the kappa values obtained in this study should only be considered a guide, and do not reflect the reproducibility of the SYNTAX score in a different patient population with a different prevalence of CAD.

Additional limitations include the experience of the investigators in this study, who have each individually assessed the SYNTAX score in over a thousand angiograms. A repeat assessment of the same angiograms using investigators less familiar with the definitions, and less experienced in using the SYNTAX score may well provide different results.

CONCLUSIONS

This study has demonstrated moderate intra-observer reproducibility of the SYNTAX score when assessed by a team of three interventional cardiologists, which is consistent with previous evaluations by core lab analysts. The scoring of bifurcation lesions remains a source of inconsistency, which may be improved by the use of additional imaging modalities together with a review of its definition.

REFERENCES

1. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–972.
2. Seung KB, Park DW, Kim YH, Lee SW, Lee CW, et al. Stents versus coronary-artery bypass grafting for left main coronary artery disease. N Engl J Med 2008;358:1781–1792.
3. Serruys P, Garg S. Percutaneous coronary interventions for all patients with complex coronary artery disease: Triple vessel disease or left main coronary artery disease. Yes? No? Don't know? Rev Esp Cardiol 2009;62:719–725.
4. Capodanno D, Capranzano P, Di Salvo ME, Caggegi A, Tomasello D, et al. Usefulness of SYNTAX score to select patients with left main coronary artery disease to be treated with coronary artery bypass graft. JACC Cardiovasc Interv 2009;2:731–738.
5. Kappetein AP, Dawkins KD, Mohr FW, Morice MC, Mack MJ, Russell ME, Pomar J, Serruys PW. Current percutaneous coronary intervention and coronary artery bypass grafting practices for three-vessel and left main coronary artery disease. Insights from the SYNTAX run-in phase. Eur J Cardiothorac Surg 2006;29:486–491.
6. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, et al. The SYNTAX score: An angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219–227.
7. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, et al. Assessment of the SYNTAX score in the Syntax study. EuroIntervention 2009;5:50–56.
8. Valgimigli M, Serruys PW, Tsuchida K, Vaina S, Morel MA, et al. Cyphering the complexity of coronary artery disease using the syntax score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. Am J Cardiol 2007;99:1072–1081.
9. Capodanno D, Di Salvo ME, Cincotta G, Miano M, Tamburino C, Tamburino C. Usefulness of the SYNTAX score for predicting clinical outcome after percutaneous coronary intervention of unprotected left main coronary artery disease. Circ Cardiovasc Interv 2009;2:302–308.
10. Serruys P, Onuma Y, Garg S, Vranckx P, De Bruyne B, Morice MC, Colombo A, Macaya C, Gert R, Fajadet J, Hamm C, Schuijer M, Rademaker T, Wittebols K, Stoll HP, on behalf of the ARTS-II investigators. Five-year clinical outcomes of the arterial revascularisation therapies (ARTS-II) study of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. In press. J Am Coll Cardiol 2009.
11. Herrman JP, Azar A, Umans VA, Boersma E, von Es GA, Serruys PW. Inter- and intra-observer variability in the qualitative categorization of coronary angiograms. Int J Card Imaging 1996;12:21–30.

12. Beauman GJ, Vogel RA. Accuracy of individual and panel visual interpretations of coronary arteriograms: Implications for clinical decisions. J Am Coll Cardiol 1990;16:108–113.
13. DeRouen TA, Murray JA, Owen W. Variability in the analysis of coronary arteriograms. Circulation 1977;55:324–328.
14. SYNTAXworking-group. SYNTAX score calculator: Available at: www.syntaxscore.com. Accessed date: 19th May 2009.
15. Fleiss J. Statistical methods for rates and proportions. New York. John Wiley & Sons Inc.; 1981. pp 212–236.
16. Sackett D, Haynes R, Guyatt GH, Tugwell P. Clinical epidemiology: A basic science for clinical medicine, 2nd ed. Boston: Brown and Co.; 1991. p 30.
17. Cicchetti DV, Allison TG. A new procedure for assessing reliability of scoring EEG sleep recordings. Am J EEG Tech 1971;11:101–109.
18. Singh M, Rihal CS, Gersh BJ, Lennon RJ, Prasad A, Sorajja P, Gullerud RE, Holmes DR, Jr. Twenty-five-year trends in in-hospital and long-term outcome after percutaneous coronary intervention: A single-institution experience. Circulation 2007;115: 2835–2841.
19. Federspiel J, Stearns S, Van Domburg R, Sheridan B, Lund J, Serruys P. Risk-benefit trade-offs in revascularization choices. Medical Decision Making In press.
20. Blackburn H. The exercise electrocardiogram: Differences in interpretation. Report of a technical group on exercise electrocardiography. Am J Cardiol 1968;21:871–880.
21. Hoffmann R, von Bardeleben S, Kasprzak JD, Borges AC, Ten Cate F, et al. Analysis of regional left ventricular function by cineventriculography, cardiac magnetic resonance imaging, and unenhanced and contrast-enhanced echocardiography: A multicenter comparison of methods. J Am Coll Cardiol 2006;47:121–128.
22. Zir LM, Miller SW, Dinsmore RE, Gilbert JP, Harthorne JW. Interobserver variability in coronary angiography. Circulation 1976;53:627–632.
23. Lindstaedt M, Spiecker M, Perings C, Lawo T, Yazar A, Holland-Letz T, Muegge A, Bojara W, Germing A. How good are experienced interventional cardiologists at predicting the functional significance of intermediate or equivocal left main coronary artery stenoses? Int J Cardiol 2007;120:254–261.
24. Fisher LD, Judkins MP, Lesperance J, Cameron A, Swaye P, et al. Reproducibility of coronary arteriographic reading in the coronary artery surgery study (CASS). Cathet Cardiovasc Diagn 1982;8:565–575.
25. Abizaid AS, Mintz GS, Abizaid A, Mehran R, Lansky AJ, Pichard AD, Satler LF, Wu H, Kent KM, Leon MB. One-year follow-up after intravascular ultrasound assessment of moderate left main coronary artery disease in patients with ambiguous angiograms. J Am Coll Cardiol 1999;34:707–715.
26. Hamilos M, Muller O, Cuisset T, Ntalianis A, Chlouverakis G, et al. Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. Circulation 2009;120:1505–1512.
27. Thompson WD, Walter SD. A reappraisal of the kappa coefficient. J Clin Epidemiol 1988;41:949–958.
28. Feinstein AR, Cicchetti DV. High agreement but low kappa. I. The problems of two paradoxes. J Clin Epidemiol 1990;43:543–549.

Chapter 4.4

Value of Age, Creatinine, and Ejection Fraction (ACEF score) in assessing risk in patients undergoing percutaneous coronary intervention in the "all-comers" LEADERS trial

Circ Cardiovasc Interv 2011; 4(1):47-56

Joanna Wykrzykowska, Scot Garg, Yoshi Onuma, Ton de Vries, Dick Goedhart, Marie-Angèle Morel, Gerrit-Anne van Es, Pawel Buszman, Axel Linke, Thomas Ischinger, Volker Klauss, Roberto Corti, Franz Eberli, William Wijns, Marie-claude Morice, Carlo di Mario, Robert-Jan van Geuns, Peter Juni, Stephan Windecker, Patrick W. Serruys

Value of Age, Creatinine, and Ejection Fraction (ACEF Score) in Assessing Risk in Patients Undergoing Percutaneous Coronary Interventions in the 'All-Comers' LEADERS Trial

Joanna J. Wykrzykowska, MD; Scot Garg, MBChB, MRCP; Yoshinobu Onuma, MD; Ton de Vries, MSc; Dick Goedhart, PhD; Marie-Angele Morel, BSc; Gerrit-Anne van Es, PhD; Pawel Buszman, MD; Axel Linke, MD; Thomas Ischinger, MD; Volker Klauss, MD; Roberto Corti, MD; Franz Eberli, MD, PhD; William Wijns, MD; Marie-Claude Morice, MD; Carlo di Mario, MD, PhD; Robert Jan van Geuns, MD, PhD; Peter Juni, MD, PhD; Stephan Windecker, MD, PhD; Patrick W. Serruys, MD, PhD

Background—The age, creatinine, and ejection fraction (ACEF) score (age/left ventricular ejection fraction+1 if creatinine >2.0 mg/dL) has been established as an effective predictor of clinical outcomes in patients undergoing elective coronary artery bypass surgery; however, its utility in "all-comer" patients undergoing percutaneous coronary intervention is yet unexplored.

Methods and Results—The ACEF score was calculated for 1208 of the 1707 patients enrolled in the LEADERS trial. Post hoc analysis was performed by stratifying clinical outcomes at the 1-year follow-up according to ACEF score tertiles: $ACEF_{low} \leq 1.0225$, $1.0225 < ACEF_{mid} \leq 1.277$, and $ACEF_{high} > 1.277$. At 1-year follow-up, there was a significantly lower number of patients with major adverse cardiac event–free survival in the highest tertile of the ACEF score ($ACEF_{low}$=92.1%, $ACEF_{mid}$=89.5%, and $ACEF_{high}$=86.1%; P=0.0218). Cardiac death was less frequent in $ACEF_{low}$ than in $ACEF_{mid}$ and $ACEF_{high}$ (0.7% vs 2.2% vs 4.5%; hazard ratio=2.22, P=0.002) patients. Rates of myocardial infarction were significantly higher in patients with a high ACEF score (6.7% for $ACEF_{high}$ vs 5.2% for $ACEF_{mid}$ and 2.5% for $ACEF_{low}$; hazard ratio=1.6, P=0.006). Clinically driven target-vessel revascularization also tended to be higher in the $ACEF_{high}$ group, but the difference among the 3 groups did not reach statistical significance. The rate of composite definite, possible, and probable stent thrombosis was also higher in the $ACEF_{high}$ group ($ACEF_{low}$=1.2%, $ACEF_{mid}$=3.5%, and $ACEF_{high}$=6.2%; hazard ratio=2.04, P<0.001).

Conclusions—ACEF score may be a simple way to stratify risk of events in patients treated with percutaneous coronary intervention with respect to mortality and risk of myocardial infarction.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00389220.

(*Circ Cardiovasc Interv*. 2011;4:47-56.)

Key Words: ACEF score ■ SYNTAX score ■ biolimus-eluting stent ■ sirolimus-eluting stent ■ biodegradable polymer ■ cardiac death ■ major adverse cardiac event

Several validated risk assessment scores such as the EuroSCORE have been developed for mortality risk assessment in cardiac surgery.[1] More recently, these simple scores incorporating patient clinical characteristics have also been applied to patients undergoing percutaneous coronary interventions (PCI).[2–4] In a recent study, Romagnoli et al[3] reported an area under the receiver operating characteristic (ROC) curve of 0.91 for in-hospital mortality among 1173 patients treated with PCI, indicating a good discriminatory power of the EuroSCORE in patients undergoing PCI. A

Received April 21, 2010; accepted November 29, 2010.

From the Department of Interventional Cardiology (J.J.W., S.G., Y.O., R.J.v.G., P.W.S.), Thoraxcenter, Erasmus MC, and Cardialysis BV (T.v.D., D.G., M.-A.M., G.-A.v.E.), Rotterdam, Netherlands; Medical University of Silesia (P.B.), Katowice, Poland; Herzzentrum Leipzig (A.L.), Leipzig, Germany; Department of Cardiology (T.I.), Hospital Bogenhausen, and Department of Cardiology (V.K.), University Hospital Munich (Innenstadt), Munich, Germany; Department of Cardiology (R.C., F.E.), University Hospital, Zurich, Switzerland; Department of Cardiology (W.W.), Onze Lieve Vrouw Ziekenhuis, Aalst, Belgium; Institut Cardiovasculaire (M.-C.M.), Paris-Sud, Massy, France; Department of Cardiology (C.d.M.), Royal Brompton Hospital, London, England; CTU Bern (P.J.) and Department of Cardiology (S.W.), Bern University Hospital, Bern, Switzerland; and Department of Interventional Cardiology (J.J.W.), Academic Medical Center, Amsterdam, Netherlands.

F.E. is currently at Triemlispital, Zurich, Switzerland.

Correspondence to Prof Patrick W. Serruys, MD, PhD, Interventional Cardiology, Thoraxcenter, Erasmus MC, 's Gravendijkwal 230 Bd 412, 3015CE Rotterdam, Netherlands. E-mail p.w.j.c.serruys@erasmusmc.nl

Circ Cardiovasc Interv **is available at http://circinterventions.ahajournals.org** **DOI: 10.1161/CIRCINTERVENTIONS.110.958389**

novel and even simpler score has been proposed and tested in patients undergoing coronary artery bypass graft surgery incorporating age, creatinine, and ejection fraction (ACEF score).[5] The advantage of this simplified risk model is that it avoids the problem of "overfitting" to many independent variables when applied to populations with low numbers of events. In patients undergoing isolated coronary artery bypass graft surgery, the ACEF score calculated by age/ejection fraction+1 (if creatinine >2.0 mg/dL) had an area under the ROC curve of 0.826, which was higher than that of more complex risk scores. To our knowledge, the performance of the ACEF score to predict event rates and cardiac mortality has not been tested in patients undergoing PCI. In this post hoc analysis of the "all-comers" LEADERS trial,[6] we assessed the value of the ACEF score in predicting major adverse cardiac events (MACEs) at 1-year follow-up. In addition, we have compared its predictive value for events with that of the SYNTAX score[7] and have assessed the additive value of both scores (the so-called clinical SYNTAX score). Finally, we aimed to test whether the ACEF and combined ACEF*SYNTAX scores performed as well in this all-comers population undergoing PCI as they did in the multivessel-disease patient populations undergoing coronary artery bypass graft surgery and/or PCI, for which they were initially developed and applied (shrinkage phenomenon).[8]

Clinical Perspective on p 56

Methods

Study Population

LEADERS was a European multicenter, noninferiority trial comparing the safety and efficacy of the BioMatrix Flex biolimus-eluting stent with a biodegradable polymer (Biosensors, Morges, Switzerland) with the CypherSelect sirolimus-eluting stent with a durable polymer (Cordis, NJ) in 1707 all-comer patients. Details of the study protocol can be found in the main article.[6] The study complied with the Declaration of Helsinki and was approved by all institutional ethics committees. All patients provided written, informed consent for participation in the trial.

ACEF Score and Analysis

The ACEF score was calculated according to the following formula: ACEF=age/left ventricular ejection fraction+1 (if creatinine was >2.0 mg/dL).[5] Patients were divided into tertiles based on the ACEF score. A modified clinical SYNTAX score was calculated by multiplying the ACEF score by the SYNTAX score.

Study End Points

Definitions of all end points are provided elsewhere.[6] The primary end point of this substudy was MACEs, defined as the composite of cardiac death, myocardial infarction (MI), and clinically indicated target-vessel revascularization (TVR) within 12 months. Secondary end points were any target lesion revascularization (TLR) (both clinically and nonclinically indicated), any TVR, cardiac death, death from any cause, MI, stent thrombosis (defined according to the Academic Research Council[9]), device success, and lesion success.

Statistical Analysis

A stratified post hoc analysis of clinical and angiographic outcomes was performed according to tertiles of the ACEF score. All randomized patients were included in the analysis. Angiographic outcomes were analyzed by SAS v8 Proc Mixed for continuous and Proc Genmod for binomial outcomes, taking into account the within-patient correlation structure of these data. The Cox proportional-hazards model was used to compare clinical outcomes between the groups. All analyses were performed with SAS 8.02 by a dedicated statistician. All probability values and confidence intervals were 2-sided. The multivariate model included ACEF score, diabetes, β-blocker use, stent type, and presence of acute coronary syndrome/ST-segment elevation MI as covariates. Testing for (linear) trend was done by using generalized linear models with ACEF class as a covariable for continuous variables and the Cochran-Armitage test for trend in categorical data. C-statistics and ROC curves were constructed to assess the ability of the ACEF score and ACEF*SYNTAX score (modified clinical SYNTAX score) to predict events.[10]

Results

ACEF Score and Baseline Characteristics

The ACEF score could be calculated retrospectively for 1208 of the 1707 patients enrolled in the trial. We were unable to calculate the score for 499 patients owing to the unavailability of renal function assessment or ejection fraction (mostly in patients presenting with ST-segment elevation MI). The score ranged from 0.562 to 5.403, with a mean±SD of 1.278±0.539 and a median of 1.131 (interquartile range of 0.964 to 1.398). In this post hoc analysis, the ACEF score tertiles were defined as follows: $ACEF_{low}$, <1.0225 (n=404); 1.0225≤ $ACEF_{mid}$ ≤1.277 (n=402), and $ACEF_{high}$ >1.277 (n=402). Baseline clinical and angiographic characteristics of the patients are listed in Tables 1 through 4. In addition to differences in age and the presence of renal insufficiency (creatinine >2.0 mg/dL) among the 3 tertiles of ACEF score, patients with higher ACEF scores were more likely to be female, have diabetes, smoke, have hypertension, have a prior history of MI, have concomitant peripheral vascular disease, and present with an unstable coronary syndrome. Conversely, patients with low ACEF scores were more likely to be hypercholesterolemic, have a family history of heart disease, and were more likely to present with stable angina or ST-segment elevation MI. The 3 groups did not differ significantly with respect to angiographic characteristics except for a slightly higher number of lesions, a trend for a greater number of stents implanted, and a significantly greater number of lesions with moderate to severe calcification. All 51 patients with renal insufficiency were in the high-ACEF-score group. Thus, the ACEF score calculation for the low and mid ACEF tertiles was age/left ventricular function.

One-Year Outcomes

The ACEF score significantly predicted the rate of MACEs and cardiac death, as well as the rate of MI at 360 days (Tables 5 and 6 and Figures 1 through 4). There was a significantly lower number of patients with MACE-free survival in the highest tertile of the ACEF score ($ACEF_{low}$=92.1%, $ACEF_{mid}$=89.5%, and $ACEF_{high}$=86.1%; P=0.0218). The composite end point of cardiac death, MI, and TVR occurred in 7.9% of $ACEF_{low}$ patients, 10.4% of patients with $ACEF_{mid}$ scores, and 13.9% of $ACEF_{high}$ patients (hazard ratio [HR]=1.34, P<0.007). Cardiac death occurred in 0.7% of patients with low ACEF scores, 2.2% of patients with intermediate ACEF scores, and 4.5%

Table 1. Baseline Clinical Characteristics According to ACEF Tertiles

Baseline Clinical Variables, No. (%)	ACEF <1.0225, n=404	ACEF 1.0225–1.277, n=402	ACEFF >1.277, n=402	*P* Value on Trend (2-Sided)
Age >65 y	61 (15.1)	227 (56.5)	305 (75.9)	<0.001
Mean age, y	56	66	71	<0.001
Male	320 (79.2)	302 (75.1)	286 (71.1)	0.009
Diabetes	82 (20.3)	89 (22.1)	114 (28.4)	0.008
Current smoking	148 (36.6)	87 (21.6)	83 (20.7)	<0.001
Hypertension	277 (68.6)	318 (79.1)	320 (79.6)	<0.001
Hypercholesterolemia	281 (69.6)	277 (68.9)	248 (61.7)	0.019
Family history	173 (42.8)	166 (41.3)	137 (34.1)	0.012
Renal insufficiency (creatinine >2.0 mg/dL)	0	0	51 (12.7)	<0.001
Mean ejection fraction, %	64	58	45	<0.001
Previous MI	102 (25.5)	121 (30.1)	161 (40.1)	<0.001
Previous PCI	138 (34.2)	158 (39.3)	157 (39.1)	0.16
PVD	18 (4.5)	32 (8.0)	45 (11.2)	<0.001
Previous stroke	12 (3.0)	14 (3.5)	17 (4.2)	0.34
Clinical presentation				
Stable	139 (34.4)	130 (32.3)	94 (23.4)	<0.001
Unstable	100 (24.8)	94 (23.4)	71 (17.7)	0.015
STEMI	50 (12.4)	51 (12.7)	96 (23.9)	<0.001
Non-STEMI	79 (19.6)	82 (20.4)	94 (23.4)	0.20
Silent Ischaemia	36 (8.9)	45 (11.1)	47 (11.7)	0.21

STEMI indicates ST-segment MI.

of patients with high ACEF scores (HR=2.22, P=0.002). The rate of MI was significantly higher in patients with high ACEF scores (6.7% for $ACEF_{high}$ vs 5.2% for $ACEF_{mid}$ and 2.5% for $ACEF_{low}$; HR=1.6, P=0.006). Clinically driven TVR also tended to be higher in the $ACEF_{high}$ group, but the difference among the 3 groups did not reach statistical significance ($ACEF_{low}$=5.4%, $ACEF_{mid}$=6.5%, and $ACEF_{high}$=8%; HR=1.22, P=0.16).

Table 2. Baseline Characteristics According to ACEF*SYNTAX Score Tertiles

Baseline Clinical Variables, No. (%)	ACEF*SYNTAX <8.80, n=356	ACEF*SYNTAX 8.80–18.74, n=355	ACEF*SYNTAX >18.74, n=356	*P* Value on Trend (2-Sided)
Age >65 y	131 (36.8)	157 (44.2)	216 (60.7)	<0.001
Mean age, y	56	66	71	<0.001
Male	271 (76.1)	268 (75.5)	257 (72.2)	0.25
Diabetes	69 (19.4)	78 (22.0)	93 (26.1)	0.035
Current smoking	118 (33.2)	88 (24.8)	93 (26.1)	0.041
Hypertension	264 (74.2)	266 (75.0)	269 (75.6)	0.70
Hypercholesterolemia	243 (68.3)	245 (69.0)	215 (60.4)	0.030
Family history	145 (40.7)	142 (40.0)	122 (34.3)	0.08
Renal insufficiency	4 (1.1)	7 (2.0)	33 (9.3)	<0.001
Mean ejection fraction, %	64	58	45	<0.001
Previous MI	97 (27.3)	108 (30.4)	117 (32.9)	0.11
Previous PCI	132 (37.1)	131 (36.9)	119 (33.4)	0.33
PVD	16 (4.5)	23 (6.5)	30 (8.4)	0.039
Previous stroke	9 (2.5)	13 (3.7)	11 (3.1)	0.75
Clinical presentation				
Stable	107 (30.1)	112 (31.6)	78 (21.9)	0.017
Unstable	95 (26.7)	70 (19.7)	68 (19.1)	0.016
STEMI	35 (9.8)	61 (17.2)	94 (26.4)	<0.001
Non-STEMI	77 (21.6)	79 (22.3)	81 (22.8)	0.75
Silent ischemia	42 (11.8)	33 (9.3)	35 (9.8)	0.42

STEMI indicates ST-segment MI.

Table 3. Baseline Angiographic Characteristics According to ACEF Tertiles

Angiographic Variable	ACEF <1.0225, n=404	ACEF 1.0225–1.277, n=402	ACEFF >1.277, n=402	*P* Value
No. of diseased lesions per patient (based on SYNTAX application), mean±SD	2.21±1.31	2.46±1.32	2.50±1.41	0.004
No. of treated lesions per patient (as defined by Corelab), mean±SD	1.35±0.63	1.50±0.76	1.42+0.67	0.17
Ratio of diseased to treated lesions	1.63	1.64	1.76	NA
Coronary artery treated				
LAD	188 (46.5)	199 (49.5)	195 (48.5)	0.57
LCX	131 (32.4)	137 (34.1)	112 (27.9)	0.16
RCA	160 (39.6)	162 (40.3)	153 (38.1)	0.67
Two-vessel disease	72 (17.9)	94 (23.9)	67 (17.4)	0.88
Three-vessel disease	5 (1.2)	8 (2.0)	11 (2.9)	0.11
Stent type				
Biolimus	208 (51.5)	201 (50.0)	192 (47.8)	0.29
Sirolimus	196 (48.5)	201 (50.0)	210 (52.2)	0.29
No. of implanted stents, mean±SD	1.78+1.13	1.90+1.17	1.93+1.17	0.07
Total stent length/patient, mean±SD, mm	32.0+22.2	33.5+21.7	34.7+21.8	0.08
Chronic total occlusion	9 (2.2)	9 (2.2)	12 (3.0)	0.49
Moderate to severe calcification	47 (12.8)	86 (23.8)	98 (28.9)	<0.001
Bifurcation lesion	107 (26.5)	127 (31.6)	117 (29.1)	0.41
Use of glycoprotein 2b3a inhibitors	91 (22.5)	84 (20.9)	109 (27.1)	0.13

NA indicates not applicable; LAD, left anterior descending; LCX, left circumflex; and RCA, right coronary artery.

The rate of composite definite, possible, and probable stent thrombosis was also higher in the high-ACEF group ($ACEF_{low}$=1.2%, $ACEF_{mid}$=3.5%, and $ACEF_{high}$=6.2%; HR=2.04, $P<0.001$). Patients treated with biolimus- and sirolimus-eluting stents had equivalent event rates across all 3 ACEF tertiles.

Multivariate Model

In a multivariate model, the ACEF score remained a significant predictor of MACEs and mortality (Tables 5 and 6; note that the HRs are adjusted for the following variables: ACEF score, diabetes, β-blocker use, stent type, and presence of ST-segment elevation MI/acute coronary

Table 4. Baseline Angiographic Characteristics According to ACEF*SYNTAX Score Tertiles

Angiographic Variable	ACEF*SYNTAX <8.80, n=356	ACEF *SYNTAX 8.80–18.74, n=355	ACEF*SYNTAX >18.74, n=356	*P* Value
No. of diseased lesions per patient (based on SYNTAX application), mean±SD	1.49+0.66	2.41+1.09	3.28+1.50	<0.001
No. of treated lesions per patient (as defined by Corelab), mean±SD	1.20+0.44	1.48+0.73	1.62+0.80	<0.001
Ratio of diseased to treated lesions	1.24	1.63	2.03	NA
Coronary artery treated				
LAD	119 (33.4)	184 (51.8)	231 (64.9)	<0.001
LCX	104 (29.2)	115 (32.4)	114 (32.0)	0.42
RCA	167 (46.9)	154 (43.4)	127 (35.7)	0.002
Two-vessel disease	35 (9.8)	82 (23.1)	97 (27.3)	<0.001
Three-vessel disease	0 (0)	10 (2.8)	14 (3.9)	<0.001
Stent type				
Biolimus	184 (51.7)	173 (48.7)	178 (50.0)	0.65
Sirolimus	172 (48.3)	182 (51.3)	178 (50.0)	0.65
No. of implanted stents, mean±SD	1.45+0.77	1.95+1.19	2.25+1.32	<0.001
Total stent length/patient, mean±SD, mm	25.6+15.9	35.0+23.0	40.9+24.3	<0.001
Chronic total occlusion	3 (0.8)	10 (2.8)	12 (3.4)	0.026
Moderate to severe calcification	18 (5.2)	66 (18.6)	146 (41.0)	<0.001
Bifurcation lesion	51 (14.3)	117 (33.0)	136 (38.2)	<0.001
Use of glycoprotein 2b3a inhibitors	66 (18.5)	85 (23.9)	116 (32.6)	<0.001

NA indicates not applicable; LAD, left anterior descending; LCX, left circumflex; and RCA, right coronary artery.

Table 5. Clinical Outcomes at 360 Days After Index PCI Based on Tertiles of ACEF Score

Type of Event	Low, n	Low, %	Middle, n	Middle, %	High, n	High, %	*P* Value ACEF	HR (CI)
Patients, No.	404		402		402			
Death	3	0.7	11	2.7	27	6.7	<0.001	2.71 (1.69–4.35)
Cardiac death	3	0.7	9	2.2	18	4.5	0.002	2.22 (1.33–3.71)
MI	10	2.5	21	5.2	27	6.7	0.006	1.60 (1.14–2.24)
All TVR	34	8.4	39	9.7	42	10.4	0.27	1.14 (0.91–1.42)
Clinically justified TVR	22	5.4	26	6.5	32	8.0	0.16	1.22 (0.93–1.6)
All TLR	24	5.9	31	7.7	36	9.0	0.10	1.24 (0.96–1.6)
Clinically justified TLR	16	4.0	22	5.5	30	7.5	0.041	1.37 (1.01–1.85)
Composite of cardiac death/MI/TVR clinically indicated	32	7.9	42	10.4	56	13.9	0.007	1.34 (1.08–1.67)
Composite of cardiac death MI	12	3.0	25	6.2	40	10.0	<0.001	1.79 (1.32–2.41)
Stent thrombosis	5	1.2	14	3.5	25	6.2	<0.001	2.04 (1.35–3.07)
Definite stent thrombosis	3	0.7	10	2.5	15	3.7	0.012	1.92 (1.15–3.18)
Possible stent thrombosis	1	0.2	4	1.0	7	1.7	0.058	2.20 (0.98–4.96)
Probable stent thrombosis	2	0.5	1	0.2	4	1.0	0.27	1.72 (0.65–4.52)

syndrome, the same variables used in the assessment of the predictive value of the SYNTAX score in the LEADERS trial).[7] Patients in the $ACEF_{high}$ group had a 34% higher risk of the composite end point of cardiac death, MI, and clinically indicated TVR than did patients in the $ACEF_{mid}$ group ($P=0.007$), which was comparable to the 60% higher composite event rate among diabetics ($P=0.012$). Use of a biolimus-eluting stent conferred a nonsignificant 12% reduction in events and with β-blocker use, a 16% reduction was observed, but there was no difference in events due to acute coronary syndrome presentation.

C-Statistics for ACEF Score and ACEF*SYNTAX Score

The ACEF score c-statistic values for predicting cardiac death and the occurrence of MI were 0.727 and 0.615, respectively, in this all-comers patient population (Table 7). This compares favorably with SYNTAX score c-statistics of 0.647 for cardiac death and 0.561 for MI in the same population of the LEADERS trial. Conversely, the ACEF score's ability to assess the risk of overall MACEs and TVR was lower (0.577 and 0.527, respectively). The SYNTAX score in the same population was a better predictor of MACEs and TVR, with c-statistics of 0.61 and 0.58, respectively. Combining the ACEF with the SYNTAX score in the modified clinical SYNTAX score (ACEF*SYNTAX score) resulted in improvement in area under the ROC curves for MACEs (from 0.577 to 0.618) and TLR (0.527 to 0.575; Table 7). However, the area under the ROC curves for cardiac death and MI decreased after combining the SYNTAX score with the ACEF score.

Table 6. Clinical Outcomes at 360 Days After Index PCI Based on Tertiles of ACEF*SYNTAX Score (Clinical Syntax Score)

Type of Event	Low, n	Low, %	Middle, n	Middle, %	High, n	%	*P* Value ACEF*SYNTAX	HR (CI)
Patients, No.	356		355		356			
Death	6	1.7	7	2.0	22	6.2	0.002	2.06 (1.3–3.28)
Cardiac death	3	0.8	7	2.0	18	5.1	0.002	2.40 (1.38–4.16)
MI	13	3.7	17	4.8	23	6.5	0.07	1.37 (0.98–1.93)
All TVR	28	7.9	31	8.7	39	11	0.10	1.23 (0.96–1.57)
Clinically justified TVR	19	5.3	23	6.5	27	7.6	0.21	1.21 (0.9–1.62)
All TLR	23	6.5	23	6.5	33	9.3	0.12	1.24 (0.94–1.64)
Clinically justified TLR	17	4.8	18	5.1	24	6.7	0.25	1.21 (0.88–1.66)
Composite of cardiac death/MI/TVR clinically indicated	28	7.9	34	9.6	52	14.6	0.003	1.42 (1.12–1.79)
Composite of cardiac death, MI	14	3.9	19	5.4	37	10.4	<0.001	1.70 (1.25–2.31)
Stent thrombosis	5	1.4	10	2.8	24	6.7	<0.001	2.19 (1.4–3.43)
Definite stent thrombosis	4	1.1	7	2.0	14	3.9	0.028	1.81 (1.06–3.07)
Possible stent thrombosis	1	0.3	2	0.6	7	2.0	0.034	2.90 (1.09–7.77)
Probable stent thrombosis	0	0	3	0.8	4	1.1	0.08	2.83 (0.9–8.88)

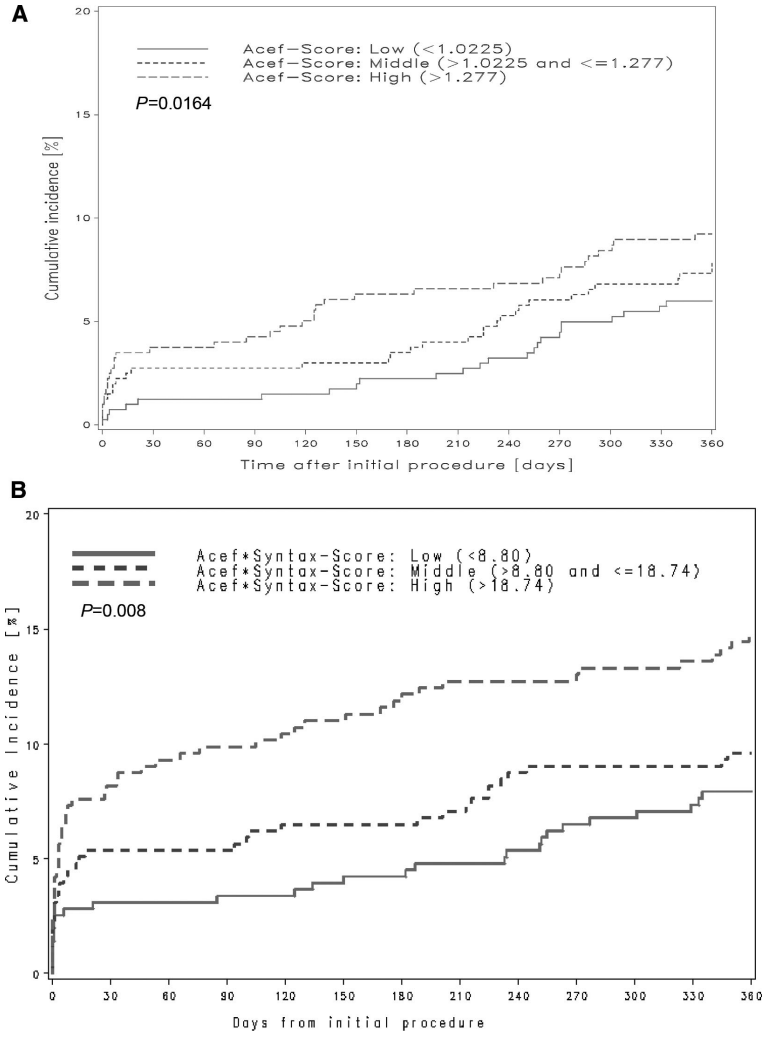


Figure 1. A, Kaplan-Meier curve for MACEs at 360 days according to ACEF score tertiles. B, Kaplan-Meier curve for MACEs at 360 days according to ACEF*SYNTAX score tertiles.

Discussion

With the rapidly expanding indications for PCI and the concomitant increasing age and clinical complexity of patients undergoing these procedures, risk assessment with respect to overall MACE rate and particularly mortality rate has become a very important aspect of daily clinical decision making. Multiple risk-assessment models have been developed for surgical patients and are starting to be used increasingly in the assessment of patients undergoing PCIs, particularly when decisions are needed with respect to the appropriateness of surgical versus percutaneous revascularization in patients with extensive coronary artery disease and multiple comorbidities. Some of these risk scores, such as SYNTAX, have excellent prognostic value[7,11–13] but are based solely on anatomic information and only indirectly incorporate clinical characteristics, in so far as patients who are older and have renal insufficiency tend to also have more calcified vessels and more diffuse disease. Many of the surgical risk models incorporate too many variables, which results in inaccuracies and the overfitting associated with

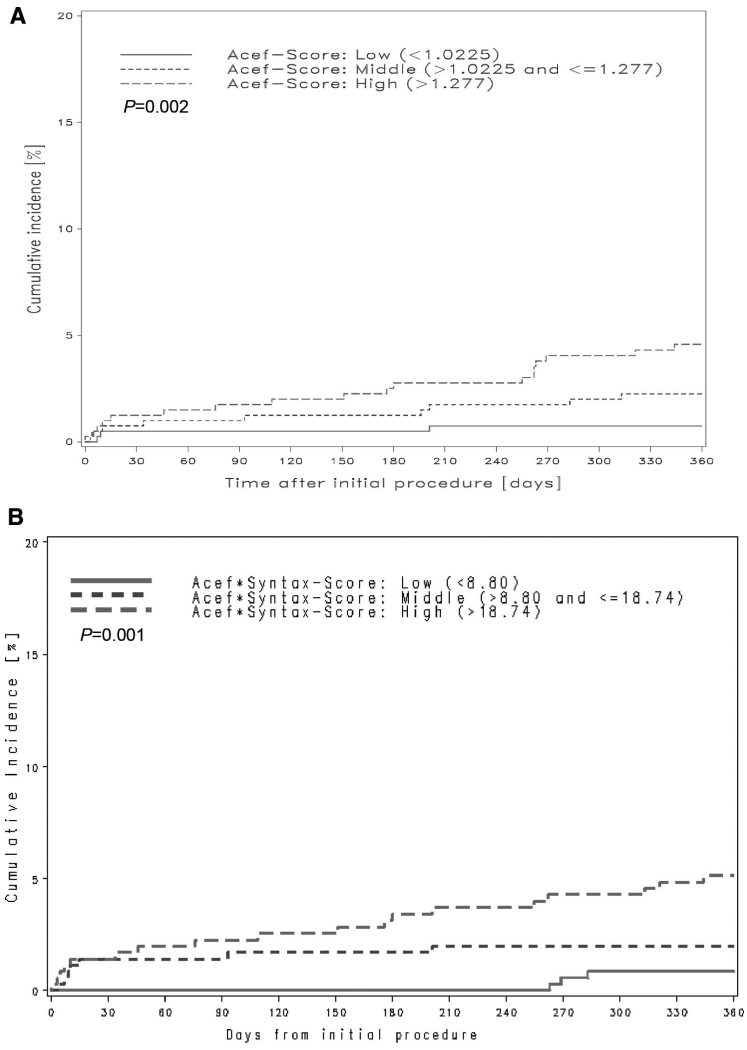


Figure 2. A, Kaplan-Meier score for cardiac death at 360 days according to ACEF score tertiles. B, Kaplan-Meier score for cardiac death at 360 days according to ACEF*SYNTAX score tertiles.

them; in addition, some models incorporate several patient characteristics that impart high risk to surgical patients only but not necessarily to patients undergoing PCI. The ACEF score, though only currently validated in a surgical patient group, is simple and easy to calculate and combines 3 important clinical characteristics, namely, age, creatinine (renal insufficiency), and left ventricular ejection fraction.[5] As such, it is extremely useful and applicable to patients undergoing PCI. In this substudy of the all-comers LEADERS trial, which well reflects the real-world population of patients being treated in tertiary PCI centers, we tested for the first time the predictive value of the ACEF score for MACEs. Indeed, the ACEF score appears highly predictive of cardiac death and MI risk. It is less robust in its ability to predict the overall composite primary end point, which is largely due to the lower ability to assess the risk of repeat revascularization.

We have recently performed an analysis on the ability of the SYNTAX score to predict events in the LEADERS study.[7]

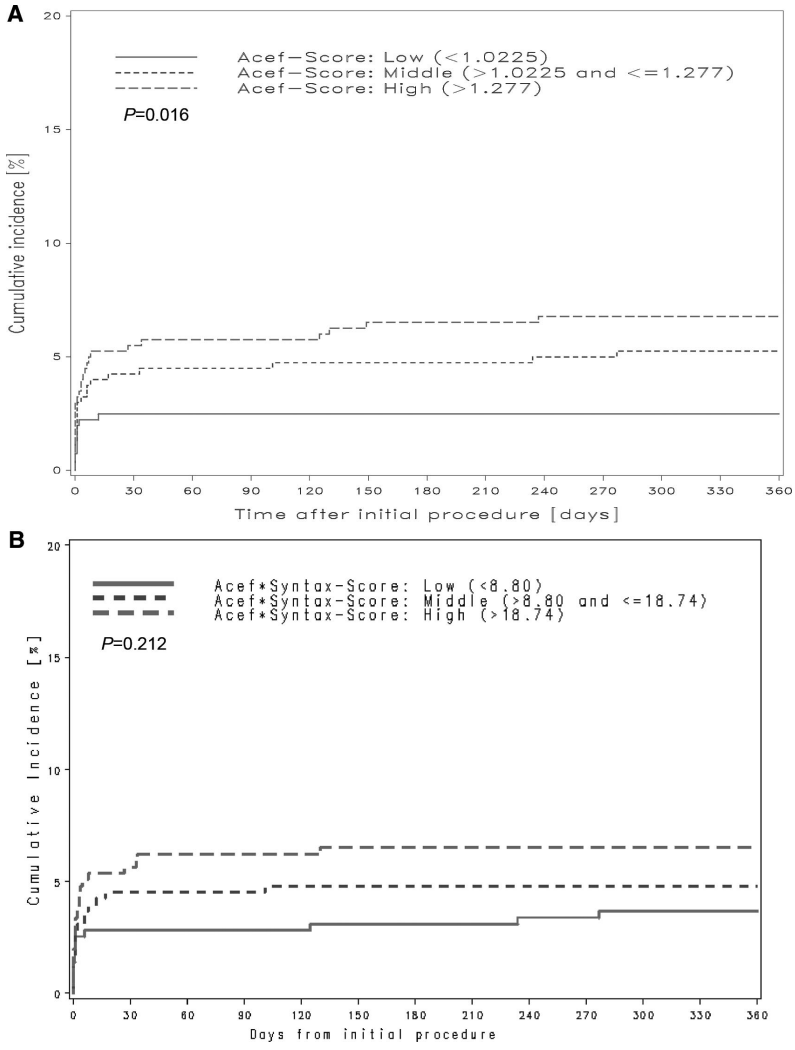


Figure 3. A, Kaplan-Meier curve for MI at 360 days according to ACEF tertiles. B, Kaplan-Meier curve for MI at 360 days according to ACEF*SYNTAX score tertiles.

Compared with the ACEF score, the SYNTAX score was better at predicting overall MACEs and the risk of repeat revascularization. However, the ACEF score was a better model to predict risk of cardiac death and MI. The use of the ACEF and SYNTAX score in combination in this all-comers patient population with a median ACEF score of 1.131 and a median SYNTAX score of 12 did not result in a better explanatory model for risk assessment, which is likely to be the result of the low number of events and the aforementioned overfitting. This finding contrasts with our analysis performed in the higher-risk multivessel-disease population enrolled in the ARTS-II study, who had a median SYNTAX score of 19 and a modified ACEF score of 1.1, wherein the combination of the 2 scores in the so-called clinical SYNTAX score resulted in higher c-statistics and better predictive values for both mortality and overall MACEs at 5 years of follow-up.[14]

In summary, this first assessment of the performance of the ACEF score as a risk model to predict cardiac death and MI in

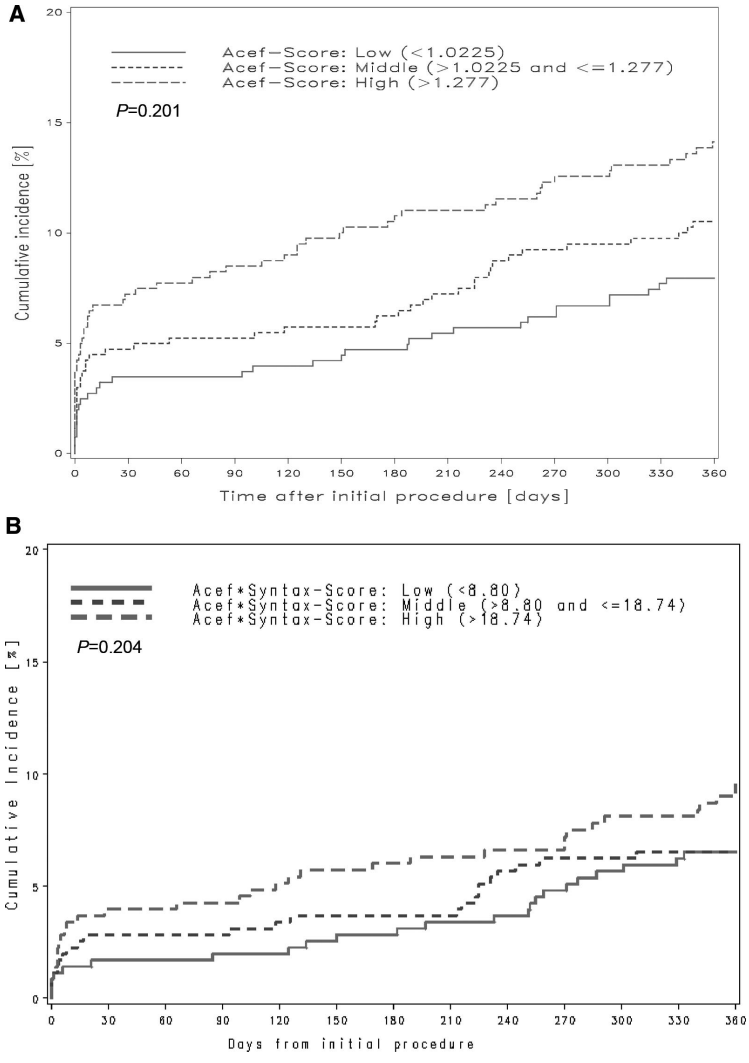


Figure 4. A, Kaplan-Meier curve for TLR at 360 days according to ACEF score tertiles. B, Kaplan-Meier curve for TLR at 360 days according to ACEF*SYNTAX score tertiles.

an all-comers population of patients undergoing PCI with drug-eluting stents appears adequate. One may consider using anatomically based scores, such as SYNTAX, to more accurately assess the risk of repeat revascularization. The combination of these 2 scores may be needed in particularly challenging and high-risk patient populations, such as those with multivessel disease, to improve the accuracy of risk prediction. In addition, the SYNTAX score is better validated in guiding the treatment choice of coronary artery bypass graft versus PCI.[11,12] On the other hand, the ACEF score is composed of objectively measured variables, whereas the SYNTAX score assessment involves a subjective evaluation of an angiogram, which may be prone to interobserver variability.[15,16]

Limitations

We acknowledge that this substudy suffers from the limitations of post hoc analysis. In addition, the ACEF score has not been

Table 7. C-Statistics

Event	ACEF Score c-Statistic	ACEF*SYNTAX Score c-Statistic
MACEs	0.577	0.618
Cardiac death	0.727	0.71
MI	0.615	0.597
TLR	0.527	0.575

previously validated in patients undergoing PCI, and further validation will be necessary in a larger cohort of patients from a pooling of multiple PCI studies. Lastly, the follow-up in this substudy of LEADERS and thus assessment of the predictive value of the ACEF score are limited to 1 year. In one third of patients, the ACEF score could not be calculated owing to missing creatinine or ejection fraction values (mostly in patients presenting with ST-segment elevation MI).

Sources of Funding

This study was funded by Biosensors Europe SA, Switzerland.

Disclosures

Stephan Windecker is a consultant to Biosensors, Cordis, Boston Scientific, Medtronic, and Abbott. All other authors report no conflicts of interest.

References

1. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg*. 1999;16:9–13.
2. Kim YH, Ahn JM, Park DW, Lee BK, Lee CW, Hong MK, Kim JJ, Park SW, Park SJ. EuroSCORE as a predictor of death and myocardial infarction after unprotected left main coronary stenting. *Am J Cardiol*. 2006;98:1567–1570.
3. Romagnoli E, Burzotta F, Trani C, Siviglia M, Biondi-Zoccai GG, Niccoli G, Leone AM, Porto I, Mazzari MA, Mongiardo R, Rebuzzi AG, Schiavoni G, Crea F. EuroSCORE as predictor of in-hospital mortality after percutaneous coronary intervention. *Heart*. 2009;95:43–48.
4. Rodes-Cabau J, Deblois J, Bertrand OF, Mohammadi S, Courtis J, Larose E, Dagenais F, Dery JP, Mathieu P, Rousseau M, Barbeau G, Baillot R, Gleeton O, Perron J, Nguyen CM, Roy L, Doyle D, De Larochelliere R, Bogaty P, Voisine P. Nonrandomized comparison of coronary artery bypass surgery and percutaneous coronary intervention for the treatment of unprotected left main coronary artery disease in octogenarians. *Circulation*. 2008;118:2374–2381.
5. Ranucci M, Castelvecchio S, Menicanti L, Frigiola A, Pelissero G. Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony. *Circulation*. 2009;119:3053–3061.
6. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Juni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet*. 2008;372:1163–1173.
7. Wykrzykowska J, Garg S, Girasis C, de Vries T, Morel MA, van Es GA, Buszman P, Linke A, Ischinger T, Klauss V, Corti R, Eberli F, Wijns W, Morice MC, di Mario C, van Geuns RJ, Juni P, Windecker S, Serruys PW. Value of the SYNTAX score (SX) for risk assessment in the 'all-comers' population of the randomized multicenter LEADERS Trial. *J Am Coll Cardiol*. 2010;56:272–277.
8. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996;15:361–387.
9. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344–2351.
10. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27:157–172; discussion 207–212.
11. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961–972.
12. Capodanno D, Capranzano P, Di Salvo ME, Caggegi A, Tomasello D, Cincotta G, Miano M, Patane M, Tamburino C, Tolaro S, Patane L, Calafiore AM. Usefulness of SYNTAX score to select patients with left main coronary artery disease to be treated with coronary artery bypass graft. *J Am Coll Cardiol Cardiovasc Interv*. 2009;2:731–738.
13. Capodanno D, Di Salvo ME, Cincotta G, Miano M, Tamburino C, Tamburino C. Usefulness of the SYNTAX score for predicting clinical outcome after percutaneous coronary intervention of unprotected left main coronary artery disease. *Circ Cardiovasc Intervent*. 2009;2:302–308.
14. Garg S, Sarno G, Garcia-Garcia HM, Girasis C, Wykrzykowska J, Dawkins KD, Serruys PW. A new tool for the risk stratification of patients with complex coronary artery disease: the clinical SYNTAX score. *Circ Cardiovasc Intervent*. 2010;3:317–326.
15. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, Van Dyck N, Mack M, Holmes D, Feldman T, Morice MC, Colombo A, Bass E, Leadley K, Dawkins KD, van Es GA, Morel MA, Mohr FW. Assessment of the SYNTAX score in the SYNTAX study. *EuroIntervention*. 2009;5:50–56.
16. Garg S, Girasis C, Sarno G, Goedhart D, Morel MA, Garcia-Garcia HM, Bressers M, Es GA, Serruys PW. The SYNTAX score revisited: a reassessment of the SYNTAX score reproducibility. *Catheter Cardiovasc Intervent*. 2010;75:946–952.

CLINICAL PERSPECTIVE

Risk stratification is becoming an increasingly important part of the assessment of patients who are candidates for coronary revascularization. We have recently reported that the SYNTAX score, which was initially developed for risk assessment in patients with multivessel disease, is also predictive of major cardiovascular events in an all-comers patient population undergoing percutaneous coronary intervention. The SYNTAX score, which is based entirely on the extent of coronary disease, has its limitations and does not take into account important clinical variables that may also influence outcomes. The ACEF score, defined as age/left ventricular ejection fraction+1 (if creatinine >2.0 mg/dL), was initially validated in a cohort of patients undergoing bypass surgery and incorporates important clinical factors. In the current study, we demonstrate that this simple score is also a valid predictor of outcomes in an all-comers patient population undergoing percutaneous coronary intervention. The combination of the 2 scores may be particularly useful in very clinically complex patients, enabling physicians to provide an individualized assessment of risk, which is vital for appropriate informed consent.

Chapter 4.5

A new tool for the risk stratification of patients with complex coronary artery disease: The Clinical SYNTAX score

Circ Cardiovasc Interv 2010; 3(4): 317-326

Scot Garg, Giovanna Sarno, Hector M. Garcia-Garcia, Chrysafios Girasis, Joanna Wykrzykowska, Keith D. Dawkins, Patrick W. Serruys

A New Tool for the Risk Stratification of Patients With Complex Coronary Artery Disease

The Clinical SYNTAX Score

Scot Garg, MB, ChB, MRCP; Giovanna Sarno, MD, PhD;
Hector M. Garcia-Garcia, MD, PhD; Chrysafios Girasis, MD; Joanna Wykrzykowska, MD;
Keith D. Dawkins, MD; Patrick W. Serruys, MD, PhD; on behalf of the ARTS-II Investigators

Background—Presently, no effective risk model exists to predict long-term mortality or other major adverse cardiovascular and cerebrovascular events (MACCE) in those patients undergoing percutaneous coronary intervention (PCI). This study aimed to assess whether the Clinical SYNTAX Score (CSS) calculated by multiplying the SYNTAX Score to a modified ACEF score (age/ejection fraction +1 for each 10 mL the creatinine clearance <60 mL/min per 1.73 m^2) would improve the ability of either score to predict mortality and MACCE.

Methods and Results—The CSS was calculated in 512 patients enrolled in the ARTS-II study who had serum creatinine levels, ejection fraction, and body weight recorded at baseline. Clinical outcomes in terms of MACCE and mortality at 1- and 5-year follow-up were stratified according to CSS tertiles: $CSS_{LOW} \leq 15.6$ (n=170), $15.6 < CSS_{MID} \leq 27.5$ (n=171), and $CSS_{HIGH} > 27.5$ (n=171). At 1-year follow-up, rates of repeat revascularization and MACCE were significantly higher in the highest tertile group. At 5-year follow-up, CSS_{HIGH} had a comparable rate of myocardial infarction, a trend toward a significantly higher rate of death, and significantly higher rates of repeat revascularization and overall MACCE compared with patients in the lower 2 tertiles. The respective C-statistics for the CSS, SYNTAX Score, and ACEF score for 5-year mortality were 0.69, 0.62, and 0.65 and for 5-year MACCE were 0.62, 0.59, and 0.57.

Conclusions—An improvement in the ability of the SYNTAX Score to predict MACCE and mortality can be achieved by combining the SYNTAX Score with a simple clinical risk score incorporating age, ejection fraction, and creatinine clearance to produce the Clinical SYNTAX score.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00235170.

(*Circ Cardiovasc Interv*. 2010;3:317-326.)

Key Words: SYNTAX score ■ complex coronary artery disease ■ risk stratification

Coronary artery bypass grafting (CABG) has historically been the preferred method of revascularization in patients with complex coronary artery disease (CAD); however, recent evidence indicates that in specific groups of patients, percutaneous coronary intervention (PCI) can offer a safe and suitable alternative.[1–4] This expanding use of PCI[5] has consequently increased the importance of developing a systematic approach for risk stratifying these complex patients so that they might receive the appropriate revascularization option. The ability to objectively decide which patients with complex CAD are suitable for PCI has gained new ground recently after the introduction of the SYNTAX Score.[6,7] Not only can this lesion-based scoring system quantify coronary anatomic complexity, but studies also demonstrate that it has a role in the short- and long-term risk stratification of patients undergoing PCI.[1,4,8–11]

Clinical Perspective on p 326

One of the limitations of using the SYNTAX Score in this context is that lesion-based scoring systems have been shown to have a lower ability to predict mortality when compared with scoring systems using clinical characteristics.[12] In patients undergoing PCI, there are currently only limited data available on the use of risk scores that rely solely on clinical characteristics, such as the euroSCORE.[13–15] Moreover, it has been suggested that the use of too many individual variables may reduce the overall accuracy of data.[16] The recently introduced ACEF score, for example, uses just age, left ventricular ejection fraction (LVEF), and serum creatinine (SCr) and appears to be as good as more complex scores in predicting mortality in patients undergoing elective CABG.[17] An acceptable modification to the ACEF score is to use the

Received October 6, 2009; accepted May 6, 2010.

From the Department of Interventional Cardiology (S.G., G.S., C.G., J.W., P.W.S.), Erasmus MC, Rotterdam, The Netherlands; Cardialysis (H.M.G.-G.), Rotterdam, The Netherlands; and Boston Scientific Corporation (K.D.D.), Natick, Mass.

The online-only Data Supplement is available at http://circinterventions.ahajournals.org/cgi/content/full/CIRCINTERVENTIONS.109.914051/DC1.

Correspondence to Patrick W. Serruys, MD, PhD, Ba583a, Thoraxcentre, Erasmus MC,'s-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands. E-mail p.w.j.c.serruys@erasmusmc.nl

Circ Cardiovasc Interv **is available at http://circinterventions.ahajournals.org** **DOI: 10.1161/CIRCINTERVENTIONS.109.914051**

derived creatinine clearance (CrCl) instead of SCr because this not only represents a better estimate of underlying renal function but has also been previously shown to improve the predictive accuracy of cardiac risk models such as the euroSCORE.[18]

The aim of this study was to investigate whether a Clinical SYNTAX Score (CSS), representing a multiplication of the SYNTAX score with a modified ACEF score (through the incorporation of CrCl), would improve the individual ability of either of these scores to predict mortality in patients with complex CAD undergoing PCI, who were enrolled in the Arterial Revascularization Therapies Study Part II (ARTS-II).

Methods

Study Population

The ARTS-II study has been published previously.[19] In brief, the study was a multicenter, nonrandomized, open-label trial designed to compare the safety and efficacy of the sirolimus eluting stent (SES) in 607 patients with de novo multivessel CAD, using the surgical group of ARTS-I as historic controls.

Patient Selection

Patients with stable angina, unstable angina, or silent ischemia, who had ≥2 coronary lesions located in different major epicardial vessels and/or their side branches (not including the left main stem [LMS]) that were potentially amenable to stent implantation, were eligible for inclusion. All patients enrolled into the ARTS-II study were required to have a lesion with a diameter stenosis >50% in the left anterior descending artery and ≥1 other major epicardial coronary artery.

The goal was to achieve complete anatomic revascularization. Coronary lesions were required to be amenable to stenting using a SES with a diameter of 2.5 to 3.5 mm and length of 13 to 33 mm; there was no restriction on the total implanted stent length. Decisions to place stents in lesions with bifurcations, fresh thrombus, calcification, diffuse disease, complex anatomy, or stenting of side branches were left to the discretion of the operators.

The major exclusion criteria were patients with previous PCI, LMS disease, overt congestive heart failure, LVEF <30%, history of a cerebrovascular accident, transmural myocardial infarction (MI) in the preceding week, severe hepatic or renal disease, neutropenia or thrombocytopenia, an intolerance or contraindication to acetylsalicylic acid or thienopyridines, the need for concomitant major surgery, and life-limiting major concomitant noncardiac diseases. Written informed consent was obtained from each patient prior to enrolment, and the study was approved by the ethics committee of each participating site.

Clinical SYNTAX Score

The CSS was calculated retrospectively for each patient using the formula CSS=[SYNTAX Score]×[modified ACEF score].

The SYNTAX Score for each patient was calculated retrospectively by scoring all coronary lesions with a diameter stenosis ≥50%, in vessels ≥1.5 mm, using the SYNTAX Score algorithm, which is described in full elsewhere[6,7] and is available on the SYNTAX Score website (www.syntaxscore.com). All angiographic variables pertinent to SYNTAX Score calculation were computed by blinded core laboratory analysts (Cardialysis B.V., Rotterdam, The Netherlands).

The modified ACEF score ($ACEF_{CrCl}$) was calculated retrospectively using the formula age/ejection fraction +1 point for every 10 mL/min reduction in CrCl below 60 mL/min per 1.73 m^2 (up to a maximum of 6 points). Therefore, a CrCl of between 50 to 59 mL/min per 1.73 m^2, 40 to 49 mL/min per 1.73 m^2 and 30 to 39 mL/min per 1.73 m^2 would receive 1, 2, and 3 points, respectively. The LVEF used was the value recorded before the index PCI, and in the event of multiple available values was the lowest recorded figure. Creatinine clearance was calculated using the Cockcroft-Gault equation,[20] using the patient's age, weight, and SCr recorded before the index PCI.

Presently, the only published prospective validation of the SYNTAX score comes from the SYNTAX trial.[1] This study only enrolled patients with complex CAD (3-vessel disease [3VD] and/or LMS), and, in view of this, analysis of the CSS in patients who only had treatment for 3VD is shown in an online Data Supplement. For comparison, additional analyses in patients with 3VD have also been performed using the CSS calculated using the standard ACEF score (ie, using SCr, [$ACEF_{SCr}$]); the SYNTAX score combined by multiplication with the additive euroSCORE ($EURO_{ADD}$) and logistic euroSCORE ($EURO_{LOG}$); and the Mayo Clinic Risk Score (MCRS); these can all be found in the online Data Supplement.

End Points

The primary end point of this post hoc study was mortality at 1-year follow-up. The secondary end points were major adverse cardiovascular events (MACCE), defined as a composite of death, cerebrovascular accident, any revascularization (percutaneous or surgical), and MI at 1- and 5-year follow-up.

Definitions

Deaths included mortality from any cause. Cerebrovascular accidents included transient ischemic attacks, reversible neurological deficits, intracranial hemorrhage, and ischemic stroke.[21] MI was defined in the first 7 days after the intervention, if there was documentation of new abnormal Q waves and either a ratio of serum creatinine kinase MB (CK-MB) isoenzyme to total creatinine kinase (CK) that was ≥0.1, or a CK-MB value that was 5 times the upper limit of normal. Serum CK and CK-MB isoenzyme concentrations were measured 6, 12, and 18 hours after the intervention. Commencing 8 days after the intervention (the length of the hospital stay after surgery), either abnormal Q waves or enzymatic changes were sufficient for a diagnosis of MI. An MI was only confirmed after the relevant ECGs had been analyzed by the core laboratory and adjudicated by the clinical events committee. This 2-part method of defining MI was developed for ARTS-I to address the difficulty in diagnosing an MI after cardiac surgery.[21] These definitions have been adopted by the ARC Consortium and are applied whenever a comparison between PCI and coronary artery surgery is performed. In the final report, the window of 7 days is not specifically mentioned, and this window has been maintained for the sake of comparison with the historical data from ARTS-I.

Statistical Methods

All variables were stratified according to CSS tertiles. Continuous variables are expressed as mean± SD and were compared using 1-way ANOVA. Categorical data are presented as frequency (percentages) and were compared using the Fisher exact test or the Pearson χ^2 test. The distribution of the SYNTAX Score, $ACEF_{SCr}$ score, and CSS were assessed before and after logarithmic transformation using the Kolmogorov-Smirnov test. Clinical outcomes are presented as hierarchical and nonhierarchical outcomes, with the hierarchical outcomes only reporting the worst outcome (following the order death, stroke, MI [Q-wave, followed by non–Q-wave], and repeat revascularization [CABG then PCI]) that the patient experiences. Survival curves were constructed for time-to-event variables using Kaplan-Meier estimates and compared by the log-rank test. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Cox regression analysis was used to find independent predictors of MACCE, with those variables with a probability value of <0.10 in the univariate analysis being included in the backward stepwise multivariable model. Receiver operator curves (ROC) were used to compare the performance and predictive accuracy of the CSS, SYNTAX Score, $ACEF_{SCr,}$ $ACEF_{CrCl,}$ $EURO_{ADD}$, $EURO_{LOG}$, MCRS, and the SYNTAX score combined with the euroSCORE (additive and logistic) for MACCE and mortality at 5-year follow-up. A probability value of <0.05 was

Table 1. Baseline and Procedural Characteristics of Patients

Variable, n (%) Unless Stated	CSS ≤15.6 (n=170)	15.6< CSS ≤27.5 (n=171)	CSS >27.5 (n=171)	*P* Value
Baseline characteristics				
Male sex	139 (81.8)	128 (74.9)	128 (74.9)	0.22
Age, y, ±SD	57.4±9.1	61.6±8.5	67.6±8.4	<0.0001
Body mass index, ±SD	27.8±4.2	27.9±3.7	26.7±4.0	0.006
Risk factors				
Previous MI	51 (30.0)	64 (37.4)	63 (36.8)	0.28
Diabetes	36 (21.2)	49 (28.7)	55 (32.2)	0.07
Hypertension	108 (63.5)	113 (66.1)	129 (75.4)	0.045
Hypercholesterolemia	127 (74.7)	122 (72.2)	127 (74.3)	0.85
Family history of ischemic heart disease	75 (44.1)	62 (36.5)	47 (27.8)	0.008
Current smoker	39 (22.9)	36 (21.1)	21 (12.3)	0.03
Peripheral vascular disease	9 (5.3)	7 (4.1)	15 (8.8)	0.17
Chronic obstructive airways disease	4 (2.4)	6 (3.5)	11 (6.4)	0.15
Previous cerebrovascular accident	2 (1.2)	0 (0.0)	2 (1.2)	0.37
Creatinine clearance, mL/1.73 m^2±SD	95.2±23.4	91.4±23.5	74.3±27.5	<0.0001
Indication for treatment				
Stable angina	86 (50.6)	96 (56.1)	81 (47.4)	0.26
Unstable angina	69 (40.6)	58 (33.9)	67 (39.2)	0.41
Silent ischemia	15 (8.8)	17 (9.9)	23 (13.5)	0.35
Medications at screening				
Aspirin	147 (86.5)	145 (84.8)	150 (87.7)	0.73
β-blockers	127 (74.7)	117 (68.4)	124 (72.5)	0.42
ACE inhibitors/angiotensin 2 blockers	88 (51.8)	76 (44.4)	88 (51.5)	0.31
Statins	117 (68.8)	122 (71.3)	123 (71.9)	0.80

ACE indicates angiotensin-converting enzyme.

considered significant, and all tests were 2-tailed. Data were analyzed with SPSS version 17.0 software (SPSS Inc, Chicago, Ill).

Results

The ARTS-II study recruited 607 patients, of whom 512 (84.3%) had 2- or 3-vessel intervention at the time of the index PCI and had LVEF, SCr, and body weight recorded at baseline. Median (interquartile range, IQR) follow-up was 1800 (IQR, 0) days. The results of analyses performed in the 239 (39.3%) patients in the ARTS-II study who had treatment for only 3VD and had LVEF, SCr, and body weight recorded at baseline are shown in the online Data Supplement.

SYNTAX, $ACEF_{SCr}$, and CSS Scores

The SYNTAX Score ranged from 4 to 58, with a mean± SD of 20.8±9.6 and a median of 19 (IQR, 11.9). The $ACEF_{SCr}$ score ranged from 0.5 to 2.3, with a mean± SD of 1.07±0.27 and a median of 1.1 (IQR=0.3). The CSS ranged from 4 to 209, with a mean± SD of 27.2±23.8, and a median of 20.5 (IQR=18.7). All 3 scores were initially nonparametric (Kolmogorov-Smirnov test, $P<0.05$) and became normally distributed after logarithmic transformation (Supplementary Figure 1).

In this post hoc analysis, the 512 patients (1645 treated lesions) were divided according to their CSS into tertiles defined as CSS_{LOW}≤15.6 (n=170), 15.6≤CSS_{MID}<27.5 (n=171), and CSS_{HIGH}>27.5 (n=171).

Baseline Angiographic and Procedural Characteristics

Baseline angiographic and procedural characteristics of the study population, stratified according to CSS tertiles, are shown in Tables 1 and 2. Patient age and hypertension were both significantly higher in the CSS_{HIGH} tertile, whereas body mass index, family history of CAD, current smoking, and CrCl were all significantly lower in the CSS_{HIGH}. Table 2 demonstrates that indicators of lesion complexity, such as lesion length and lesion type, were significantly greater in the CSS_{HIGH} tertile, reflecting the higher calculated SYNTAX Score for these lesions.

Outcomes at 12 Months

Hierarchical and nonhierarchical clinical outcomes at 12 months are shown in Table 3. Overall the primary end point of mortality was comparable among each CSS tertile. MACCE (18.7% CSS_{HIGH} versus 7.6% CSS_{MID} versus 6.5% CSS_{LOW}, $P=0.001$) and repeat revascularization (15.8% CSS_{HIGH} versus 6.4% CSS_{MID} versus 5.3% CSS_{LOW}, $P=0.002$) were both significantly higher in the CSS_{HIGH} tertile, compared with the lower 2 groups.

Long-Term Outcomes

Figure 1 demonstrates the rates of death, MI, repeat revascularization, and MACCE according to CSS tertiles during

Table 2. Angiographic and Procedural Characteristics of the Study Population

Variable, n (%) Unless Stated	CSS ≤15.6 (n=170)	15.6< CSS ≤27.5 (n=171)	CSS >27.5 (n=171)	*P* Value
Ejection fraction	64.1±10.0	60.2±11.5	56.3±11.3	<0.0001
Lesion characteristics				
Lesion length, visual, % of lesions				
Discreet, <10 mm	323 (65.9)	328 (60.4)	327 (53.4)	<0.0001
Tubular, 10 to 20 mm	127 (25.9)	121 (22.3)	169 (27.6)	
Diffuse, >20 mm	36 (7.3)	67 (12.3)	86 (14.1)	
Lesion classification, % of lesions				<0.0001
Type A	39 (8.0)	34 (6.3)	42 (7.0)	
Type B1	124 (25.4)	141 (26.2)	125 (20.7)	
Type B2	287 (58.8)	280 (52.0)	338 (56.0)	
Type C	38 (7.8)	83 (15.4)	99 (16.4)	
Moderate/heavy calcification	156 (31.8)	150 (27.6)	223 (37.6)	<0.0001
Thrombus-containing lesions	3 (0.6)	5 (0.9)	0 (0.0)	0.06
Eccentric lesion	403 (82.2)	452 (83.2)	499 (81.5)	0.001
TIMI flow 3	439 (89.6)	463 (85.3)	527 (86.1)	0.09
1.5≤ RVD <2.5	11 (2.2)	38 (7.0)	52 (8.5)	<0.0001
Procedural characteristics				
Bifurcation requiring double wiring	139 (28.4)	178 (32.8)	199 (32.5)	0.24
No. of stents implanted, ±SD	3.2±1.1	3.7±1.5	4.2±1.7	<0.0001
Total stent length, mm	60.7±23.4	74.0±29.1	83.8±35.9	<0.0001
Maximum dilatation pressure, atm, ±SD	16.2±2.7	16.2±2.7	16.8±2.9	0.07
Direct stenting, % of lesions	227 (46.3)	203 (37.4)	144 (23.5)	<0.0001
Use of glycoprotein IIb/IIIa inhibitors	55 (32.4)	50 (29.2)	52 (30.4)	0.82
Completeness of revascularization	128 (75.3)	96 (56.1)	83 (48.5)	<0.0001
Postprocedural hospital stay, days, ±SD	2.8±1.5	3.3±2.7	4.1±2.8	<0.0001

RVD indicates reference vessel diameter; and atm, atmosphere.

long-term follow-up. There were no significant differences in events (death/MI/repeat revascularization/MACCE) between patients in the low and mid CSS tertiles. Patients in the CSS_{HIGH} tertile had significantly higher rates of repeat revascularization and MACCE when compared with the lower 2 tertiles. In addition, mortality was significantly higher with CSS_{HIGH} compared CSS_{LOW}, whereas the rate of MI was comparable for all 3 groups.

Multivariable Analysis

The results of the Cox multivariable analysis are shown in Table 4. The log CSS, log SYNTAX Score, and log $ACEF_{SCr}$ score were all univariate predictors of long-term MACCE. After multivariate adjustment, the independent predictors of MACCE at 5-year follow-up were the log CSS and the presence of incomplete revascularization, diabetes, or peripheral vascular disease.

CSS Versus SYNTAX Score Versus $ACEF_{SCr}$

The ROC curves for mortality and MACCE at 5-year follow-up are shown in Figure 2. The respective C-statistics for the CSS, SYNTAX Score, and $ACEF_{SCr}$ score for 5-year mortality were 0.69, 0.62, and 0.65 and for 5-year MACCE were 0.62, 0.59, and 057 ($P<0.05$ for all).

CSS Versus MCRS Versus $EURO_{ADD}$ Versus $EURO_{LOG}$

The Kaplan-Meier curves for 5-year mortality and MACCE-free survival stratified according to tertiles of the CSS, MCRS, $EURO_{ADD}$, and $EURO_{LOG}$ are shown in Figure 3. Overall, there were no significant differences between corresponding tertiles for the CSS, MCRS, $EURO_{ADD}$, and $EURO_{LOG}$. For each score, patient mortality and MACCE among those in the lowest tertile were significantly better than those in the highest tertile and comparable with the intermediate tertile. A significant difference in mortality was observed between the intermediate and highest tertile with the use of the MCRS and $EURO_{ADD}$ but not the $EURO_{LOG}$ or CSS. Conversely, the significant difference in MACCE between the intermediate and highest tertile observed with the CSS was not observed with the other 3 scores.

The ROC curves for mortality and MACCE at 5-year follow-up for the CSS_{CrCl}, CSS_{SCr}, $ACEF_{CrCl}$, $ACEF_{SCr}$, SYNTAX score, MCRS, $EURO_{ADD}$, $EURO_{LOG}$, and SYNTAX score combined with the euroSCORE (additive and logistic) are shown in Figure 4, and Table 5.

The results of these analyses performed specifically in patients with 3VD can all be found in the online Data Supplement.

Table 3. Clinical Outcomes at 1-Year Follow-Up

Variable, n (%) Unless Stated	CSS ≤15.6 (n=170)	15.6< CSS ≤27.5 (n=171)	CSS >27.5 (n=171)	*P* Value
Hierarchical				
Death	1 (0.6)	0 (0.0)	4 (2.3)	0.09
Cerebrovascular accident	0 (0.0)	1 (0.6)	3 (1.8)	
MI	2 (1.2)	1 (0.6)	4 (2.3)	
Q wave	1 (0.6)	1 (0.6)	2 (1.2)	
Non-Q wave	1 (0.6)	0 (0.0)	2 (1.2)	
Repeat revascularization	8 (4.7)	11 (6.4)	21 (12.3)	
CABG	2 (1.2)	2 (1.2)	5 (2.9)	
PCI	6 (3.5)	9 (5.3)	16 (9.4)	
MACCE	11 (6.5)	13 (7.6)	32 (18.7)	0.001
Nonhierarchical				
Cerebrovascular accident	0 (0.0)	1 (0.6)	3 (1.8)	0.33
MI	2 (1.2)	1 (0.6)	6 (3.5)	0.14
Q wave	1 (0.6)	1 (0.6)	3 (1.8)	0.63
Non-Q wave	1 (0.6)	0 (0.0)	3 (1.8)	0.23
Repeat revascularization	9 (5.3)	11 (6.4)	27 (15.8)	0.002
PCI	7 (4.1)	9 (5.3)	21 (12.3)	0.009
CABG	2 (1.2)	3 (1.8)	6 (3.5)	0.41

Discussion

To the best of our knowledge, this is the first description of the CSS that represents a risk score combining both clinical and angiographic variables. The main findings from this study are that the CSS has an ability superior to either the SYNTAX Score or $ACEF_{SCr}$ score alone in the prediction of MACCE and mortality at 5-year follow-up in patients with complex CAD undergoing PCI. Furthermore, the log CSS is an independent predictor of long-term MACCE in this group of patients.

Risk stratification and the assessment of risk-benefit are 2 important aspects of clinical medicine,[22] and should form an integral part of the patient informed consent process. Technological advances mean that the majority of coronary lesions are amendable to PCI; however, this may not always be the most appropriate treatment for an individual patient. The final decision of whether to perform PCI or CABG in patients with complex CAD is no longer simply based only on the views of the interventional cardiologist and cardiac surgeon; patient choice now plays an important part in the decision. Consequently, to enable patients to make the most appropriate informed decision for them as an individual, a suitable method of quantifying risk is essential. The importance of risk stratification in these patients is further emphasized when considering the escalating complexity of CAD being treated with PCI and the increasing age of patients undergoing PCI,[23] both of which are associated with less favorable clinical outcomes and greater procedural related morbidity.[24] Unfortunately, despite the unquestionable need, and in contrast to patients having CABG, few risk models have become established into regular clinical practice for patients undergoing PCI. The recently introduced SYNTAX Score offers the potential to meet this unmet clinical need.[1,3]

The SYNTAX Score is derived entirely from the coronary anatomy and lesion characteristics and is calculated using dedicated software, enabling complex coronary artery anatomy to be quantified.[6,7] The score, which was an integral part of the SYNTAX trial design,[25] was initially devised as a method to ensure that both the cardiologist and cardiac surgeon accurately reviewed the angiogram of patients with complex CAD, enabling a consensus regarding the optimal method and completeness of revascularization to be reached. Importantly, the SYNTAX Score was calculated a priori, before the outcome of revascularization was known. The results of the SYNTAX trial have subsequently demonstrated that the score has an important role in stratifying patients with complex CAD to aid revascularization decisions.[1,26] Further evaluation of the score has also indicated its ability to predict clinical outcomes. In patients with 3VD, the SYNTAX Score has been shown to be an independent predictor of MACCE at both 1-year[8] and 5-year follow-up.[10] Similarly, in patients with LMS disease, Capodanno et al[9] reported that the SYNTAX Score was able to predict both cardiac death ($P<0.001$) and MACCE ($P=0.04$) at short-term follow-up. More recently, analysis of SYNTAX scores collected prospectively in the LEADERS study and retrospectively in the SIRTAX study indicates that risk stratification using the SYNTAX Score can be expanded to include all patients with CAD, irrespective of severity.[11,27]

The SYNTAX Score is independent of a patient's clinical characteristics, some of which, for example, patient age, have been consistently shown to be an independent predictor of mortality.[28] Furthermore, previous studies have demonstrated the superior performance of clinical based risk models, such as the MCRS, in the prediction of morbidity and mortality when compared with lesion-based scores such as the Amer-

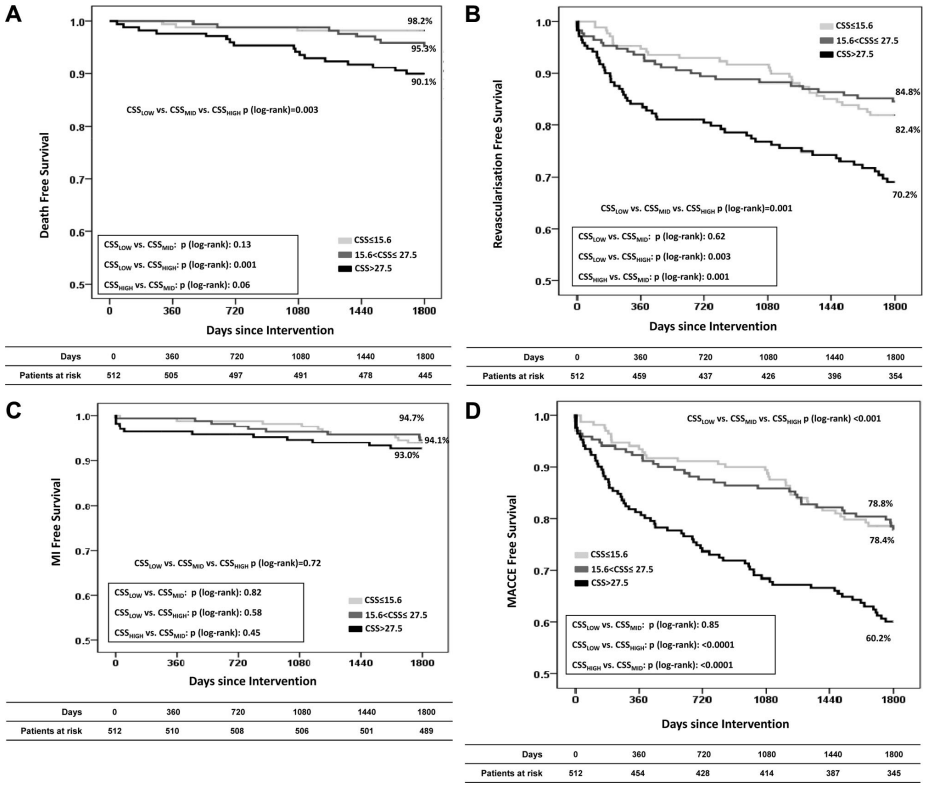


Figure 1. Kaplan Meier curves for death (A), repeat revascularization (B), myocardial infarction (MI) (C), and major adverse cardiovascular and cerebrovascular events (MACCE) (D) at 1800-day follow-up stratified accord to CSS tertile.

ican Heart Association lesion classification.[12] Therefore, the absence of any clinical characteristics in the calculation of the SYNTAX Score is a potential limitation to its use in risk stratification.

The CSS described in the present study for the first time represents a modification of the SYNTAX Score to accommodate for these inherent limitations. The present study has indicated that the inclusion of patient characteristics does

Table 4. Univariate and Multivariable Predictors of MACCE at 5-Year Follow-Up

	Univariate Predictors of MACCE at 5 Years		Multivariable Predictors of MACCE at 5 Years	
Variable	[95% CI]	*P* Value	[95% CI]	*P* Value
Age	1.02 [1.00–1.04]	0.03		
Diabetes	1.80 [1.28–2.54]	0.001	1.55 [1.09–2.19]	0.01
Peripheral vascular disease	2.01 [1.18–3.44]	0.01	1.97 [1.14–3.41]	0.02
Log SYNTAX score	5.62 [2.32–13.62]	<0.0001		
Log ACEF	7.11 [1.56–32.45]	0.01		
Log clinical SYNTAX score	1.81 [1.42–2.29]	<0.0001	1.77 [1.02–3.07]	0.04
No. of diseased lesions	1.43 [1.17–1.73]	<0.0001		
Incomplete revascularization	1.56 [1.12–2.17]	0.009	1.43 [1.01–2.02]	0.045

CI indicates confidence interval.

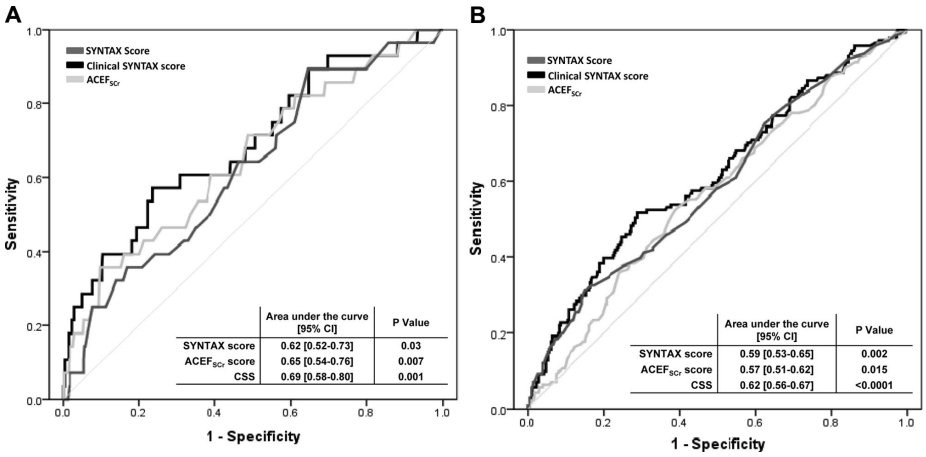


Figure 2. ROC curve for the SYNTAX score, $ACEF_{SCr}$, and CSS for mortality (A) and MACCE (B). The use of the CSS leads to an improvement in the C-statistic for both outcomes.

improve the ability of the score, as indicated by the ROC curves, to predict MACCE and mortality compared with the original score.

Intuitively, the use of multiple clinical variables should improve the accuracy of a risk model; however, this accuracy may ultimately be contaminated by the desire to create the "perfect model."[16] In practice, Ranucci et al[17] illustrated this by demonstrating that a simple scoring method using just age, LVEF, and SCr ($ACEF_{SCr}$ score) is as good as complex scores such as the euroSCORE (17 clinical variables) and Parsonnet score in predicting mortality in patients undergoing elective CABG. These 3 variables are known to affect the risk of both CABG[17] and PCI,[28–30] and therefore even though the score has not previously been validated in patients undergoing PCI, it was considered acceptable to use as a basis for the development of the CSS. Retrospective justification for using the ACEF score as an integral part of the CSS come in part from the comparable C-statistics for MACCE and mortality between the validated MCRS and the $ACEF_{CrCl}$ (Table 5, Figure 4, and Supplementary Figure 2). Of note, the combination of the SYNTAX score with the euroSCORE only offered an advantage over the CSS in the prediction of mortality among those patients with 2- and 3VD (Table 5, Figure 4, and Supplementary Figures 2 and 3).

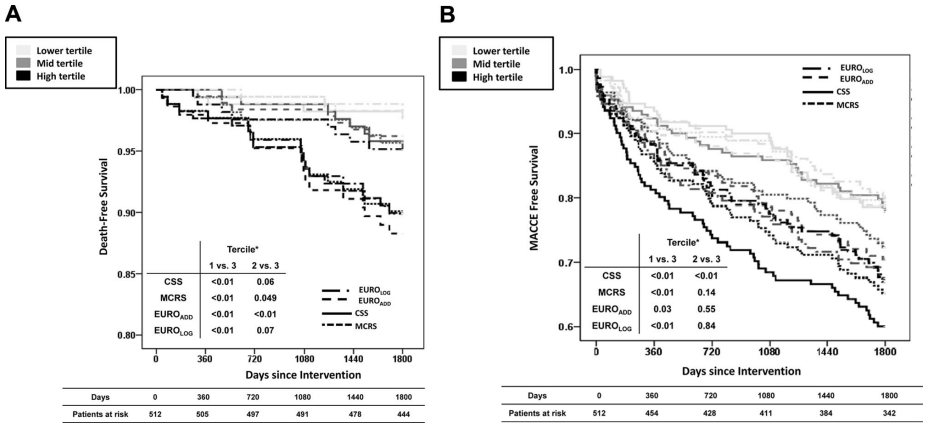


Figure 3. Kaplan-Meier curve showing the 5-year mortality (A) and MACCE-free survival (B) stratified according to tertiles of the CSS, Mayo Clinic Risk Score (MCRS), Additive euroSCORE ($EURO_{ADD}$) and Logistic euroSCORE ($EURO_{LOG}$). No significant difference was observed between outcomes in Tertiles 1 and 2 (probability values not shown). **P* (log-rank) values.

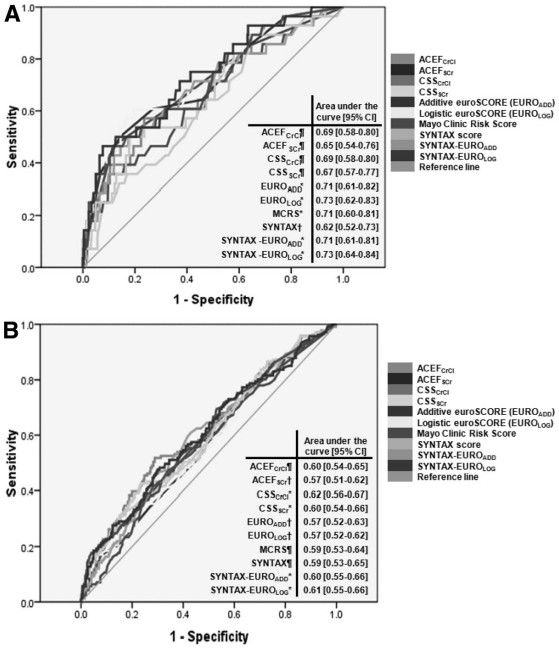


Figure 4. ROC curve for mortality (A) and MACCE (B) at 5-year follow-up for different risk scores. *$P<0.001$, †$P<0.05$, ¶$P<0.01$.

The modification to the ACEF score to incorporate CrCl has also not previously been validated. Notably, in previous PCI studies that have identified renal dysfunction as a marker of adverse outcome either SCr or CrCl has been used, not both.[31,32] Conversely, CrCl has been shown to be a better predictor when compared with SCr of risk in patients undergoing surgical revascularization.[18,33] Incorporation of CrCl into the ACEF score can therefore be justified prospectively by extrapolation of these previous results and retrospectively by the improvements in the C-statistic for MACCE (0.60 versus 0.62) and mortality (0.67 versus 0.69) observed in this study when the CSS was calculated using the $ACEF_{CrCl}$ instead of $ACEF_{SCr}$ (Figure 4 and Table 5).

This study demonstrates a superior ability of the CSS to predict long-term MACCE and mortality when compared with the individual SYNTAX and ACEF scores. Importantly, after calculating the SYNTAX Score, which remains an important aid to deciding the appropriate revascularization strategy, the CSS can be derived quickly, using easily available variables that are not subject to any interobserver

Table 5. Comparison of C-Statistics Between 3VD and 2VD/3VD Patient Cohorts

	Mortality		MACCE	
Risk Score	2VD and 3VD (512 Patients)	3VD (239 Patients)	2VD and 3VD (512 Patients)	3VD (239 Patients)
ACEF, creatinine clearance	0.69	0.82	0.60	0.64
ACEF, serum creatinine	0.65	0.73	0.57	0.59
Clinical SYNTAX score, creatinine clearance	0.69	0.80	0.62	0.67
Clinical SYNTAX score, serum creatinine	0.67	0.75	0.60	0.65
euroSCORE, additive	0.71	0.79	0.57	0.61
euroSCORE, logistic	0.73	0.82	0.57	0.61
Mayo Clinic Risk Score	0.71	0.82	0.59	0.64
SYNTAX score	0.62	0.70	0.59	0.64
SYNTAX-euroSCORE, additive	0.71	0.81	0.60	0.66
SYNTAX-euroSCORE, logistic	0.73	0.81	0.61	0.65

variability. The current analysis also indicates that whereas the CSS has a similar ability to predict mortality when compared with the MCRS and euroSCORE, it offers an additional advantage in the prediction of ischemic end points, which, as suggested by the C-statistics, are a somewhat harder end point to predict than mortality. Clearly, additional research is required to evaluate the potential of this new score in more diverse patient populations undergoing PCI.

Limitations

The current study is limited by its post hoc nature. In addition, the ROC method of analysis, although well suited for diagnostic purposes, may not be appropriate for prognostic models because these models must incorporate the dimension of time, which adds a stochastic element.[34] It has therefore been suggested that ROC analysis methods are not well validated for the assessment of time-censored data; however, in the current study the same methods have been used to assess both scoring systems, and these methods are consistent with previous published studies evaluating these risk models.[17]

Other potential limitations include that lack of validation of the ACEF score in patients having PCI and the lack of any external validation in patients having either PCI or CABG. We accept that the current population may be too small to make definitive conclusions; however, at present, in view of its recent introduction, only select patient populations with complex disease have a SYNTAX score calculation and adjudicated long-term outcomes. The small sample size may account for the similar outcomes between low- and intermediate-risk groups when using the CSS, MCRS, EURO$_{ADD}$, EURO$_{LOG}$, SYNTAX-euroSCORE (logistic), and MCRS (Figures 1 and 3 and Supplementary Figures 3 and 4). It must also be acknowledged that there is a reduction in the predictive ability of the CSS when it is used in patients with 2VD and 3VD, as opposed to when it is used in only patients with 3VD. Importantly, however, this same observation is seen with both the established scores such as the MCRS and euroSCORE and the newer scores tested in this analysis (Table 5).

Conclusion

An improvement in the ability of the SYNTAX Score to predict MACCE and mortality can be achieved by combining the SYNTAX Score with a simple clinical risk score incorporating age, ejection fraction, and creatinine clearance to produce the Clinical SYNTAX Score.

Disclosures

Dr Dawkins is a full-time employee and holds stock in Boston Scientific.

References

1. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961–972.
2. Seung KB, Park DW, Kim YH, Lee SW, Lee CW, Hong MK, Park SW, Yun SC, Gwon HC, Jeong MH, Jang Y, Kim HS, Kim PJ, Seong IW, Park HS, Ahn T, Chae IH, Tahk SJ, Chung WS, Park SJ. Stents versus coronary-artery bypass grafting for left main coronary artery disease. *N Engl J Med*. 2008;358:1781–1792.
3. Serruys P, Garg S. Percutaneous coronary interventions for all patients with complex coronary artery disease: triple vessel disease or left main coronary artery disease. Yes? No? Don't Know? *Rev Esp Cardiol*. 2009; 62:719–725.
4. Capodanno D, Capranzano P, Di Salvo ME, Caggegi A, Tomasello D, Cincotta G, Miano M, Patane M, Tamburino C, Tolaro S, Patane L, Calafiore AM. Usefulness of SYNTAX score to select patients with left main coronary artery disease to be treated with coronary artery bypass graft. *J Am Coll Cardiol Cardiovasc Interv*. 2009;2:731–738.
5. Kappetein AP, Dawkins KD, Mohr FW, Morice MC, Mack MJ, Russell ME, Pomar J, Serruys PW. Current percutaneous coronary intervention and coronary artery bypass grafting practices for three-vessel and left main coronary artery disease: insights from the SYNTAX run-in phase. *Eur J Cardiothorac Surg*. 2006;29:486–491.
6. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Van Dyck N, Russell ME, Mohr F, Serruys P. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. *Eurointervention*. 2005;1:219–227.
7. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, Van Dyck N, Mack M, Holmes D, Feldman T, Morice MC, Colombo A, Bass E, Leadley K, Dawkins KD, van Es GA, Morel MA, Mohr FW. Assessment of the SYNTAX score in the Syntax study. *EuroIntervention*. 2009;5:50–56.
8. Valgimigli M, Serruys PW, Tsuchida K, Vaina S, Morel MA, van den Brand MJ, Colombo A, Morice MC, Dawkins K, de Bruyne B, Kornowski R, de Servi S, Guagliumi G, Jukema JW, Mohr FW, Kappetein AP, Wittebols K, Stoll HP, Boersma E, Parrinello G. Cyphering the complexity of coronary artery disease using the syntax score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. *Am J Cardiol*. 2007;99: 1072–1081.
9. Capodanno D, Di Salvo ME, Cincotta G, Miano M, Tamburino C, Tamburino C. Usefulness of the SYNTAX score for predicting clinical outcome after percutaneous coronary intervention of unprotected left main coronary artery disease. *Circ Cardiovasc Intervent*. 2009;2: 302–308.
10. Serruys PW, Onuma Y, Garg S, Vranckx P, De Bruyne B, Morice MC, Colombo A, Macaya C, Richardt G, Fajadet J, Hamm C, Schuijer M, Rademaker T, Wittebols K, Stoll HP. 5-Year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the Sirolimus-Eluting Stent in the Treatment of Patients With Multivessel De Novo Coronary Artery Lesions. *J Am Coll Cardiol*. 2010;55:1093–1101.
11. Wykrzykowska J, Garg S, Girasis C, de Vries T, Morel MA, van Es GA, Buszman P, Linke A, Ischinger T, Klauss V, Corti R, Eberli F, Wijns W, Morice MC, di Mario C, van Geuns RJ, Juni P, Windecker S, Serruys PW. Value of the Syntax Score (SX) for risk assessment in the "All-comers" Population of the Randomized Multicenter Leaders Trial. *J Am Coll Cardiol*. 2010;56:272–277.
12. Singh M, Rihal CS, Lennon RJ, Garratt KN, Holmes DR Jr. Comparison of Mayo Clinic risk score and American College of Cardiology/American Heart Association lesion classification in the prediction of adverse cardiovascular outcome following percutaneous coronary interventions. *J Am Coll Cardiol*. 2004;44:357–361.
13. Romagnoli E, Burzotta F, Trani C, Siviglia M, Biondi-Zoccai GG, Niccoli G, Leone AM, Porto I, Mazzari MA, Mongiardo R, Rebuzzi AG, Schiavoni G, Crea F. EuroSCORE as predictor of in-hospital mortality after percutaneous coronary intervention. *Heart*. 2009;95:43–48.
14. Kim YH, Ahn JM, Park DW, Lee BK, Lee CW, Hong MK, Kim JJ, Park SW, Park SJ. EuroSCORE as a predictor of death and myocardial infarction after unprotected left main coronary stenting. *Am J Cardiol*. 2006;98:1567–1570.
15. Garg S, Serruys PW. Interventional cardiology: coronary angioplasty: do we need to EuroSCORE? *Nat Rev Cardiol*. 2009;6:267–268.
16. Concato J, Feinstein AR, Holford TR. The risk of determining risk with multivariable models. *Ann Intern Med*. 1993;118:201–210.
17. Ranucci M, Castelvecchio S, Menicanti L, Frigiola A, Pelissero G. Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony. *Circulation*. 2009;119: 3053–3061.
18. Walter J, Mortasawi A, Arnrich B, Albert A, Frerichs I, Rosendahl U, Ennker J. Creatinine clearance versus serum creatinine as a risk factor in cardiac surgery. *BMC Surg*. 2003;3:4.

19. Serruys PW, Ong ATL, Morice M-C, Bruyne BD, Colombo A, Macaya C, Richardt G, Fajadet J, Hamm C, Dawkins K, O'Malley AJ, Bressers M, Dennis D, on behalf of the ARTS II Investigators. Arterial Revascularisation Therapies Study Part II: sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. *Eurointervention.* 2005;1:147–156.
20. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31–41.
21. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schonberger JP, Buller N, Bonser R, van den Brand MJ, van Herwerden LA, Morel MA, van Hout BA. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med*. 2001;344: 1117–1124.
22. Federspiel J, Stearns S, Van Domburg R, Sheridan B, Lund J, Serruys PW. Risk-benefit trade-offs in revascularization choices. *EuroIntervention.* In press.
23. Singh M, Rihal CS, Gersh BJ, Lennon RJ, Prasad A, Sorajja P, Gullerud RE, Holmes DR Jr. Twenty-five-year trends in in-hospital and long-term outcome after percutaneous coronary intervention: a single-institution experience. *Circulation*. 2007;115:2835–2841.
24. LeGrand V, Garg S, Serruys PW, Virtanen K, Szurawitzki G, Voudris V, Fontanelli A, Endersen K, Kranjec I, Rademaker T, Stefanidis C, Wittebols K. Influence of age on the clinical outcomes of coronary revascularization for the treatment of patients with multivessel de novo coronary artery lesions: sirolimus-eluting stent vs coronary artery bypass surgery and bare metal stent: insight from the Multicenter Randomized Arterial Revascularization Therapy Study Part I (ARTS-I) and Part II (ARTS-II) [published online ahead of print June 2010]. *Eurointervention.* 2010.
25. Ong AT, Serruys PW, Mohr FW, Morice MC, Kappetein AP, Holmes DR Jr, Mack MJ, van den Brand M, Morel MA, van Es GA, Kleijne J, Koglin J, Russell ME. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. *Am Heart J*. 2006;151:1194–1204.
26. Kappetein AP. Optimal revascularization strategy in patients with three-vessel disease and/or left main disease: the 2-year Outcomes of the SYNTAX Trial. Presentation at the ESC Congress, Barcelona, September 2, 2009. Available at: www.syntaxscore.com.
27. Girasis C, Garg S, Raber L, Sarno G, Morel MA, Garcia Garcia HM, Serruys P, Windecker S. Prediction of 5-year clinical outcomes using the SYNTAX score in patients undergoing PCI from the Sirolimus eluting stent compared with paclitaxel eluting stent for coronary revascularisation (SIRTAX) trial. Abstract presented at the American College of Cardiology meeting, March 14 to 16, 2010, Atlanta Ga.
28. Feldman DN, Gade CL, Slotwiner AJ, Parikh M, Bergman G, Wong SC, Minutello RM. Comparison of outcomes of percutaneous coronary interventions in patients of three age groups (<60, 60 to 80, and >80 years) (from the New York State Angioplasty Registry). *Am J Cardiol*. 2006; 98:1334–1339.
29. Shaw JA, Andrianopoulos N, Duffy S, Walton AS, Clark D, Lew R, Sebastian M, New G, Brennan A, Reid C, Ajani AE. Renal impairment is an independent predictor of adverse events post coronary intervention in patients with and without drug-eluting stents. *Cardiovasc Revasc Med*. 2008;9:218–223.
30. Keelan PC, Johnston JM, Koru-Sengul T, Detre KM, Williams DO, Slater J, Block PC, Holmes DR Jr. Comparison of in-hospital and one-year outcomes in patients with left ventricular ejection fractions <or=40%, 41% to 49%, and >or=50% having percutaneous coronary revascularization. *Am J Cardiol*. 2003;91:1168–1172.
31. Ix JH, Mercado N, Shlipak MG, Lemos PA, Boersma E, Lindeboom W, O'Neill WW, Wijns W, Serruys PW. Association of chronic kidney disease with clinical outcomes after coronary revascularization: the Arterial Revascularization Therapies Study (ARTS). *Am Heart J*. 2005;149: 512–519.
32. Latif F, Kleiman NS, Cohen DJ, Pencina MJ, Yen CH, Cutlip DE, Moliterno DJ, Nassif D, Lopez JJ, Saucedo JF. In-hospital and 1-year outcomes among percutaneous coronary intervention patients with chronic kidney disease in the era of drug-eluting stents: a report from the EVENT (Evaluation of Drug Eluting Stents and Ischemic Events) registry. *J Am Coll Cardiol Cardiovasc Interv*. 2009;2:37–45.
33. Noyez L, Plesiewicz I, Verheugt FW. Estimated creatinine clearance instead of plasma creatinine level as prognostic test for postoperative renal function in patients undergoing coronary artery bypass surgery. *Eur J Cardiothorac Surg*. 2006;29:461–465.
34. Soreide K. Receiver-operating characteristic curve analysis in diagnostic, prognostic and predictive biomarker research. *J Clin Pathol*. 2009;62:1–5.

CLINICAL PERSPECTIVE

Risk stratification is becoming an increasingly important part of the assessment of patients who are candidates for coronary revascularization. The recently published SYNTAX study indicates that percutaneous coronary intervention disease is only appropriate in a subset of those with complex disease. Patient outcomes were assessed according to the SYNTAX score, which is based on the extent of coronary disease. The absence of patient features has limited the score for risk assessment in everyday practice because the complexity of coronary disease is not the only factor that affects patient risk. The Clinical SYNTAX score combines the SYNTAX score with a simple patient score. The Clinical SYNTAX score improves the predictive ability for the majority of patients undergoing percutaneous coronary intervention and enables a physician to provide an individualized assessment of risk, which is vital for appropriate informed consent. Moreover, the Clinical SYNTAX score can be used to adjust for the differences in case mix between hospitals and individual operators to allow a meaningful comparison of performance.

Supplementary Material

This appendix complements the main manuscript, and provides the results from additional analyses in those patients who had treatment for three vessel disease.

Contents

1. Clinical SYNTAX score: only patients with triple vessel disease in ARTS-II.

Methods

The main manuscript presents the results of the Clinical SYNTAX score (CSS) amongst the 512 (84.3%) patients in the ARTS-II study who had treatment for two or triple vessel disease (3VD), and had a serum creatinine (SCr), left ventricular ejection fraction (LVEF) and body weight recorded prior to the index percutaneous coronary intervention (PCI). Currently however the only published prospective validation of the SYNTAX score comes from the SYNTAX trial[1] which only enrolled those patients with 3VD and/or left main stem lesions. Therefore the results of the CSS applied to only those 239 (39.3%) patients who had treatment of 3VD and had their body weight, SCr and LVEF recorded at baseline are presented here.

Results

The mean± standard deviation of the SYNTAX score, $ACEF_{SCr}$ score and CSS for this population was 22.3±9.9, 1.1±0.3, and 30.7±27.9 respectively. Further analysis of the CSS was performed after dividing the 239 patients (939 treated lesions) into CSS tertiles defined as: $CSS_{LOW} \leq 16.5$ (n=80), $16.5 < CSS_{MID} \leq 31.2$ (n=79) and $CSS_{HIGH} > 31.2$ (n=80).

Supplementary Table 1. Baseline and procedural characteristics of patients

Variable n,(%) unless stated	CSS≤16.5 N=80	16.5<CSS≤31.2 N=79	CSS>31.2 N=80	P Value
Baseline Characteristics				
Male gender	65 (81.3)	63 (79.7)	57 (71.3)	0.26
Age (years±SD)	57.7±8.6	63.4±9.4	68.5±8.4	<0.0001
Body Mass Index ±SD	28.1±3.9	27.9±3.8	27.1±4.3	0.22
Risk factors				
Previous Myocardial infarction	19 (23.8)	30 (38.0)	32 (40.0)	0.06
Diabetes	11 (13.8)	20 (25.3)	25 (31.3)	0.03
Hypertension	50 (62.5)	57 (72.2)	62 (77.5)	0.11
Hypercholesterolemia	65 (81.3)	61 (77.2)	60 (75.0)	0.63
Family history ischaemic heart disease	39 (48.8)	24 (30.4)	22 (27.8)	0.01
Current smoker	15 (18.8)	16 (20.3)	7 (8.8)	0.10
Peripheral vascular disease	6 (7.2)	7 (8.3)	6 (7.1)	0.95
Chronic obstructive airways disease	0 (0.0)	3 (3.8)	5 (6.3)	0.09
Previous cerebrovascular accident	2 (2.5)	0 (0.0)	2 (2.5)	0.37
Creatinine Clearance (ml/1.73m^2±SD)	92.5±22.1	91.7±26.8	72.5±25.6	<0.0001
Indication for Treatment				
Stable angina	47 (58.8)	46 (58.2)	37 (46.3)	0.20
Unstable angina	27 (33.8)	26 (32.9)	38 (47.5)	0.10
Silent ischemia	6 (7.5)	7 (8.9)	5 (6.3)	0.82
Medications at screening				
Aspirin	67 (83.8)	67 (83.8)	67 (83.8)	0.98
ß-blockers	55 (68.8)	58 (73.4)	55 (68.8)	0.76
ACE-inhibitors/Angiotension-2 blockers	47 (58.8)	33 (41.8)	42 (52.5)	0.10
Statins	54 (67.5)	56 (70.9)	54 (67.5)	0.87

SD indicates standard deviation; CSS, clinical SYNTAX Score; ACE, Angiotensin converting enzyme

Supplementary Table 2. Angiographic and procedural characteristics of study population

Variable n (%) unless stated	CSS≤16.5 N=80	16.5<CSS≤31.2 N=79	CSS>31.2 N=80	P Value
Ejection fraction	65.6±9.9	59.4±11.6	55.2±11.5	<0.0001
Lesion Characteristics				
Mean No. of diseased lesions with stenosis > 50%	3.7±0.8	4.4±1.1	4.8±1.2	<0.0001
Mean No. of treated lesions	3.2±0.9	3.4±1.2	3.2±1.0	0.33
Lesion Length (visual)(% of lesions)				
Discreet (<10mm)	182 (64.5)	191 (59.1)	179 (53.6)	0.02
Tubular (10-20mm)	76 (27.0)	80 (24.8)	87 (26.0)	0.83
Diffuse (>20mm)	23 (8.2)	37 (11.5)	49 (14.7)	0.04
Lesion Classification (% of lesions)				
Type A	20 (7.1)	19 (6.0)	23 (7.0)	0.44
Type B1	61 (21.6)	88 (27.7)	74 (22.4)	0.29
Type B2	177 (62.8)	165(51.9)	174 (52.7)	0.04
Type C	24 (8.5)	46 (14.5)	59 (17.9)	0.001
Moderate/Heavy calcification	91 (32.3)	89 (27.6)	124 (37.1)	0.001
Thrombus containing lesions	3 (1.1)	1 (0.3)	0 (0.0)	0.01
Eccentric lesion	245 (86.9)	271 (83.9)	267 (79.9)	0.05
TIMI flow 3	252 (89.4)	283 (87.6)	286 (85.6)	0.38
1.5≤RVD<2.5	7 (2.5)	25 (7.7)	30 (9.0)	0.003
Procedural Characteristics				
Bifurcation requiring double wiring	81 (27.4)	101 (29.4)	121 (31.8)	0.44
Number of stents implanted ±SD	4.0±0.9	4.6±1.3	5.0±1.6	<0.0001
Total stent length (mm)	76.1±21.6	87.5±26.6	100.0±36.7	<0.0001
Maximum dilatation pressure (Atm±SD)	16.6±3.0	16.4±2.7	17.1±3.1	0.32
Direct stenting (% of lesions)	129 (45.7)	109 (33.7)	68 (20.4)	<0.0001
Use of glycoprotein IIb/IIIa inhibitors	27 (35.1)	25 (32.5)	25 (32.5)	0.94
Completeness of Revascularisation	61 (76.3)	41 (51.9)	40 (50.0)	0.001
Post procedural Hospital stay (days±SD)	2.8±1.6	3.4±1.8	4.2±3.0	0.001

Atm indicates atmosphere; SD, standard deviation; CSS, Clinical SYNTAX Score; No., number; RVD, reference vessel diameter

Baseline patient characteristics, together with lesion and procedural data stratified according to CSS tertile are shown in Supplementary Tables 1 and 2. Hierarchical and non-hierarchical outcomes at 1-year follow-up, which are shown in Supplementary Table 3, demonstrates poorer outcomes in those patients in the highest CSS tertile compared to the low- and mid- tertiles.

Supplementary Figure 5 demonstrates the rates of death, myocardial infarction (MI), repeat revascularisation and major adverse cardio- and cerebrovascular events (MACCE) according to CSS tertile at 5-years follow-up. Similar to the full patient cohort, there was no significant difference between outcomes between patients in the low and mid tertiles.

The ROC curves for MACCE and mortality are shown in Supplementary Figure 6, and demonstrate the superiority of the CSS compared to the $ACEF_{SCr}$, and SYNTAX score. Of note, and as shown in Table 5 (main manuscript), the C-statistics were greater in this cohort of patients with 3VD, when compared with the results from patients with 2- and 3-VD.

Supplementary Table 3. Clinical Outcomes at One Year Follow-up

Variable n,(%) unless stated	CSS≤16.5 N=80	16.5<CSS≤31.2 N=79	CSS>31.2 N=80	P Value
Hierarchical Events				
Death	0 (0.0)	0 (0.0)	2 (2.5)	0.34
Cerebrovascular Accident	0 (0.0)	1 (1.3)	2 (2.5)	
Myocardial Infarction	1(1.3)	0 (0.0)	1(1.3)	
Q wave	0 (0.0)	0 (0.0)	1(1.3)	
Non-Q wave	1(1.3)	0 (0.0)	0 (0.0)	
Repeat Revascularization	4 (5.0)	3 (3.8)	11 (13.8)	
CABG	1 (1.3)	0 (0.0)	3 (3.8)	
PCI	3 (3.8)	3 (3.8)	8 (10.0)	
Any MACCE	5 (6.3)	4 (5.1)	16 (20.0)	0.008
Non-Hierarchical				
Cerebrovascular Accident	0 (0.0)	1 (1.3)	2 (2.5)	0.78
Myocardial Infarction	1 (1.3)	0 (0.0)	2 (2.5)	0.64
Q wave	0 (0.0)	0 (0.0)	1 (1.3)	1.00
Non-Q wave	1 (1.3)	0 (0.0)	1 (1.3)	0.78
Repeat Revascularization	5 (6.3)	3 (3.8)	12 (15.0)	0.03
PCI	4 (5.0)	3 (3.8)	9 (11.3)	0.12
CABG	1 (1.3)	0 (0.0)	3 (3.8)	0.32

PCI indicates percutaneous coronary intervention; CABG, coronary artery bypass grafting; CSS, Clinical SYNTAX Score; MACCE, major adverse cardiovascular and cerebrovascular events

The results of the Cox multi-variate analysis are shown in Supplementary Table 4 and demonstrate that the log CSS remains an independent predictor of MACCE at 5-years follow-up in this more complex cohort of patients.

Supplementary Table 4. Univariate and multivariable predictors of MACCE at 5-years follow-up.

Variable	Univariate predictors of MACCE at 5 years		Multivariable predictors of MACCE at 5 years	
	95% [CI]	P value	95% [CI]	P value
Age	1.03 [1.00-1.06]	0.03		
Diabetes	2.27 [1.39-3.73]	0.001	1.77 [1.06-2.95]	0.03
Current Smoking	0.50 [0.23-1.01]	0.08		
Peripheral vascular disease	2.55 [1.30-5.00]	0.007	2.22 [1.11-4.45]	0.02
Log SYNTAX Score	3.27 [1.79-5.95]	<0.0001		
Log $ACEF_{SCr}$	2.99 [1.16-7.71]	0.02		
Log Clinical SYNTAX Score	2.21 [1.58-3.08]	<0.0001	2.11 [1.47-3.04]	<0.0001
Number of diseased lesions	1.43[1.17-1.73]	<0.0001		
Incomplete revascularisation	1.93 [1.20-3.13]	0.007	1.84 [1.13-3.00]	0.01

CI indicates confidence interval

Summary

The results for the use of the CSS in this group of patients mirror the results from the larger cohort of patients. Of note, is the improvement in the ability to predict mortality and MACCE with the CSS in this 3VD population compared to the larger cohort.

2. Clinical SYNTAX score: calculated using original ACEF in patients with triple vessel disease

Methods

The main manuscript, and section 1 of this appendix, presents the results of the CSS calculated combining the SYNTAX score with a modified ACEF score that uses the creatinine clearance (CrCl, $ACEF_{CrCl}$) as opposed to the serum creatinine (SCr, $ACEF_{SCr}$) as originally described by Ranucci *et al*.[2] The CSS can be calculated using the original ACEF score (SYNTAX score x ACEF score) and the results of this analysis in the 251 (41.4%) patients who had three vessel intervention at the time of the index PCI, and had left ventricular ejection function (LVEF) and creatinine levels recorded at baseline are presented here.

Results

The SYNTAX score ranged from 4 to 56, with a mean ±standard deviation of 22.3±9.8, and a median of 21 (inter-quartile range: 13). The $ACEF_{SCr}$ score ranged from 0.6 to 2.3, with a mean±standard

Supplementary Table 5. Baseline and procedural characteristics of patients

Variable n,(%) unless stated	CSS≤16 N=83	16<CSS≤26 N=84	CSS>26 N=84	P Value
Baseline Characteristics				
Male gender	65 (78.3)	62 (73.8)	67 (79.8)	0.63
Age (years±SD)	58.1±9.0	63.6±8.9	67.8±9.1	<0.0001
Body Mass Index ±SD	28.3±4.0	27.3±3.9	27.7±4.1	0.30
Risk factors				
Previous Myocardial infarction	21 (25.3)	31 (36.9)	34 (40.5)	0.10
Diabetes	11 (19.3)	23 (27.4)	23 (27.4)	0.04
Hypertension	52 (62.7)	60 (71.4)	62 (73.8)	0.26
Hypercholesterolemia	66 (79.5)	61 (72.6)	64 (76.2)	0.58
Family history ischaemic heart disease	40 (48.2)	25 (29.8)	24 (28.9)	0.01
Current smoker	17 (20.5)	14 (16.7)	12 (14.3)	0.56
Peripheral vascular disease	6 (7.2)	7 (8.3)	6 (7.1)	0.95
Chronic obstructive airways disease	1 (1.2)	3 (3.6)	4 (4.8)	0.41
Previous cerebrovascular accident	2 (2.4)	1 (1.2)	1 (1.2)	0.77
Indication for Treatment				
Stable angina	48 (57.8)	47 (56.0)	43 (48.8)	0.47
Unstable angina	29 (34.9)	32 (38.1)	35 (41.7)	0.67
Silent ischemia	6 (7.2)	5 (6.0)	8 (9.5)	0.68
Medications at screening				
Aspirin	70 (84.3)	70 (83.3)	72 (85.7)	0.91
ß-blockers	58 (69.9)	60 (71.4)	60 (71.4)	0.97
ACE-inhibitors/Angiotension-2 blockers	49 (59.0)	37 (44.0)	42 (50.0)	0.15
Statins	56 (67.5)	61 (72.6)	57 (67.9)	0.72

SD indicates standard deviation; CSS, clinical SYNTAX Score; ACE, Angiotensin converting enzyme

Supplementary Table 6. Angiographic and procedural characteristics of study population

Variable n (%) unless stated	CSS≤16 N=83	16<CSS≤26 N=84	CSS>26 N=84	P Value
Ejection fraction	65.9±9.8	61.5±11.9	53.3±10.1	<0.0001
Lesion Characteristics				
Lesion Length (visual)(% of lesions)				0.002
Discreet (<10mm)	184 (63.2)	200 (57.6)	185 (54.1)	
Tubular (10-20mm)	84 (28.9)	84 (24.2)	90 (26.3)	
Diffuse (>20mm)	20 (6.9)	44 (12.7)	50 (14.6)	
Lesion Classification (% of lesions)				0.001
Type A	22 (7.6)	21 (6.2)	20 (5.9)	
Type B1	62 (21.3)	94 (27.6)	76 (22.5)	
Type B2	186 (63.9)	170(49.9)	183 (54.1)	
Type C	21 (7.2)	56 (16.4)	59 (17.5)	
Moderate/Heavy calcification	94 (32.3)	91 (26.2)	131 (38.3)	0.001
Thrombus containing lesions	3 (1.0)	2 (0.6)	0 (0.0)	0.008
Eccentric lesion	248 (85.2)	285 (82.1)	283 (82.7)	0.046
TIMI flow 3	258 (88.7)	305 (87.9)	291 (85.1)	0.36
1.5≤RVD<2.5	9 (3.1)	25 (7.2)	32 (9.4)	0.007
Procedural Characteristics				
Bifurcation requiring double wiring	79 (27.4)	93 (27.9)	115 (33.0)	0.03
Number of stents implanted ±SD	3.9±0.9	4.7±1.5	5.0±1.5	<0.0001
Total stent length (mm)	75.4±21.7	91.8±33.1	96.2±36.0	<0.0001
Maximum dilatation pressure (Atm±SD)	16.7±3.0	16.5±2.9	17.0±2.9	0.53
Direct stenting (% of lesions)	132 (45.4)	121 (34.9)	74 (21.6)	<0.0001
Use of glycoprotein IIb/IIIa inhibitors	28 (33.7)	25 (29.8)	26 (31.0)	0.85
Completeness of Revascularisation	63 (75.9)	55 (65.5)	33 (39.3)	<0.0001
Post procedural Hospital stay (days±SD)	2.8±1.6	3.2±1.6	4.4±3.0	<0.0001

Atm indicates atmosphere; SD, standard deviation; CSS, clinical SYNTAX score; No., number; RVD, reference vessel diameter

deviation of 1.1±0.3, and a median of 1.0 (inter-quartile range: 0.4). The CSS ranged from 4 to 111, with a mean ± SD of 24.9±15.0, and a median of 21.7 (inter-quartile range of 17.8). The 251 patients (980 treated lesions) were divided according to their CSS into tertiles defined as: CSS_{LOW} ≤16 (n=83), 16<CSS_{MID}≤26 (n=84) and CSS_{HIGH}>26 (n=84).

Baseline patient characteristics, together with lesion and procedural data stratified according to CSS tertile are shown in Supplementary Tables 5 and 6. Hierarchical and non-hierarchical outcomes at 1-year follow-up are shown in Supplementary Table 7. Overall the primary end-point of mortality at 1-year was comparable amongst each CSS tertile. MACCE (19.0% CSS_{HIGH} vs. 3.6% CSS_{MID} vs. 6.0% CSS_{LOW}, p=0.002) and repeat revascularisation (14.3% CSS_{HIGH} vs. 1.2% CSS_{MID} vs. 6.0% CSS_{LOW}, p=0.004) were both significantly higher in the CSS_{HIGH} tertile, compared to the lower two groups.

Supplementary Figure 7 demonstrates the rates of death, MI, repeat revascularisation and MACCE according to CSS tertiles during long-term follow-up, whilst the ROC curves for mortality and MACCE at 5-year follow-up are shown in Supplementary Figure 8.

Although the C-statistics for the CSS calculated using the $ACEF_{SCr}$ are inferior to the CSS calculated using the $ACEF_{CrCl}$ for both MACCE (0.59 vs. 0.64) and mortality (0.73 vs. 0.82), the CSS still performed better, in terms of area-under the curve,

Supplementary Table 7. Clinical Outcomes at One Year Follow-up

Variable n,(%) unless stated	CSS≤16 N=83	16<CSS≤26 N=84	CSS>26 N=84	P Value
Hierarchical Events				
Death	0 (0.0)	0 (0.0)	2 (2.4)	0.33
Cerebrovascular Accident	0 (0.0)	1 (1.2)	2 (2.4)	
Myocardial Infarction	1(1.2)	1(1.2)	1(1.2)	
Q wave	0 (0.0)	0 (0.0)	1(1.2)	
Non-Q wave	1 (1.2)	1(1.2)	0 (0.0)	
Repeat Revascularization	4 (4.8)	1 (1.2)	11 (13.1)	
CABG	1 (1.2)	0 (0.0)	3 (3.6)	
PCI	3 (3.6)	1 (1.2)	8 (9.5)	
Any MACCE	5 (6.0)	3 (3.6)	16 (19.0)	0.002
Non-Hierarchical				
Cerebrovascular Accident	0 (0.0)	1 (1.2)	2 (2.4)	0.78
Myocardial Infarction	1 (1.2)	1 (1.2)	2 (2.4)	1.00
Q wave	1 (1.2)	1 (1.2)	1 (1.2)	1.00
Non-Q wave	0 (0.0)	0 (0.0)	1 (1.2)	1.00
Repeat Revascularization	5 (6.0)	1 (1.2)	12 (14.3)	0.004
PCI	4 (4.8)	1 (1.2)	9 (10.7)	0.004
CABG	1 (1.2)	0 (0.0)	3 (3.6)	0.23

PCI indicates percutaneous coronary intervention; CABG, coronary artery bypass grafting; CSS, Clinical SYNTAX Score; MACCE, major adverse cardiovascular and cerebrovascular events

when compared with the SYNTAX score, and the $ACEF_{SCr}$ score (Supplementary Figure 2 and Table 5).

The results of the Cox multi-variate analysis are shown in Supplementary Table 8. The log CSS, SYNTAX score and $ACEF_{SCr}$ score were all uni-

Supplementary Table 8. Univariate and multivariable predictors of MACCE at 5-years follow-up.

Variable	Univariate predictors of MACCE at 5 years		Multivariable predictors of MACCE at 5 years	
	95% [CI]	P value	95% [CI]	P value
Age	1.03 [1.00-1.06]	0.03		
Diabetes	2.27 [1.39-3.73]	0.001	1.68 [1.00-2.82]	0.048
Current Smoking	0.50 [0.23-1.01]	0.08		
Peripheral vascular disease	2.55 [1.30-5.00]	0.007	2.56 [1.24-5.28]	0.011
Log SYNTAX Score	15.3 [3.87-60.55]	<0.0001		
Log $ACEF_{SCr}$	12.2 [1.40-10.99]	0.02		
Log Clinical SYNTAX Score	8.82 [3.12 24.91]	<0.0001		
Number of diseased lesions	1.43[1.17-1.73]	<0.0001		
Incomplete revascularisation	1.93 [1.20-3.13]	0.007		

CI indicates confidence interval

variate predictors of long-term MACCE. After adjustment only the presence of diabetes and peripheral vascular disease, were independent predictors of MACCE at 5-years follow-up.

Summary

These results indicate that the CSS calculated using the original ACEF score is still superior to the SYNTAX score and $ACEF_{SCr}$ score in terms of its ability to predict MACCE and mortality, however its appears to be poorer than the CSS calculated using the modified ACEF score which utilizes the creatinine clearance, in patients with 3VD, or 2- and 3-VD as indicated in Supplementary Figure 2, together with Table 5, and Figure 4 of the main manuscript

3. Clinical SYNTAX score compared to a SYNTAX-euroSCORE combination

Methods

The European System for Cardiac Operative Risk Evaluation (euroSCORE)[3] relies on patient clinical characteristics, and has been used for many years to predict post-operative mortality in patients undergoing CABG. Recent data indicate that it may also have a role in the risk assessment of patients having PCI.[4-6] As opposed to the ACEF score which uses just three variables, the additive euroSCORE ($EURO_{ADD}$) relies on 17 clinical parameters, 14 of which are relevant for PCI; importantly knowledge of the coronary anatomy is not required. Studies suggest that in those patients at highest risk, the $EURO_{ADD}$ tends to under-estimate risk, and in these situations the logistic euroSCORE ($EURO_{LOG}$), is advised.[7] Of note, the benefits of using the $EURO_{ADD}$ and $EURO_{LOG}$ have already been examined in Table 5, Figure 3 and Figure 4 of the main manuscript, and are further examined in Supplementary Figure 2.

The Clinical SYNTAX score has been calculated using a simple 3 variable patient based score, however to determine the effect of adding more clinical variables the SYNTAX score was combined with the $EURO_{ADD}$ and $EURO_{LOG}$ using the formula: SYNTAX-euroSCORE= [SYNTAX score] x [$EURO_{ADD}$] or [SYNTAX score] x [$EURO_{LOG}$]. The analysis was performed in same cohort of 239 patients described in this appendix.

Results

Supplementary Figures 3 shows the 5-year MACCE-free survival stratified according to tertiles of the CSS, SYNTAX-$EURO_{ADD}$, and the SYNTAX-$EURO_{LOG}$. Overall there was no significant difference between corresponding tertiles for the CSS, SYNTAX-$EURO_{ADD}$ and SYNTAX-$EURO_{LOG}$.

Patients in the lowest SYNTAX-$EURO_{ADD}$ tertile had significantly better outcomes than those in the mid (p[log-rank]=0.005) and highest (p[log-rank]<0.001) tertile, whilst no significant difference in outcomes existed between patients in the mid and high SYNTAX-$EURO_{ADD}$ tertile (p[log-rank]=0.34). Conversely the outcomes according to the SYNTAX-$EURO_{LOG}$ mirrored those of the CSS, with no significant difference in events between the lower two SYNTAX-$EURO_{LOG}$ tertiles (p[log-rank]=0.41), and significantly more events in the highest SYNTAX-$EURO_{LOG}$ tertile when compared to the low (p[log-rank]=0.005) and mid (p[log-rank]=0.04) tertile.

The ROC curves for MACCE and mortality at 5-year follow-up for the CSS, SYNTAX-$EURO_{ADD}$, and SYNTAX-$EURO_{LOG}$, which are shown in Supplementary Figure 2, demonstrate comparable C-statistics for all three scores.

Summary

These results indicate that there is no added advantage in patients with 3VD of combining the SYNTAX score with a detailed patient based score such as the euroSCORE (either additive or logistic), when compared to the combination of the SYNTAX score and a simple three variable patient based score, such as the $ACEF_{CrCl}$ score.

4. Clinical SYNTAX score compared to Mayo Clinic Risk Score.

The Mayo Clinic Risk score (MCRS) is a validated patient based risk model, designed as a bed side tool, which uses a mixture of seven clinical variables (age, creatinine, LVEF, and presence of pre-procedural shock, MI within 24 hours, congestive cardiac failure and peripheral vascular disease) to predict in-hospital mortality after either PCI or CABG.[8]

Results

As mentioned in the main manuscript the ACEF is not currently validated for use in PCI, however as shown in Table 5, the C-statistic for the validated MCRS and the $ACEF_{CrCl}$ for both 5-year MACCE and mortality were similar providing some in-direct justification for the use of the ACEF score as an integral part of the CSS.

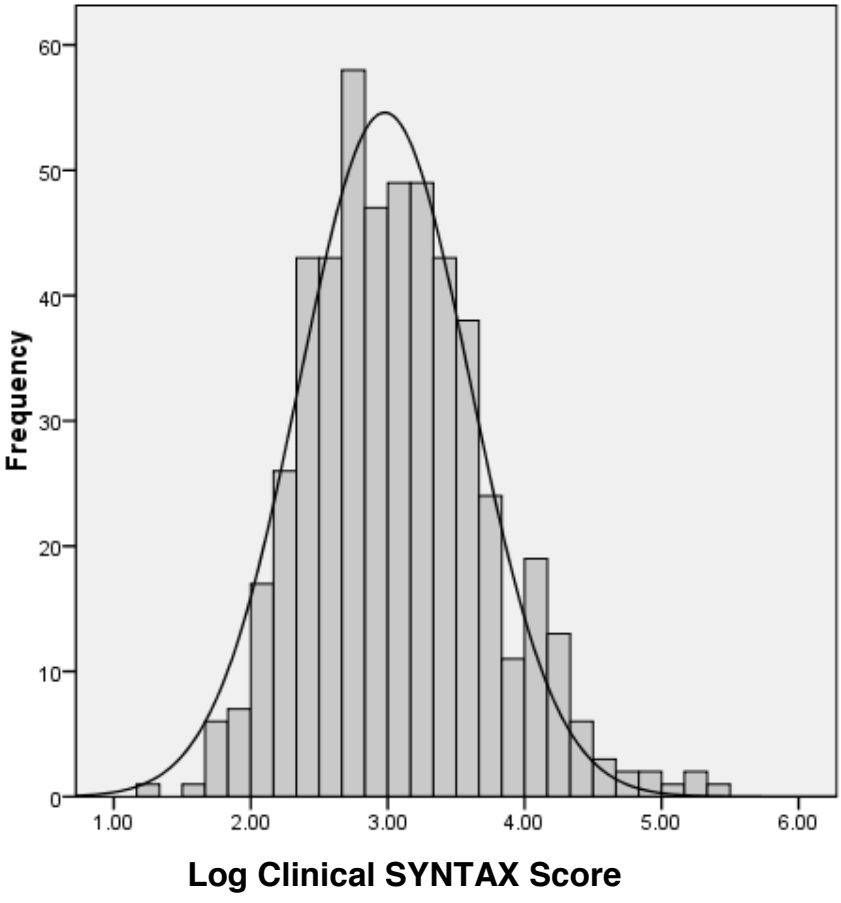
Supplementary Figure 4 shows the 5-year MACCE-free survival stratified according to tertiles of the CSS, and the MCRS in patients with 3VD. Overall there were no significant differences in outcomes between corresponding tertiles for the CSS, and the MCRS. In addition, as with the CSS and SYNTAX-$EURO_{LOG}$, there were no significant differences in event rates between patients in the lower and mid tertiles for the MCRS ($MCRS_{LOW}$ vs. $MCRS_{MID}$, p[log rank]=0.77), whilst outcomes were significantly poorer in the highest tertile compared to the lower two tertiles ($MCRS_{LOW}$ vs. $MCRS_{HIGH}$, p[log rank]=0.002 and $MCRS_{MID}$ vs. $MCRS_{HIGH}$, p[log rank]=0.009). The ROC curves for MACCE and mortality at 5-year follow-up for the CSS, and MCRS are shown in Supplementary Figure 2. Consistent with the other scores tested in this analysis, there was a reduction in C-statistics between the 3VD patient cohort, and the 2- and 3-VD patient cohort (Table 5).

Summary

These results indicate that PCI risk scores based purely on clinical characteristics (e.g. the MCRS) are superior to those scores incorporating anatomical characteristics (e.g. SYNTAX score or CSS) for the prediction of mortality, but inferior for the prediction of MACCE.

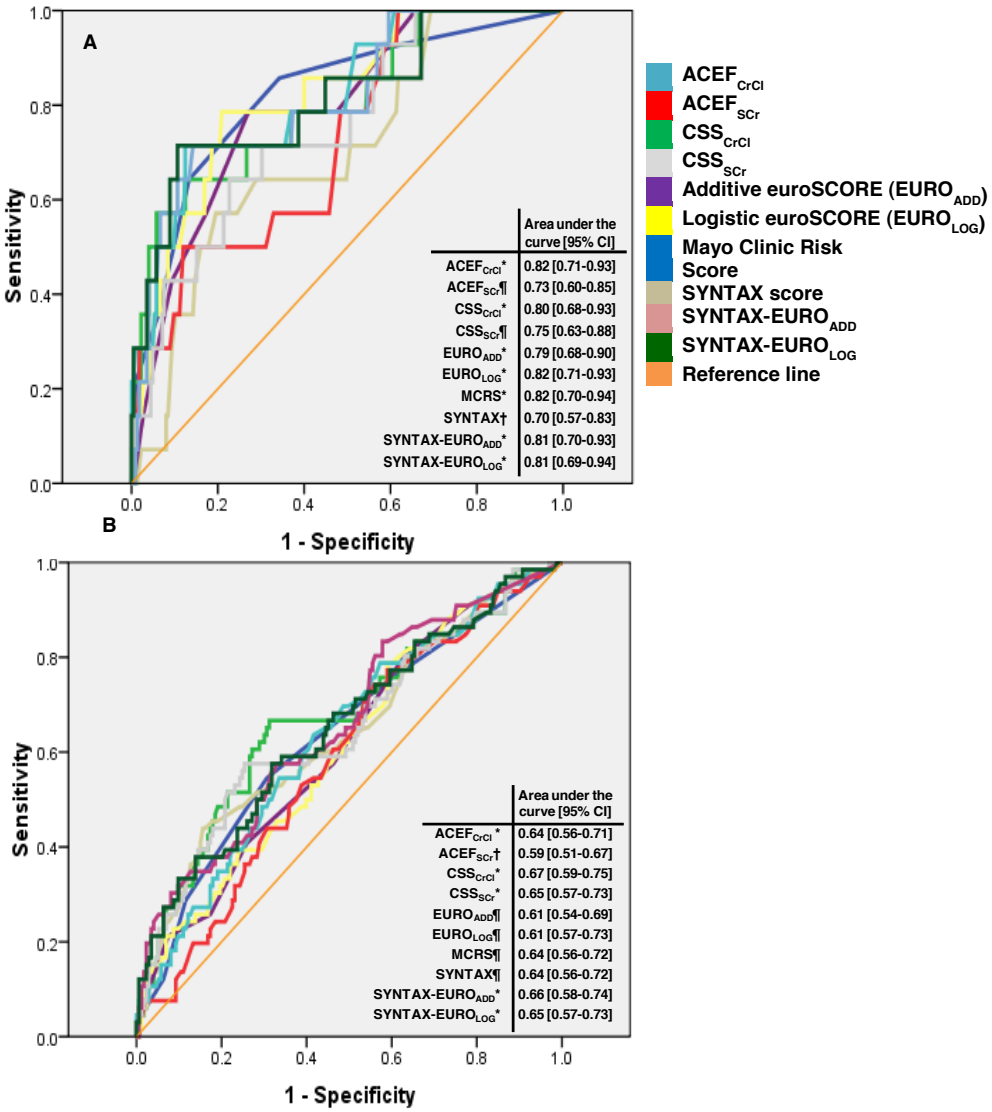
.

Supplementary Figure 1



Supplementary Figure 1: Logarithmic distribution of the Clinical SYNTAX score (CSS). The CSS is normally distributed after logarithm transformation.

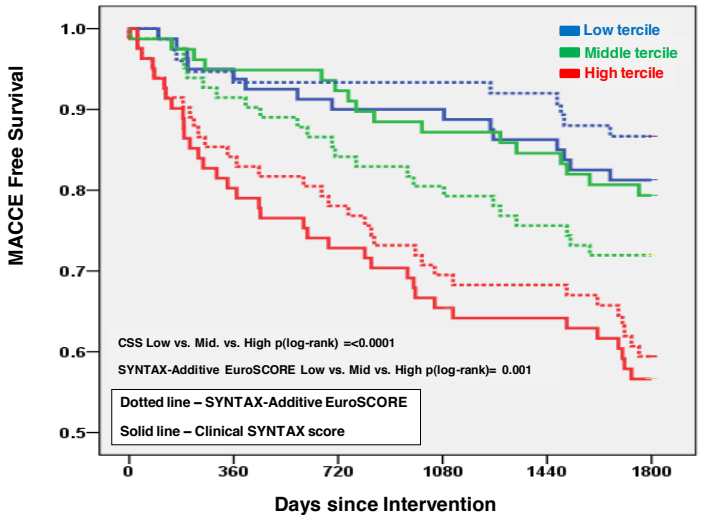
Supplementary Figure 2



Supplementary Figure 2: ROC curves for (A) mortality, (B) MACCE at 5-years follow-up for different risk scores amongst the 239 patients in the ARTS-II study who had treatment for triple vessel disease, and had serum creatinine, left ventricular function and body weight recorded at baseline.*p<0.001, †p<0.05, ¶ p<0.01.

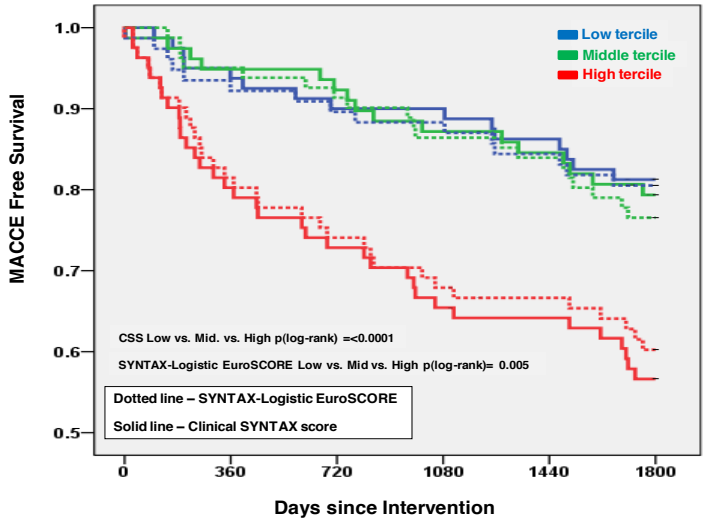
Supplementary Figure 3

A



Days	0	360	720	1080	1440	1800
Patients at risk	239	214	203	193	185	162

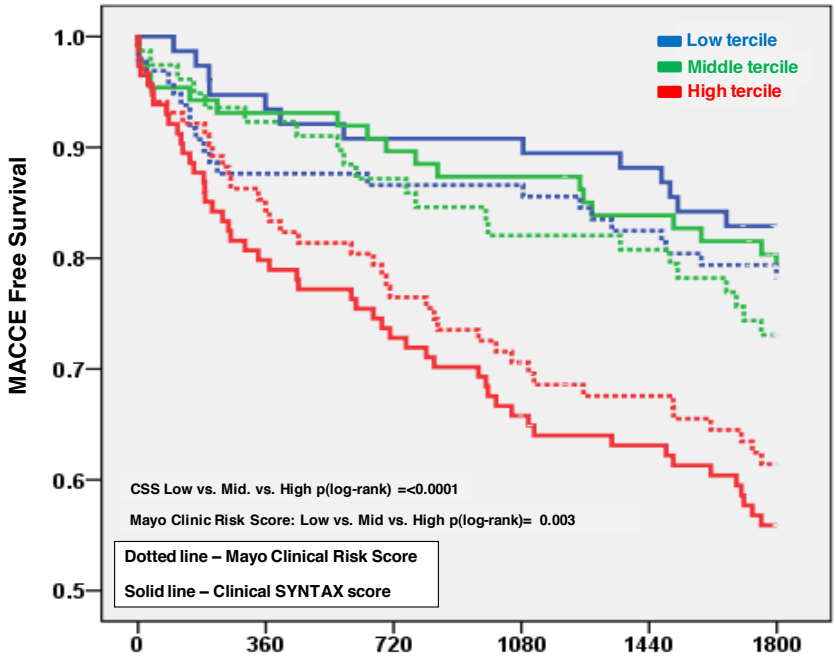
B



Days	0	360	720	1080	1440	1800
Patients at risk	239	214	203	193	185	162

Supplementary Figure 3: Kaplan Meier curve showing the 5-year MACCE-free survival stratified according to tertiles of the CSS, and (A) the SYNTAX-EURO$_{ADD}$, and (B) the SYNTAX-EURO$_{LOG}$.

Supplementary Figure 4

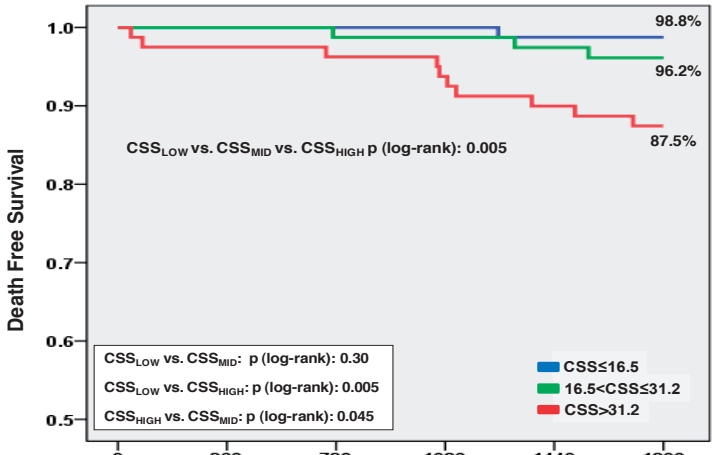


Days	0	360	720	1080	1440	1800
Patients at risk	239	214	203	193	185	162

Supplementary Figure 4: Kaplan Meier curve showing the 5-year MACCE-free survival stratified according to tertiles of the CSS, and the MCRS.

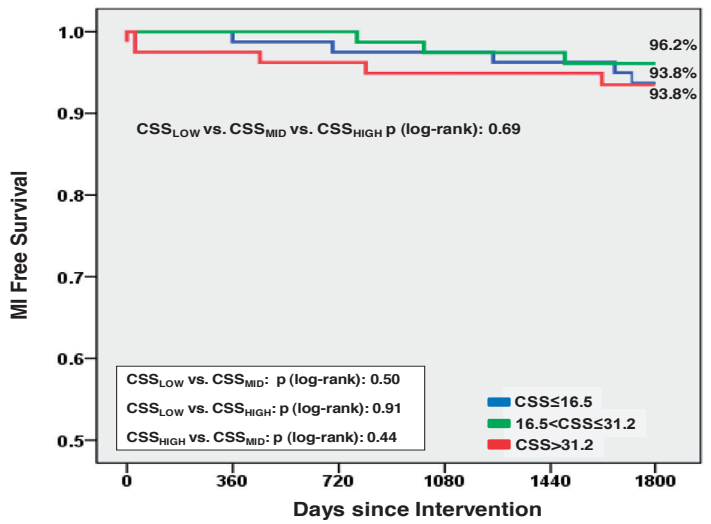
Supplementary Figures 5A and 5B

A



Days	0	360	720	1080	1440	1800
Patients at risk	239	237	235	233	225	207

B

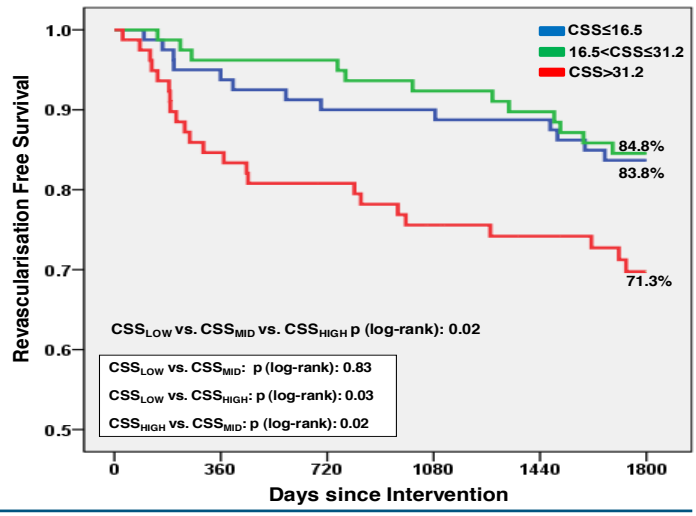


Days	0	360	720	1080	1440	1800
Patients at risk	239	234	230	226	218	198

Supplementary Figure 5: Kaplan Meier curves for (A) death, (B) myocardial infarction, (C) repeat revascularisation and (D) MACCE at 5-years follow-up amongst 239 patients with three vessel disease in the ARTS-II study with a Clinical SYNTAX score.

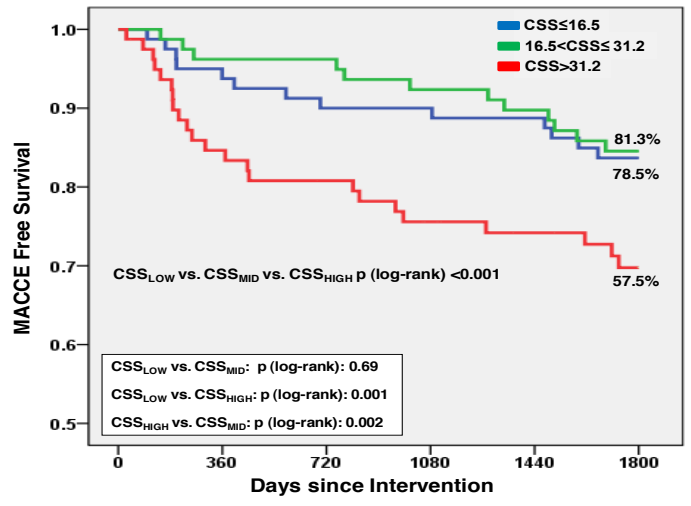
Supplementary Figures 5C and 5D

C



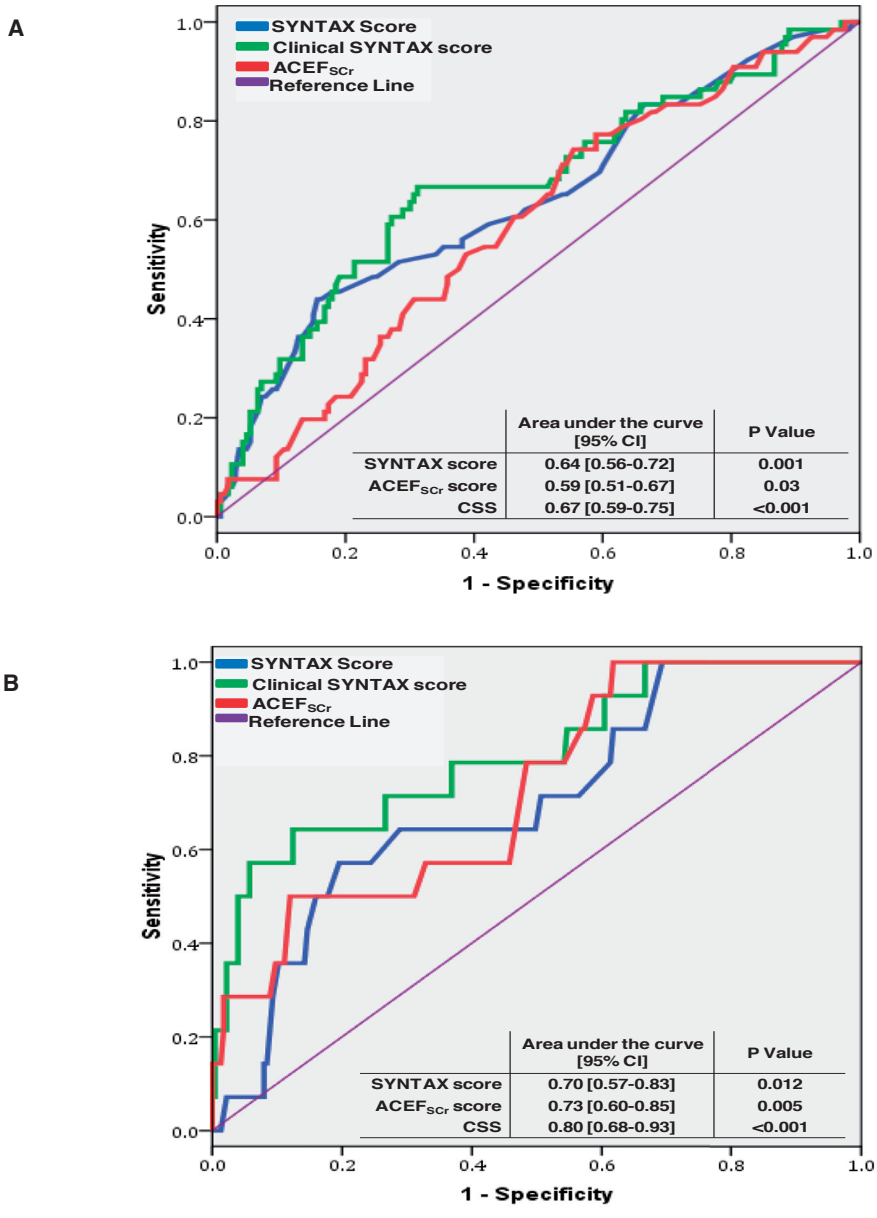
Days	0	360	720	1080	1440	1800
Patients at risk	239	217	209	200	191	167

D



Days	0	360	720	1080	1440	1800
Patients at risk	239	214	203	193	185	162

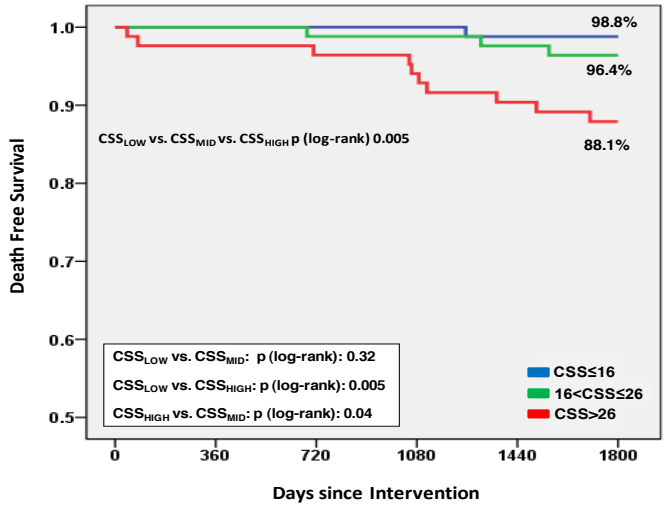
Supplementary Figure 6



Supplementary Figure 6: ROC curves for (A) mortality, (B) MACCE at 5-years follow-up amongst the 239 patients with three vessel disease in the ARTS-II study with a Clinical SYNTAX score.

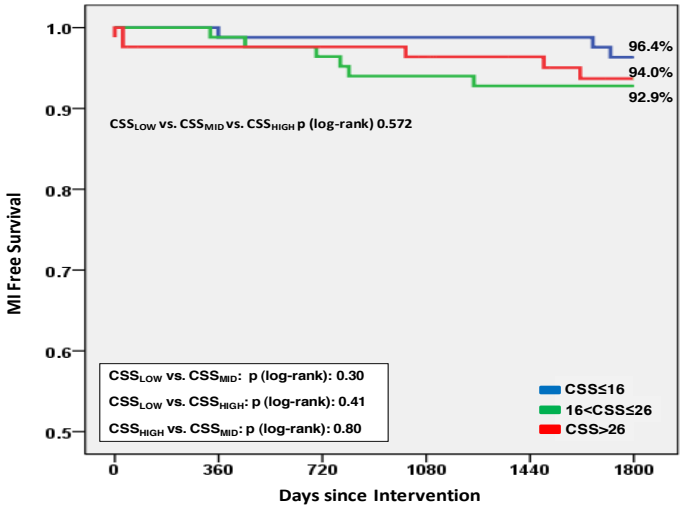
Supplementary Figures 7A and 7B

A



Days	0	360	720	1080	1440	1800
Patients at risk	251	249	247	246	235	217

B

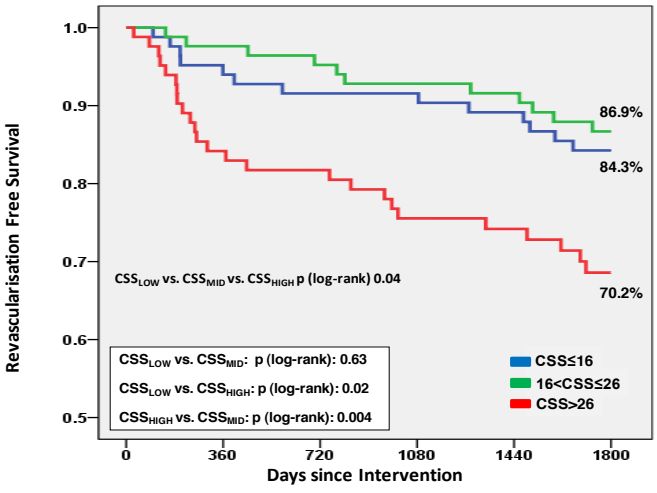


Days	0	360	720	1080	1440	1800
Patients at risk	251	245	241	237	228	208

Supplementary Figure 7: Kaplan Meier curves for (A) death, (B) myocardial infarction, (C) repeat revascularisation and (D) MACCE at 5-years follow-up amongst all 251 patients in the ARTS-II study with a Clinical SYNTAX score calculated using the serum creatinine.

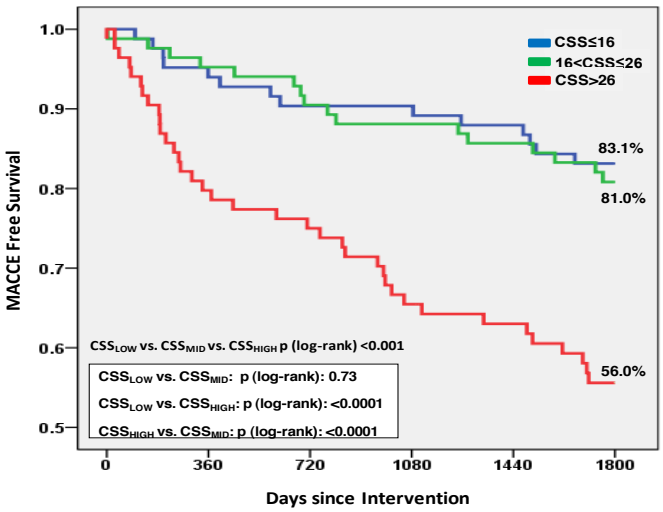
Supplementary Figures 7C and 7D

C



Days	0	360	720	1080	1440	1800
Patients at risk	251	229	221	212	202	177

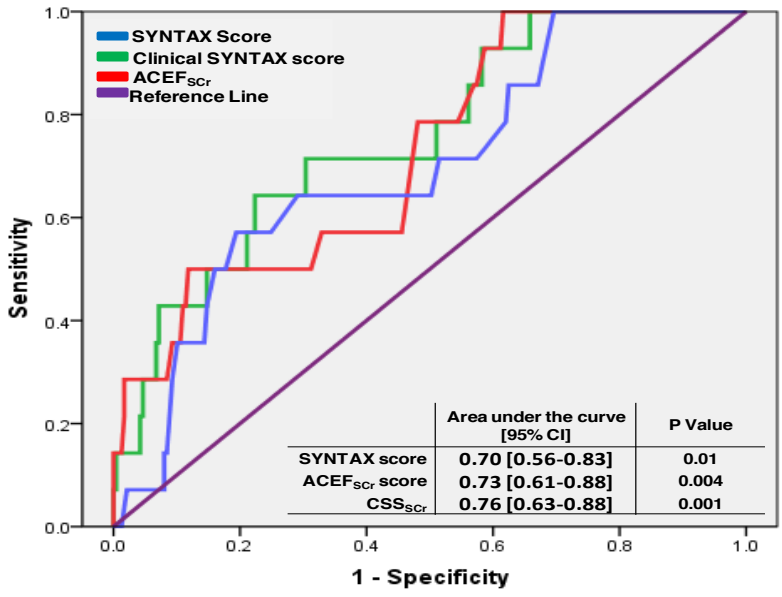
D



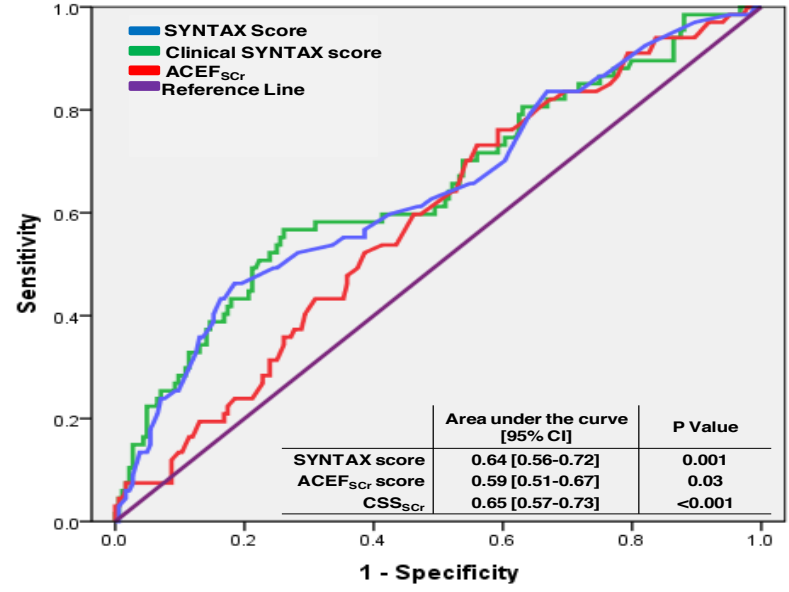
Days	0	360	720	1080	1440	1800
Patients at risk	251	234	230	222	218	210

Supplementary Figure 8

A



B



Supplementary Figure 8: Receiver Operator Curves for (A) mortality, (B) MACCE at 5-years follow-up amongst all 251 patients in the ARTS-II study with a Clinical SYNTAX score calculated using the serum creatinine.

Supplementary References

1. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med. 2009;360(10):961-972.

2. Ranucci M, Castelvecchio S, Menicanti L, Frigiola A, Pelissero G. Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony. Circulation. 2009;119(24):3053-3061.

3. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg. 1999;16(1):9-13.

4. Romagnoli E, Burzotta F, Trani C, Siviglia M, Biondi-Zoccai GG, Niccoli G, Leone AM, Porto I, Mazzari MA, Mongiardo R, Rebuzzi AG, Schiavoni G, Crea F. EuroSCORE as predictor of in-hospital mortality after percutaneous coronary intervention. Heart. 2009;95(1):43-48.

5. Kim YH, Ahn JM, Park DW, Lee BK, Lee CW, Hong MK, Kim JJ, Park SW, Park SJ. EuroSCORE as a predictor of death and myocardial infarction after unprotected left main coronary stenting. Am J Cardiol. 2006;98(12):1567-1570.

6. Garg S, Serruys PW. Interventional cardiology: Coronary angioplasty: do we need to EuroSCORE? Nat Rev Cardiol. 2009;6(4):267-268.

7. Roques F, Michel P, Goldstone AR, Nashef SAM. The logistic EuroSCORE. Eur Heart J. 2003;24(9):882-.

8. Singh M, Rihal CS, Lennon RJ, Spertus J, Rumsfeld JS, Holmes DR. Bedside Estimation of Risk From Percutaneous Coronary Intervention: The New Mayo Clinic Risk Scores. Mayo Clinic Proceedings. 2007;82(6):701-708.

Chapter 4.6

Clinical and angiographic risk assessment in left main disease

J Am Coll Cardiol Intv 2010; 3(9):891-901

Scot Garg, Gregg W. Stone, Arie-Pieter Kappetein, Joseph Sabik III, Charles Simonton, Patrick W. Serruys

STATE-OF-THE-ART PAPER

Clinical and Angiographic Risk Assessment in Patients With Left Main Stem Lesions

Scot Garg, MB, ChB,* Gregg W. Stone, MD, PhD,‡ Arie-Peter Kappetein, MD, PhD,† Joseph F. Sabik III, MD,§ Charles Simonton, MD,‖ Patrick W. Serruys, MD, PhD*

Rotterdam, the Netherlands; New York, New York; Cleveland, Ohio; and Santa Clara, California

Percutaneous coronary intervention of unprotected left main stem lesions has been shown to be a suitable alternative to cardiac surgery in selected patients, emphasizing the need for appropriate risk stratification prior to selection of revascularization modality. Several risk models based on clinical and angiographic variables have been developed to guide patient selection, each of which has significant limitations. This paper reviews contemporary and newly proposed risk models for patients undergoing left main stem revascularization.
(J Am Coll Cardiol Intv 2010;3:891–901)

The left main stem is rarely longer than 15 mm, but in view of its extensive myocardial distribution, it is a vitally important part of the coronary arterial tree. Unprotected left main stem (ULM) lesions carry the worst prognosis of any coronary lesion, mainly because of the extensive amount myocardium placed at jeopardy by such lesions. The mortality for nonrevascularized ULM disease has been reported to be as high as 37% at 3 years (1). The optimal therapy for patients with ULM disease remains the subject of continuing debate (2,3).

Coronary artery bypass grafting (CABG) was established as the gold standard for treatment of patients with ULM disease on the basis of trials that randomly assigned patients to CABG versus medical therapy (4). Historically, patients with ULM disease have been excluded from randomized trials comparing percutaneous coronary intervention (PCI) to CABG (5,6). Nevertheless, surveys of real-world practice have indicated that approximately one-third of patients with ULM lesions are treated by PCI (7). Percutaneous coronary intervention for ULM disease is usually "accepted" when: 1) patients require bailout ULM PCI following complications during PCI; 2) ULM disease occurs in the setting of acute myocardial infarction (MI); 3) the left main is protected by a functional coronary bypass graft; 4) patients are turned down for CABG; or 5) patients refuse surgery. Less settled are the indications for left main PCI in patients who are good candidates for CABG.

Recently, important studies have been published specifically relating to selection of revascularization modalities of the ULM (8). These data suggest that in certain groups of patients with ULM disease, such as those with ostial or shaft lesions, revascularization with PCI remains a valid alternative therapy to CABG (8–10). Consequently, in the recent focused update from the American College of Cardiology/American Heart Association (ACC/AHA), PCI for ULM lesions has been upgraded from a Class III to a Class IIb indication in those patients with "anatomical conditions which are associated with a low risk from PCI procedural complications and clinical conditions which predict adverse surgical outcomes" (11).

In view of this recommendation, there is now a clear need to appropriately identify which patients with ULM should undergo revascularization with PCI or CABG. This highly relevant topic was briefly touched upon in a recent white paper on

*From the Department of Interventional Cardiology, Erasmus Medical Center, Rotterdam, the Netherlands; †Department of Cardiothoracic Surgery, Erasmus Medical Center, Rotterdam, the Netherlands; ‡Columbia University Medical Center and the Cardiovascular Research Foundation, New York, New York; §Department of Thoracic and Cardiovascular Surgery, The Cleveland Clinic Foundation, Cleveland, Ohio; and ‖Abbott Vascular, Santa Clara, California. Dr. Stone a member of the scientific advisory board of Boston Scientific and Abbott Vascular. Dr. Kappetein is a member of the Steering Committee in a trial funded by Boston Scientific and in a trial funded by Abbott Vascular. Dr. Sabik is a consultant for Medtronic, Inc. and has received speaker fees from Edwards Lifesciences. Dr. Simonton is a Chief Medical Officer for Abbott Vascular. All other authors report that they have no relationships to disclose. This manuscript follows a similarly titled presentation given by Patrick W. Serruys at the American College of Cardiology meeting in Atlanta 2010.

Manuscript received May 24, 2010, accepted June 11, 2010.

PCI for ULM (8); however, its importance to everyday clinical practice necessitates a more detailed review. The aim of this paper is to review the currently available methods for risk stratifying those patients with ULM lesions requiring revascularization.

Does the ULM Need Revascularization?

Prior to embarking on the assessment of risk and formulation of a revascularization strategy for patients with an angiographically identified ULM lesion, it is important to determine whether the lesion is in actual need of revascularization (i.e., is hemodynamically significant). The anatomic location of the ULM, together with vessel foreshortening and overlap makes angiographic visualization and accurate lesion assessment notoriously difficult. Specifically, ostial left main lesions may appear more significant than they truly are due to catheter-induced artifacts, and the severity of distal bifurcation lesions may be notoriously difficult to accurately delineate. In part due to these reasons, lesions in the left main stem are subject to the greatest degree of angiographic intraobserver and interobserver variability compared with lesions located elsewhere in the coronary tree (12,13). Importantly, studies have shown a favorable prognosis in patients with ULM lesions that are not functionally significant (14). Conversely, bypass grafts placed to nonhemodynamically significant lesions have a high rate of early failure (15). Therefore, in practice, a suspicious or borderline ULM lesion warrants further evaluation with intravascular ultrasound, coronary computed tomography, and/or functional assessment with fractional flow reserve (12,14,16), before either suggesting the need for revascularization or dismissing the need altogether.

Abbreviations and Acronyms

ACC = American College of Cardiology

ACEF = Age, Creatinine, Ejection Fraction

AHA = American Heart Association

CABG = coronary artery bypass grafting

CSS = clinical SYNTAX score

EuroSCORE = European System for Cardiac Operative Risk Evaluation

GRC = Global Risk Classification

MACCE = major adverse cardiovascular and cerebrovascular events

MACE = major adverse cardiac events

MCRS = Mayo Clinic risk score

MI = myocardial infarction

PCI = percutaneous coronary intervention

STS = Society of Thoracic Surgery

SXscore = SYNTAX score

ULM = unprotected left main stem

Is There a Need for Risk Stratification in ULM Revascularization?

An assessment of procedural risk is imperative once the decision has been made that revascularization of the ULM is required. Technological advances, such as the availability of left ventricular assist devices during high-risk cases (17), have increased the number of patients in whom PCI is now feasible; however, the appropriateness of ULM intervention cannot be considered without a proper assessment of the risk and benefits of both PCI and CABG.

Procedural risk stratification (for both PCI and CABG) serves several purposes. In the short term, it provides clinicians with supplementary information that can help guide treatment strategy, particularly in view of the latest guidelines "allowing," with a Class IIb recommendation, ULM PCI only in cases in which procedural success is high and procedural risk is low. In addition, and perhaps most importantly, procedural risk stratification enables patients to be more adequately informed about the risks/benefits of the alternative revascularization strategies available, allowing them to make an informed decision. Ultimately, it is the duty of a clinician to convey full and understandable information to their patients (18). Contrary to popular belief, after being offered CABG, very few patients actually refuse. In the SYNTAX (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery) trial, the rate of refusal was 0.4% (9). Surgeons raise the valid concern that patients who refuse CABG may not have had the opportunity to discuss matters with a surgeon and may have been swayed in their decision by a relatively 1-sided discussion (1). Good clinical practice should ensure that patients with significant ULM disease have the opportunity to speak to both a cardiac surgeon and interventional cardiologist together (the "Heart Team," often with a noninvasive cardiologist) to enable an interactive discussion wherein all issues are discussed and addressed (1). With the current state of evidence, ad hoc ULM PCI should not be performed in the stable patient.

Risk stratification models, and collections of decisions resulting from patient-physician discussions, provide a vital measure of patient care and may identify future directions to further improve outcomes. In terms of clinical governance and the public reporting of results, risk stratification is imperative to enable a suitable comparison of performance between clinicians and government standards. Their significance is further enhanced as it becomes increasingly essential for clinicians to be able to justify clinical decisions to patients, peers, and regulatory bodies.

What Methods of Risk Stratification Are Available for Patients With ULM Lesions?

A variety of different methods of stratifying risk in patients undergoing ULM revascularization is available; however, each has been applied to different study populations, limiting the comparisons that can be made among different risk models. In essence, risk models can be divided into those using clinical-based variables, those using angiographic data, and those using a combination of both. Table 1

Table 1. Summary of Contemporary and Newly Developed Risk Models for Assessment of Risk in Patients Undergoing Revascularization

Risk Model	Number of Variables Used to Calculate Score		Validated in PCI/CABG		Specific Evaluation in ULM Patients?
	Clinical	Angiographic	PCI	CABG	
EuroSCORE (9,19–28)	17	0	+	+	+
Mayo Clinic Risk Score (30–32)	17	0	+	+	–
ACEF (33)	3	0	–	+	–
AHA/ACC lesion classification (36–38,40)	0	11 (per lesion)	+	–	+
SYNTAX score (6,9,24,26,34,39–48)	0	11 (per lesion)	+	+	+
Society of Thoracic Surgery score (31,49–51)	40	2	–	+	–
Clinical SYNTAX score (52)	3	11 (per lesion)	+	–	–
Global Risk Classification (54)	17	11 (per lesion)	+	+	+

AHA/ACC = American Heart Association/American College of Cardiology; ACEF = Age, Creatinine, Ejection Fraction; CABG = coronary artery bypass grafting surgery; EuroSCORE = European System for Cardiac Operative Risk Evaluation; PCI = percutaneous coronary intervention; SYNTAX = Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery; ULM = unprotected left main stem.

summarizes various contemporary risk models that are described in more detail herein.

Clinical-Based Scores

These risk scores only incorporate clinical variables and do not require any data from the angiogram. They offer the advantage of being able to be computed relatively quickly, usually at the bedside, and principally include variables that are not subject to user interpretation, thereby ensuring excellent reproducibility.

EuroSCORE. The European System for Cardiac Operative Risk Evaluation (EuroSCORE) (19) is an additive clinical score, calculated using 17 different objective clinical variables (Table 2), which has been used since 1999 to predict in-hospital mortality in patients undergoing cardiac surgery (19). Subsequent studies have confirmed the ability of the EuroSCORE to also predict long-term mortality (20–22).

There have been no dedicated studies of the EuroSCORE (additive or logistic) in patients with isolated ULM lesions

Table 2. The Additive EuroSCORE

		Score
Patient characteristics		
Age	Per 5 years or part thereof over the age of 60 years	1
Sex	Female	1
Chronic pulmonary disease	Long-term use of bronchodilators or steroids for respiratory disease	1
Peripheral arteriopathy	*Claudication, carotid stenosis >50%, previous or planned intervention on the abdominal aorta, limb arteries, or carotids	2
Neurological dysfunction	Severely affected mobility or day-to-day function	2
Previous cardiac surgery	Previous opening of the pericardium	3
Serum creatinine	Pre-operatively >200 μmol/l	2
Active endocarditis	Antibiotic therapy at time of surgery	3
Critical pre-operative state	*Pre-operative cardiac arrest, ventilation, renal failure, inotropic support, intra-aortic balloon pump use, ventricular arrhythmia	3
Cardiac-related factors		
Unstable angina	Rest pain requiring IV nitrates	2
Left ventricular function	Moderate (30%–50%) Poor (<30%)	1 3
Recent MI	Within 90 days	2
Pulmonary hypertension	Systolic pulmonary pressure >60 mm Hg	2
Operation-related factors		
Emergency	Operation performed before the start of next working day	2
Other than isolated CABG	Major cardiac procedure other than or in addition to CABG	2
Surgery on thoracic aorta		3
Post-infarct septal rupture		4

The additive EuroSCORE is calculated by summating the individual score from 17 different variables (19). *Any of the following.
IV = intravenous; MI = myocardial infarction; other abbreviations as in Table 1.

undergoing surgical revascularization. However, the initial validation of these scores utilized a large patient database, which included over 4,000 (22%) patients with a ULM lesion (19,23), thereby indirectly confirming the utility of the EuroSCORE in the assessment of patients undergoing CABG for ULM disease.

The utility of using the EuroSCORE in patients undergoing PCI has been assessed in the multicenter randomized SYNTAX study (9,24) and several additional nonrandomized studies (25–28). Four of these studies specifically evaluated the EuroSCORE in patients with ULM disease (24–27), with most except the study by Kim et al. (27) including a surgical treatment arm for the comparison of outcomes.

All studies have identified the additive EuroSCORE as an independent predictor of major adverse cardiovascular and cerebrovascular events (MACCE) in patients with ULM disease undergoing PCI (24–27). In addition, all studies that include a surgical control group have reported that the additive EuroSCORE is an independent predictor of MACCE for patients with a ULM lesion undergoing CABG (24–26). In the left main stem subgroup of the SYNTAX study, the additive EuroSCORE was shown to be an independent predictor of MACCE at 1-year follow-up irrespective of the method of revascularization (odds ratio [OR]: 1.21; 95% confidence interval [CI]: 1.12 to 1.32; $p < 0.001$) (24). Rodés-Cabau et al. (25) reported similar results among 249 octogenarians with ULM disease, with a EuroSCORE ≥ 9 identified as the best predictor of MACCE after PCI and CABG out to a mean of 23 months of follow-up (25). The C-statistic for the ability of the EuroSCORE to predict MACCE was reported as 0.65. More recently, retrospective analysis of the large MAIN COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty versus Surgical Revascularization from Multicenter Registry), which included 1,580 patients with ULM, demonstrated that the additive EuroSCORE was an independent predictor of death/MI/stroke in patients having PCI or CABG out to 3-year follow-up (26).

In a study without a comparative surgical arm, Kim et al. (27) evaluated the potential of the EuroSCORE in 324 patients undergoing PCI for ULM disease, at a median of 26.3 months of follow-up. A EuroSCORE >5, commonly accepted as a high-risk surgical group (19), was shown to be an independent predictor of death/MI (hazard ratio [HR]: 3.4; $p = 0.02$), with a C-statistic for the ability of the EuroSCORE to predict death/MI of 0.61. In contrast, Romagnoli et al. (28) reported a C-statistic of 0.91 for the prediction of in-hospital mortality using the EuroSCORE. The superior C-statistic in this report (28) may be attributed to Romagnoli et al. limiting outcome measures to only the hard end point of mortality and restricting the period of follow-up to only in-hospital events. Of note, the C-statistic fell to 0.56 when assessing procedural failure.

Concerns that the additive EuroSCORE underestimated risk in surgical patients deemed to be at the highest risk (29) led to the development of the logistic EuroSCORE. In the setting of PCI, only Romagnoli et al. (28) have assessed the performance of the logistic EuroSCORE, which was subsequently shown to have a predictive ability that was similar to the additive EuroSCORE.

In summary, the limited studies that have assessed the additive EuroSCORE in patients with ULM disease suggest that the EuroSCORE in isolation is probably of little use in determining selection of revascularization strategy, as patients with high EuroSCORE have a high risk of adverse events following either PCI or CABG. Nevertheless, it is clear that the EuroSCORE is an effective method of identifying which patients, treated with PCI or CABG, are at high risk of mortality and/or MACCE. The role of the logistic EuroSCORE is as yet undetermined.

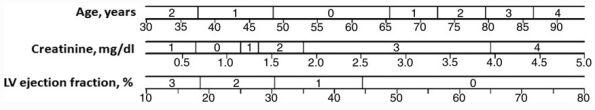
Mayo Clinic risk score. The Mayo Clinic risk score (MCRS) uses a mixture of 7 clinical variables to predict in-hospital mortality after revascularization with either PCI or CABG (Table 3). The MCRS has been validated in patients having PCI and CABG (30,31); however, no studies have been performed specifically in patients with ULM lesions. The only study to report the MCRS and specify the number of patients with a ULM lesion enrolled only 96 ULM patients, comprising 1.3% of the overall study cohort (32). This small group is clearly insufficient to allow extrapolation of the overall study results to patients with ULM disease in general. Therefore, the utility of using the MCRS for either quantifying procedural risk and/or selecting revascularization strategy in patients with ULM disease remains currently undefined.

ACEF score. The Age, Creatinine, Ejection Fraction (ACEF) score (33) is calculated using the formula [patient age ÷ ejection fraction (%)] + [1 if creatinine >2 mg/dl]. The only published data at present relate to patients undergoing elective CABG, where the ACEF score was shown to have a similar accuracy and calibration for in-hospital mortality compared with other more complicated surgical risk scores such as the EuroSCORE and the Cleveland Clinic Score. The development and validation of this score included 8,648 patients; however, the proportion of patients with a ULM lesion was not specified. Furthermore, as with the MCRS, the value of the ACEF score in either determining revascularization strategy and/or procedural risk in patients undergoing PCI is as yet undetermined by virtue of the lack of any data in PCI patients. Ultimately, the role of the ACEF score in the assessment of patients with ULM disease requires further investigation.

In summary, the different clinical-based risk scores have been found to be useful in predicting early and late mortality and MACCE in patients undergoing PCI and/or CABG.

Table 3. The Mayo Clinic Risk Score

Variable	Points
Age, yrs	See below
Creatinine, mg/dl	See below
Left ventricular ejection fraction, %	See below
Pre-procedural shock	9
Myocardial infarction <24 h	4
Congestive heart failure on presentation (without acute MI or shock)	3
Peripheral vascular disease	2



The Mayo Clinic risk score is calculated using data from 7 individual variables, each of which have their own weighted score (30).
Abbreviations as in Table 2.

However, no clinical-based score has been demonstrated to discriminate the relative early procedural risk or late survival between PCI and CABG.

Angiographic-Based Scores

Several angiographic-based scores have been proposed that are independent of patient clinical variables, being calculated using only angiographic data. This has obvious implications for the timing of risk stratification. More importantly, however, the intervariability inherent in angiographic assessment introduces a subjective element to the assessment of risk when using angiographic-based scores (34,35).

ACC/AHA lesion classification. The ACC/AHA lesion classification was 1 of the original angiographic scoring systems; it was first devised in 1986 and modified in 1990. The current scoring system uses 11 angiographic variables to categorize lesions into types A, B1, B2, and C. Historical studies prior to the arrival of drug-eluting stents indicated that that ACC/AHA lesion classification did have a prognostic impact on early and late outcomes (36,37). Data in contemporary practice using drug-eluting stents, however, are limited to retrospective registries. The German Cypher registry enrolled over 6,700 patients with approximately 8,000 lesions, 200 of which were ULM lesions. Results indicated the lack of any relationship between ACC/AHA lesion classification and clinical outcomes out to 6-month follow-up (38). In contrast to these results, a significant relationship between the ACC/AHA lesion score (derived by assigning 1, 2, 3, and 4 points to types A, B1, B2, and C lesions, respectively) and clinical outcomes has been demonstrated in patients with 3-vessel- (39) or ULM-disease (40) undergoing PCI. Specifically, Capodanno et al. (40) demonstrated that the ACC/AHA lesion score significantly predicted both cardiac death ($p = 0.001$) and major adverse cardiac events (MACE) ($p = 0.02$) at 1-year follow-up among 255 patients with ULM undergoing PCI with drug-eluting stents. Moreover, in this study, the ACC/AHA lesion score was found to be an independent predictor of cardiac death, but not MACE.

SYNTAX score. The SYNTAX score (SXscore) is a well-described anatomical scoring system that enables quantification of the complexity of coronary anatomy (34,41). Lesion location and adverse lesion characteristics are used to calculate the score using either a downloadable calculator or the SXscore website (42) (Table 4). The SXscore was first used prospectively in the SYNTAX trial and has since been calculated in a number of different clinical trials both in elective and acute patients, with simple or complex disease, followed up for between 1 and 5 years (6,9,34,39–41,43–46). In all studies, irrespective of follow-up duration, a higher SXscore tertile has consistently been associated with the poorest outcomes (6,9,39,40,43–46), whereas several studies also identified the SXscore as an independent predictor of MACE in patients undergoing PCI (6,39,40,43,44).

The value of the SXscore in patients with ULM disease has been specifically assessed in over 3,000 patients with follow-up between 12 months and 4 years in 4 separate studies: specifically, the 705-patient ULM subgroup of the SYNTAX trial (24,47), the CUSTOMIZE registry (appraise a CUSTOMIZED strategy for left main revascularization) ($n = 819$) (40,43), the MAIN COMPARE registry ($n = 1,580$) (26), and the Rotterdam LM (Rotterdam Left Main) registry ($n = 148$) (44). Importantly, a surgical arm was included in all but the Rotterdam LM registry, thereby allowing investigation as to the role of the SXscore for selecting revascularization strategy and/or determining procedural risk.

The ULM subgroup of the SYNTAX study represents the only prospectively recruited ULM patient group

Table 4. The SYNTAX Score Algorithm

1. Arterial dominance
2. Arterial segments involved per lesion
   Lesion characteristics
   3. Total occlusion
      i. Number of segments involved
      ii. Age of the total occlusion (>3 months)
      iii. Blunt stump
      iv. Bridging collaterals
      v. First segment beyond the occlusion visible by antegrade or retrograde filling
      vi. Side branch involvement
   4. Trifurcation
      i. Number of segments diseased
   5. Bifurcation
      i. Medina type
      ii. Angulation between the distal main vessel and the side branch <70°
   6. Aorto-ostial lesion
   7. Severe tortuosity
   8. Length >20 mm
   9. Heavy calcification
   10. Thrombus
   11. Diffuse disease/small vessels
      i. Number of segments with diffuse disease/small vessels

The SYNTAX score is calculated using this algorithm, which is applied to each individual coronary lesion that has a diameter stenosis greater than 50% and is located in a vessel that is larger than 1.5 mm in diameter (41). The individual lesion scores are added together to give the final SYNTAX score.

(24,47). The rate of MACCE out to 2-year follow-up, together with the individual components of death, stroke, MI, and repeat revascularization in patients randomly assigned to treatment with PCI or CABG, stratified according to SXscore tertiles are shown in Table 5. Of note, whereas the SXscore was an independent predictor of MACCE for patients undergoing PCI, the same was not true for those undergoing CABG. This is not surprising considering the bypass anastomosis occurs distal to the complex disease. Moreover, the relatively "flat" relationship between MACCE and SXscore in patients undergoing CABG, which contrasts with the positive relationship between MACCE and SXscore in patients undergoing PCI (Fig. 1), indicates how the SXscore, in addition to its ability to predict outcomes, is able to aid revascularization decisions in these patients. In those patients in the low and intermediate SXscore tertiles, the rates of MACCE between PCI and CABG are comparable (Table 5), whereas in those patients in the highest SXscore tertile, outcomes are significantly worse in those receiving PCI.

Similar findings have been demonstrated in retrospective registries of patients undergoing ULM PCI who have reported outcomes from 1 to 4 years of follow-up.

At 1-year follow-up, among 255 patients in the CUSTOMIZE registry, the SXscore was identified as an independent predictor of MACE (adjusted HR: 1.06; 95% CI: 1.02 to 1.10; p = 0.005) and cardiac death (adjusted HR: 1.15; 95% CI: 1.05 to 1.26; p = 0.003), with respective C-statistics of 0.64 and 0.83 (40). At 2-year follow-up, further analysis of the same registry (expanded to 819 patients) reaffirmed the ability of the SXscore to aid revascularization decisions (43). The rate of MACE among patients treated with PCI and CABG for those with an SXscore ≤34 was 8.1% and 6.2% (p = 0.46), respectively, compared with 32.7% and 8.5% (p < 0.001) for those with SXscore >34.

At 3-year follow-up in the MAIN COMPARE registry, the rate of death/stroke/MI after ULM PCI increased from 4.6%, to 9.4% and 11.4% with increasing SXscore tertile (p = 0.01) (26). A significant trend was not present, however, when rates of MACCE (composite of death, stroke, MI, and repeat revascularization) were stratified according to SXscore; of note, this population included patients treated with bare-metal stents, which may in part explain this finding. Finally, data from the Rotterdam LM registry indicate that the ability of the SXscore to identify those at high risk of adverse outcomes following ULM PCI is sustained out to at least the 4-year follow-up (44).

In contrast to these studies, which have all consistently demonstrated no interaction between the SXscore and those

Table 5. 2-Year Outcomes in the Left Main Subgroup of the SYNTAX Trial Stratified by SYNTAX Score Tertiles

	Treatment Modality		
2-Year Outcomes (47)	PCI (%)	CABG (%)	p Value
Low SYNTAX score tertile (0–22)	n = 118	n = 104	
Major adverse cardiovascular events	15.5	18.8	0.45
Death	0.9	4.9	0.07
Stroke	0.9	4.1	0.12
MI	3.6	2.0	0.53
Death/stroke/MI	4.5	9.9	0.10
Repeat revascularization	14.7	10.1	0.37
Intermediate SYNTAX score tertile (23–32)	n = 103	n = 92	
Major adverse cardiovascular events	22.4	22.4	0.91
Death	4.9	11.3	0.10
Stroke	1.0	2.3	0.46
MI	4.0	3.3	0.86
Death/stroke/MI	9.8	14.5	0.28
Repeat revascularization	14.9	12.8	0.72
High SYNTAX score tertile (≥33)	n = 135	n = 150	
Major adverse cardiovascular events	29.7	17.8	0.02
Death	10.4	4.1	0.04
Stroke	0.8	4.2	0.08
MI	8.4	6.1	0.48
Death/stroke/MI	15.6	11.5	0.32
Repeat revascularization	21.8	9.2	0.003

Abbreviations as in Tables 1 and 2.

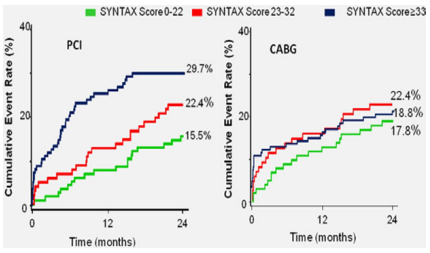


Figure 1. Clinical Outcomes (Composite of Death, Stroke, MI and Repeat Revascularization) Stratified by SYNTAX Score Tertile

Clinical outcomes (composite of death, stroke, myocardial infarction, and repeat revascularization) stratified by SYNTAX score tertile among the 705 patients randomized to treatment with percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery in the unprotect left main subgroup of the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) study (47). There is an increasing event rate among patients treated with percutaneous coronary intervention with increasing SYNTAX score tertile. Conversely, there is relatively little difference between outcomes in the coronary artery bypass grafting group. These results illustrate the utility of the SYNTAX score in determining revascularization strategy. CABG = coronary artery bypass grafting; MI = myocardial infarction.

undergoing CABG, are the results of a study by Birim et al. (48) who reported surgical outcomes in 148 patients with ULM disease stratified according to tertiles. The study, which only used 1 investigator to score all angiograms, demonstrated that the SXscore was an independent predictor of MACCE at 1-year follow-up after CABG. The small sample size and retrospective design may have influenced the results, which have not yet been repeated, or fully explained (48).

Both Valgimigli et al. (39) and Capodanno et al. (40) have reported a significant correlation between the SXscore with the ACC/AHA lesion score. However, the SXscore has been shown to have superior discriminative ability compared with the ACC/AHA lesion score for both cardiac death (SXscore 0.83 vs. 0.76 ACC/AHA) (40) and MACCE (SXscore 0.73 vs. ACC/AHA 0.56) (39).

Overall, these multiple studies indicate that the SXscore has a role to play in both stratifying clinical outcomes and assisting important revascularization decisions in those patients undergoing revascularization of ULM disease.

Combined Risk Scores

The clinical and angiographic-based scores assess completely different, but equally important, variables. Importantly, clinical and angiographic risk models may be better suited to predict different outcomes. For example, Singh et al. (32) reported that the MCRS was superior to the ACC/AHA lesion classification in the prediction of death/stroke/MI/emergent CABG, but inferior for the prediction of angiographic failure. This observation supports the notion of a model combining clinical and angiographic variables, which intuitively would be able to provide a more complete assessment of risk. In view of this, several combined clinical and angiographic risk scores have been developed. However, validation of these scores is at an early stage, such that outcome data are currently confined to small, retrospective studies, with limited follow-up. The most prominent combined risk scores include: Society of Thoracic Surgery (STS) Score, clinical SYNTAX score (CSS), and combined EuroSCORE and SYNTAX.

STS Score. The STS score is considered a combined risk score, although it only incorporates 2 angiographic variables (presence of ULM lesion and number of vessels diseased) together with 40 clinical variables. The STS risk model predicts the risk of operative mortality and morbidity after adult cardiac surgery (49,50) such that it is used exclusively by cardiac surgeons; at present, no data exist regarding the utility of the STS score in patients undergoing PCI. Previous data have indicated the STS score to be superior to the MCRS in patients having CABG (31), whereas comparisons between the EuroSCORE and STS score indicate only a slight improvement in mortality prediction with the STS score (51). There appears to be little role of the STS score in the assessment of patients with ULM disease prior to the selection of a strategy of surgical revascularization.

Clinical SYNTAX score. The notion of adding a clinical-based component to the angiographic SXscore led to the development of the CSS (52). This score incorporates, as its clinical component, the ACEF score, which is modified to include the creatinine clearance as opposed to the serum creatinine as originally described by Ranucci et al. (33). This was performed to improve the discrimination of risk as previously observed when a similar modification was incorporated into the EuroSCORE (53). The CSS is calculated by multiplying the SXscore with this modified ACEF score (Table 6). The evaluation of the CSS has only been performed thus far in 1 patient study cohort, which included

Table 6. The Clinical SYNTAX Score

$$\text{Clinical SYNTAX Score} = \text{SYNTAX Score} \times \left(\frac{\text{Age}}{\text{LV ejection fraction (\%)}} + 1 \text{ point for each 10-ml creatinine clearance}^{*} < 60 \text{ ml/min/1.73 mm}^{2} \right)$$

The clinical SYNTAX score is calculated using the patient's age, left ventricular ejection fraction, serum creatinine clearance, and SYNTAX score (52). *Calculated using the Cockcroft/Gault equation.
LV = left ventricular; other abbreviations as in Table 1.

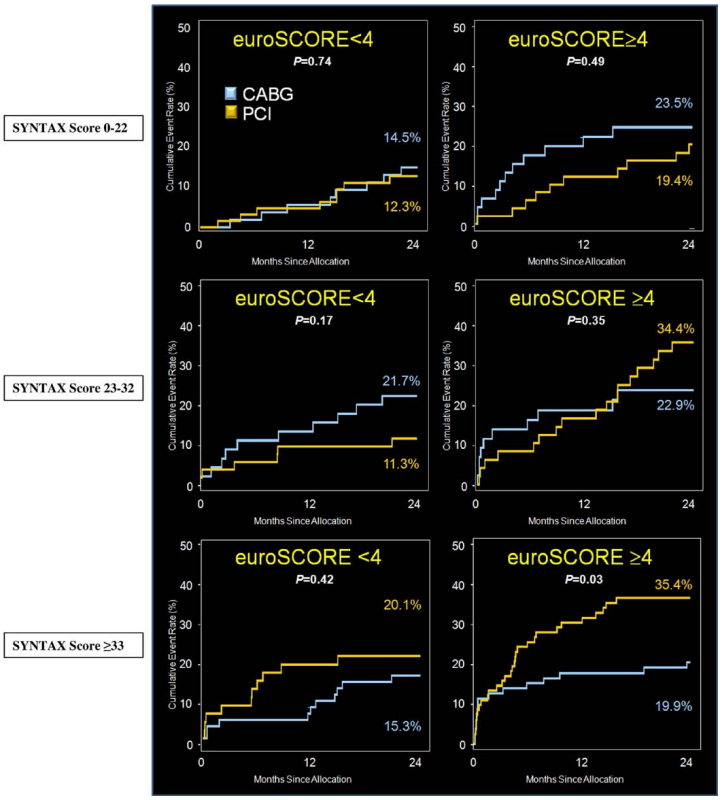


Figure 2. The Relationship Between the EuroSCORE and the SYNTAX Score as Assessed in the ULM Population Enrolled in the SYNTAX Study

All patients with a EuroSCORE (European System for Cardiac Operative Risk Evaluation) ≥4 have a greater event rate than patients with a EuroSCORE <4 irrespective of the treatment modality or their SYNTAX score tertile. Furthermore, the largest absolute difference in event rate between patients with a EuroSCORE above and below 4 occurs in patients in the intermediate SYNTAX score tertile when treated with percutaneous coronary intervention, and in the lowest SYNTAX score tertile when treated with coronary artery bypass grafting. ULM = unprotected left main stem; other abbreviations as in Figure 1.

patients with multivessel disease but excluded those with ULM lesions. At 5-year follow-up, among patients with triple-vessel disease, the CSS was shown to have a superior discriminative ability compared with the SXscore and ACEF score in the prediction of both mortality (CSS 0.80 vs. SXscore 0.70 vs. ACEF 0.73) and MACCE (CSS 0.67 vs. SXscore 0.64 vs. ACEF 0.59) (52). Further evaluation of this score is required, particularly in patients with ULM disease.

EuroSCORE and SYNTAX. The previous discussion has indicated that the EuroSCORE and SXscore are the most validated tools for risk assessing patients undergoing coronary revascularization and in particular those with ULM disease. The combination of these 2 scores appears particularly attractive given the ability of the EuroSCORE to identify patients at high risk of adverse events irrespective of treatment modality and the ability of the SXscore to assist in establishing optimal revascularization strategy.

The 2 scores have a somewhat complex relationship that is highlighted by the confusing results seen in the SYNTAX study, when patients in low, intermediate, and high SXscore tertiles were further subdivided by a EuroSCORE above or below the median of 4 (Fig. 2). The EuroSCORE was an

Table 7. The Global Risk Classification

	SYNTAX Score Tertile		
EuroSCORE	**LOW**	**INTERMEDIATE**	**HIGH**
LOW	Low	Low	Intermediate
MEDIUM	Low	Low	Intermediate
HIGH	Intermediate	Intermediate	High

The Global Risk Classification uses the patient's EuroSCORE and SYNTAX score in combination to classify patients as low, intermediate, or high risk (54). It is derived using this matrix.
Abbreviations as in Table 1.

independent predictor of MACCE for both revascularization strategies; therefore it would have been expected that outcomes in those with a high EuroSCORE were worse than those with a low EuroSCORE irrespective of the SXscore tertile. However, as is clearly seen, in the low SXscore tertile the division by EuroSCORE identified those patients at highest risk of events from surgery and had little effect on PCI outcomes. In the high SXscore tertile group the opposite was observed: whereas surgical outcomes in patients with a EuroSCORE above or below 4 were similar, PCI outcomes varied from 20% to 35%. The small number of patients in these subgroups may certainly have played its part in these observations, which therefore require further investigation with subsequent larger studies.

Although the subdivision of patients into 2 groups according to their EuroSCORE produced puzzling results, more promising results have been reported by Capodanno et al. (54) when subdividing the EuroSCORE into the historically defined groups of low (0 to 2), intermediate (3 to 5), and high risk (≥6) and combining this in a Global Risk Classification (GRC) with SXscores in low, intermediate, and high tertiles (Table 7). This GRC has so far only been applied to a population of 255 patients undergoing ULM revascularization, for which SXscores were calculated retrospectively. At 2-year follow-up, the rates of cardiac death in patients in low, intermediate, and high SXscores tertiles were 3.9%, 5.4%, and 21.9%, whereas with the GRC, rates of 1.6%, 16.0%, and 31.4% were seen in low, intermediate, and high GRC groups. Additional results indicated that the GRC had a greater discriminatory ability when compared with other risk scores, including the EuroSCORE and the SXscore, for the prediction of in-hospital and 2-year mortality. In essence, the study reiterated the importance of considering both clinical and angiographic variables in the assessment of overall risk and provided a combined scoring system that appears to hold promise; however, validation in a large patient group is required.

Limitations of Risk Models

There are numerous other variables such as diabetic status and body mass index, which have been shown to influence clinical outcomes but have not been included in most risk models. Importantly, the number of variables included in the risk model must be sufficient, on one hand, to ensure the model adequately predicts risk, but, on the other hand, the number must not be excessive to inhibit user uptake. Furthermore, inclusion of numerous variables increases the chances of colinearity between independent variables resulting in redundant information being collected (33), whereas also increasing the chances of overfitting the model, thereby reducing the overall accuracy of the results (55). Overall, it must be acknowledged that all risk scores lack the sensitivity to accurately predict events in an individual patient who may have comorbidities not accounted for in the risk model. The purpose of risk scores therefore is to report the risk of the population being studied; in a good risk model the variables selected will account for interpatient variation in comorbidities.

The accuracy of risk models can also be improved with the inclusion of treatment-specific procedural factors, such as the number of stents implanted and the stenting technique employed in patients having PCI, and the cardiopulmonary bypass time and use of off-pump surgery in patients having CABG. For example, Chen et al. (56) incorporated 4 procedural variables together with 17 clinical and 33 angiographic variables to produce a risk model that had a greater predictive accuracy than the SXscore alone in 337 patients with ULM disease treated with PCI. Despite the improved accuracy, it is important to remember that these variables cannot be reliably predicted prior to undertaking PCI or CABG, and therefore their inclusion unfortunately moves the ability to accurately calculate risk to a time point after the procedure has been completed.

Table 8. Comparison of the Different Predictive Ability of Risk Models When Assessing Hard and Soft Clinical End Points

Risk Score	Study	Hard End Point (Follow-Up)	C-Statistic	Soft End Point (Follow-Up)	C-Statistic
EuroSCORE	Romagnoli et al. (28)	Mortality (In-hospital)	0.91	Procedural failure (In-hospital)	0.56
Mayo Clinic Risk Score	Singh et al. (32)	Death/stroke/MI/emergent CABG (In-hospital)	0.78	Angiographic success (In-hospital)	0.67
AHA/ACC lesion score	Capodanno et al. (40)	Cardiac death (12 months)	0.76	Cardiac death, MI, TLR (12 months)	0.64
SYNTAX score	Capodanno et al. (40)	Cardiac death (12 months)	0.83	Cardiac death, MI, TLR (12 months)	0.64
Clinical SYNTAX score	Garg et al. (52)	All-cause death (60 months)	0.80	Death, stroke, MI, repeat revascularization (60 months)	0.67

TLR = target lesion revascularization; other abbreviations as in Table 1.

Finally, data indicate that overall ability of clinical or angiographic models to predict hard end points (such as mortality) is superior to their ability to predict softer outcomes such as angiographic failure and repeat revascularization. As shown in Table 8, this trend appears consistent with all risk models, with recent data from Garg et al. (52) indicating that combined scores such as the CSS are not exempt from this phenomenon.

Conclusions

There is a clear need for adequate risk stratification in patients undergoing revascularization of the ULM. Although numerous different risk models are available for the assessment of these patients, each has been evaluated in a different patient population and has measured different outcome end points at varying follow-up time periods. This heterogeneity identifies an important gap in the current evidence base. As a result, identification of a single best risk score for use as a day-to-day clinical tool is presently not possible. Assessment of prospectively and carefully collected data from a large ULM population undergoing long-term follow-up is required to provide the substrate from which a useful risk stratification model can be developed that is capable of optimally discriminating between PCI and CABG in patients with ULM disease requiring revascularization.

Reprint requests and correspondence: Prof. Patrick W. Serruys, Ba583a, Thoraxcenter, Erasmus Medical Center, 's-Gravendijkwal 230, Rotterdam 3015 CE, the Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl.

REFERENCES

1. Taggart DP, Kaul S, Boden WE, et al. Revascularization for unprotected left main stem coronary artery stenosis stenting or surgery. J Am Coll Cardiol 2008;51:885–92.
2. Taggart D. The DELFT (Drug Eluting stent for LeFT main) Registry: the unknowns. J Am Coll Cardiol 2008;52:1680–1.
3. Meliga E, Maree AO, Garcia-Garcia HM, Serruys PW. Reply. J Am Coll Cardiol 2008;52:1681.
4. Yusuf S, Zucker D, Peduzzi P, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. Lancet 1994;344:563–70.
5. Serruys PW, Unger F, Sousa JE, et al., on behalf of Arterial Revascularization Therapies Study Group. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 2001;344:1117–24.
6. Serruys PW, Onuma Y, Garg S, et al., on behalf of ARTS II Investigators. 5-year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. J Am Coll Cardiol 2010;55:1093–101.
7. Kappetein AP, Dawkins KD, Mohr FW, et al. Current percutaneous coronary intervention and coronary artery bypass grafting practices for three-vessel and left main coronary artery disease. Insights from the SYNTAX run-in phase. Eur J Cardiothorac Surg 2006;29:486–91.
8. Kandzari DE, Colombo A, Park SJ, et al., on behalf of American College of Cardiology Interventional Scientific Council. Revascularization for unprotected left main disease: evolution of the evidence basis to redefine treatment standards. J Am Coll Cardiol 2009;54:1576–88.
9. Serruys PW, Morice MC, Kappetein AP, et al., on behalf of SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.
10. Kappetein AP. Optimal revascularization strategy in patients with three-vessel disease and/or left main disease. The 2-year outcomes of the SYNTAX Trial. Paper presented at: ESC Congress; September 2, 2009; Barcelona.
11. Kushner FG, Hand M, Smith SC Jr., et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2009;54:2205–41.
12. Lindstaedt M, Spiecker M, Perings C, et al. How good are experienced interventional cardiologists at predicting the functional significance of intermediate or equivocal left main coronary artery stenoses? Int J Cardiol 2007;120:254–61.
13. Fisher LD, Judkins MP, Lesperance J, et al. Reproducibility of coronary arteriographic reading in the coronary artery surgery study (CASS). Cathet Cardiovasc Diagn 1982;8:565–75.
14. Hamilos M, Muller O, Cuisset T, et al. Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. Circulation 2009;120:1505–12.
15. Botman CJ, Schonberger J, Koolen S, et al. Does stenosis severity of native vessels influence bypass graft patency? A prospective fractional flow reserve-guided study. Ann Thorac Surg 2007;83:2093–7.
16. Abizaid AS, Mintz GS, Abizaid A, et al. One-year follow-up after intravascular ultrasound assessment of moderate left main coronary artery disease in patients with ambiguous angiograms. J Am Coll Cardiol 1999;34:707–15.
17. Vranckx P, Meliga E, De Jaegere PP, Van den Ent M, Regar ES, Serruys PW. The TandemHeart, percutaneous transseptal left ventricular assist device: a safeguard in high-risk percutaneous coronary interventions. The six-year Rotterdam experience. EuroIntervention 2008;4:331–7.
18. Jorgensen KJ, Brodersen J, Hartling OJ, Nielsen M, Gotzsche PC. Informed choice requires information about both benefits and harms. J Med Ethics 2009;35:268–9.
19. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999;16:9–13.
20. Toumpoulis IK, Anagnostopoulos CE, DeRose JJ, Swistel DG. European system for cardiac operative risk evaluation predicts long-term survival in patients with coronary artery bypass grafting. Eur J Cardiothorac Surg 2004;25:51–8.
21. Toumpoulis IK, Anagnostopoulos CE, Swistel DG, DeRose JJ Jr. Does EuroSCORE predict length of stay and specific postoperative complications after cardiac surgery? Eur J Cardiothorac Surg 2005;27:128–33.
22. De Maria R, Mazzoni M, Parolini M, et al. Predictive value of EuroSCORE on long term outcome in cardiac surgery patients: a single institution study. Heart 2005;91:779–84.
23. Roques F, Nashef SA, Michel P, et al. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. Eur J Cardiothorac Surg 1999;15:816–22, discussion 822–3.
24. Morice MC, Serruys PW, Kappetein AP, et al. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using TAXUS Express2 paclitaxel-eluting stent or coronary artery bypass graft treatment in the SYNTAX Trial. Circulation 2010;121:2645–53.
25. Rodés-Cabau J, Deblois J, Bertrand OF, et al. Nonrandomized comparison of coronary artery bypass surgery and percutaneous coro-

nary intervention for the treatment of unprotected left main coronary artery disease in octogenarians. Circulation 2008;118:2374–81.
26. Kim YH, Park DW, Kim WJ, et al. Validation of SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score for prediction of outcomes after unprotected left main coronary revascularization. J Am Coll Cardiol Intv 2010;3:612–23.
27. Kim YH, Ahn JM, Park DW, et al. EuroSCORE as a predictor of death and myocardial infarction after unprotected left main coronary stenting. Am J Cardiol 2006;98:1567–70.
28. Romagnoli E, Burzotta F, Trani C, et al. EuroSCORE as predictor of in-hospital mortality after percutaneous coronary intervention. Heart 2009;95:43–8.
29. Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. Eur Heart J 2003;24:881–2.
30. Singh M, Rihal CS, Lennon RJ, Spertus J, Rumsfeld JS, Holmes DR. Bedside estimation of risk from percutaneous coronary intervention: the new Mayo Clinic Risk Scores. Mayo Clin Proc 2007;82:701–8.
31. Singh M, Gersh BJ, Li S, et al. Mayo Clinic Risk Score for percutaneous coronary intervention predicts in-hospital mortality in patients undergoing coronary artery bypass graft surgery. Circulation 2008;117:356–62.
32. Singh M, Rihal CS, Lennon RJ, Garratt KN, Holmes DR Jr. Comparison of Mayo Clinic Risk Score and American College of Cardiology/American Heart Association lesion classification in the prediction of adverse cardiovascular outcome following percutaneous coronary interventions. J Am Coll Cardiol 2004;44:357–61.
33. Ranucci M, Castelvecchio S, Menicanti L, Frigiola A, Pelissero G. Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony. Circulation 2009;119:3053–61.
34. Serruys PW, Onuma Y, Garg S, et al. Assessment of the SYNTAX score in the Syntax study. EuroIntervention 2009;5:50–6.
35. Garg S, Girasis C, Sarno G, et al., on behalf of SYNTAX Trial Investigators. The SYNTAX score revisited: a reassessment of the SYNTAX score reproducibility. Catheter Cardiovasc Interv 2010;75:946–52.
36. Ryan TJ, Bauman WB, Kennedy JW, et al. Guidelines for percutaneous transluminal coronary angioplasty. A report of the American Heart Association/American College of Cardiology Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Percutaneous Transluminal Coronary Angioplasty). Circulation 1993;88:2987–3007.
37. Kastrati A, Schomig A, Elezi S, et al. Prognostic value of the modified American college of Cardiology/American Heart Association stenosis morphology classification for long-term angiographic and clinical outcome after coronary stent placement. Circulation 1999;100:1285–90.
38. Khattab AA, Hamm CW, Senges J, et al., on behalf of German Cypher Registry. Prognostic value of the modified American College of Cardiology/American Heart Association lesion morphology classification for clinical outcome after sirolimus-eluting stent placement (results of the prospective multicenter German Cypher Registry). Am J Cardiol 2008;101:477–82.
39. Valgimigli M, Serruys PW, Tsuchida K, et al., on behalf of ARTS II. Cyphering the complexity of coronary artery disease using the syntax score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. Am J Cardiol 2007;99:1072–81.
40. Capodanno D, Di Salvo ME, Cincotta G, Miano M, Tamburino C, Tamburino C. Usefulness of the SYNTAX Score for Predicting Clinical Outcome After Percutaneous Coronary Intervention of Unprotected Left Main Coronary Artery Disease. Circ Cardiovasc Interv 2009;2:302–8.
41. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219–27.
42. SYNTAX Score. Available at: www.syntaxscore.com. Accessed March 1, 2010.
43. Capodanno D, Capranzano P, Di Salvo ME, et al. Usefulness of SYNTAX score to select patients with left main coronary artery disease to be treated with coronary artery bypass graft. J Am Coll Cardiol Intv 2009;2:731–8.
44. Onuma Y, Girasis C, Piazza N, et al. Long-term clinical results following stenting of the left main stem—insights from RESEARCH and T-SEARCH Registries. J Am Coll Cardiol Intv 2010;3:584–94.
45. Wykrzykowska J, Garg S, Girasis C, et al. Value of the Syntax Score (SX) for risk assessment in the "all-comers" population of the randomized multicenter LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial. J Am Coll Cardiol 2010;56:272–7.
46. Girasis C, Garg S, Raber L, et al. Prediction of 5-year clinical outcomes using the SYNTAX score in patients undergoing PCI from the Sirolimus Eluting Stent Compared With Paclitaxel Eluting Stent for Coronary Revascularisation (SIRTAX) trial. Abstract presented at: American College of Cardiology meeting; March 14–16, 2010; Atlanta, GA.
47. Serruys PW. Left main lessons from SYNTAX (early results and 2 year follow-up): interventional perspectives. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 21, 2009; San Francisco, CA. Available at: www.tctmd.com/txshow.aspx?tid=9390768&id=83938&trid=938634. Accessed March 1, 2010.
48. Birim O, van Gameren M, Bogers AJ, Serruys PW, Mohr FW, Kappetein AP. Complexity of coronary vasculature predicts outcome of surgery for left main disease. Ann Thorac Surg 2009;87:1097–104, discussion 1104–5.
49. Shroyer AL, Coombs LP, Peterson ED, et al., on behalf of The Society of Thoracic Surgeons. The Society of Thoracic Surgeons: 30-day operative mortality and morbidity risk models. Ann Thorac Surg 2003;75:1856–64, discussion 1864–5.
50. Shahian DM, O'Brien SM, Filardo G, et al., on behalf of Society of Thoracic Surgeons Quality Measurement Task Force. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 1—coronary artery bypass grafting surgery. Ann Thorac Surg 2009;88:S2–22.
51. Ad N, Barnett SD, Speir AM. The performance of the EuroSCORE and the Society of Thoracic Surgeons mortality risk score: the gender factor. Interact Cardiovasc Thorac Surg 2007;6:192–5.
52. Garg S, Sarno G, Garcia-Garcia HM, et al., on behalf of the ARTS-II Investigators. A new tool for the risk stratification of patients with complex coronary artery disease: the Clinical SYNTAX Score. Circ Cardiovasc Interv 2010;3:317–26.
53. Walter J, Mortasawi A, Arnrich B, et al. Creatinine clearance versus serum creatinine as a risk factor in cardiac surgery. BMC Surg 2003;3:4.
54. Capodanno D, Miano M, Cincotta G, et al. EuroSCORE refines the predictive ability of SYNTAX score in patients undergoing left main percutaneous coronary intervention. Am Heart J 2010;159:103–9.
55. Concato J, Feinstein AR, Holford TR. The risk of determining risk with multivariable models. Ann Intern Med 1993;118:201–10.
56. Chen SL, Chen JP, Mintz G, et al. Comparison between the NERS (New Risk Stratification) score and the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score in outcome prediction for unprotected left main stenting. J Am Coll Cardiol Intv 2010;3:632–41.

Key Words: ACEF score ■ clinical SYNTAX score ■ coronary artery bypass grafting ■ EuroSCORE ■ global risk classification ■ percutaneous coronary intervention ■ stenting ■ SYNTAX score ■ unprotected left main stem.

Chapter 4.7

Combined clinical and angiographic risk assessment in patients with left main stem disease treated with percutaneous coronary intervention: A sub-study of the SYNTAX trial

EuroIntervention. In press

Scot Garg, Patrick W Serruys, David R. Holmes Jr., Arie-Pieter Kappetein, Marcel van den Brand, Michael Mack, Ted Feldman,Marie-Claude Morice, Elisabeth Stahle, Antonio Colombo, Nic Van Dyck, Katrin Leadley, Marie-Angèle Morel, Gerrit-Anne van Es, Friedrich W. Mohr, Keith D Dawkins

ABSTRACT

Background: Percutaneous coronary intervention in unprotected left main (ULM) lesions is increasingly acceptable in appropriately selected patients.

Aims: We assessed the utility of using the Global Risk Classification (GRC) a combination of the SYNTAX Score (SXscore) and the euroSCORE, in patients with ULM lesions receiving PCI.

Methods: The euroSCORE and SXscore were collected prospectively in 433 patients with ULM lesions who were treated with PCI and enrolled in the randomised and registry arms of the SYNTAX trial. Clinical outcomes at 2-year follow-up in terms of all-cause death, stroke, myocardial infarction (MI), repeat revascularization, a composite of death/stroke/MI and major adverse cardiovascular and cerebrovascular events (MACCE) were stratified according to groups: GRC_{LOW} (n=186, 43.0%), GRC_{MID} (n=177, 40.9%), GRC_{HIGH} (n=70, 16.2%).

Results: At 24-months the primary endpoint of all-cause death was significantly higher in the GRC_{HIGH} group (GRC_{LOW} 1.1% vs. GRC_{MID} 9.0% vs. GRC_{HIGH} 21.4%,$p<0.001$), as were the composite safety endpoint of death/stroke/MI and MACCE. One (0.5%) cardiovascular death was observed in the GRC_{LOW} group. Compared to the SXscore, the GRC appropriately reclassified 10.9 % of patients for the endpoint of mortality, and inappropriately reclassified 2.3% of patients with respect to MACCE. The C-statistic for the GRC was superior to the SXscore for all endpoints apart from repeat revascularization. In comparison with other contemporary risk models the GRC had a non-inferior C-statistic for all endpoints

Conclusions: The SXscore and the euroSCORE can be combined in the Global Risk Classification to produce a risk model which can be used effectively to risk stratify patients receiving PCI for ULM lesions.

INTRODUCTION

Although coronary artery bypass grafting (CABG) has been the accepted treatment for patients with unprotected left main (ULM) coronary lesions[1] evidence has now emerged identifying specific groups of patients in whom percutaneous coronary intervention (PCI) can offer a safe and suitable alternative.[2-7] Consequently, recent guidelines from the American College of Cardiology (ACC), the American Heart Association (AHA), and the joint European Society of Cardiology (ESC) and European Society of Cardiothoracic Surgeons (EACTS) have upgraded the recommendations for PCI of ULM lesions from a Class III to a Class IIa (ESC/EACT)[8-9] or IIb (ACC/AHA)[10] indication, in appropriately selected patients.

This patient selection relies on appropriate risk stratification. Despite the development of numerous risk models to assess risk in patients undergoing coronary revascularization, there are only limited data in patients with ULM lesions, and as such, no single model is universally endorsed.[11] One model which has shown promise in patients with ULM disease is the SYNTAX Score (SXscore).[2-4,12-15] This angiographic score based on the complexity of coronary artery disease (CAD),[16-17] has also been shown to have a role in assisting with revascularization decisions,[4,12] and has consistently identified as an independent predictor of mortality and/or major adverse cardiovascular events.[3,13,15]

One of the limitations of using the SXscore for risk stratification is the absence of clinical variables, which have repeatedly been shown to have a greater influence on the prediction of longer term endpoints such as mortality when compared to angiographic variables. Accordingly, combining the SXscore with the euroSCORE,[18] has been recently shown to improve the ability of the SXscore to predict outcomes in patients with ULM lesions undergoing PCI. Universal endorsement of this Global Risk Classification (GRC) is limited and has not been confirmed in multiple independent studies.

Given the promising initial results we sought to validate the utility of using the GRC by comparing it to the SXscore and other contemporary risk models in patients with ULM disease treated with PCI who were enrolled in the SYNergy between PCI with TAXus and Cardiac Surgery (SYNTAX) trial.[2]

METHODS

Study Population

The patient population of the SYNTAX trial has been described elsewhere.[2] In brief, the study included patients with triple vessel disease (3VD), and/or ULM disease. In order to minimize selection bias, inclusion criteria were kept broad and exclusions were limited to patients with previous revascularisation, those requiring concomitant surgery, or those who had experienced a recent myocardial infarction (MI). An interventional cardiologist and a cardiac surgeon (The Heart Team) jointly reviewed each angiogram, and patients were then entered into one of the three arms of the trial. In total 3,075 patients with complex CAD were recruited: 1,800 patients had CAD that was deemed suitable for equivalent revascularisation with either PCI or CABG and were entered into the randomised

group (903 PCI, 897 CABG); 1,077 had CAD not amenable to PCI and were entered into the CABG registry; and 198 patients with CAD deemed not suitable for surgery were entered into the PCI registry. All patients enrolled in the randomised and registry arms of the trial who received PCI and had ULM disease, defined as ≥50% stenosis by visual assessment in the LM vessel, or LM equivalent (≥50% stenosis of the ostium of the LAD and the ostium of the left circumflex) disease, with or without stenosis in other vessels, were included in the current analysis (**Figure 1**). All patients provided written informed consent, and the local medical ethics committee of each participating institution and the competent authority of each participating country approved the study (ClinicalTrials.gov number, NCT00114972.).

Study Procedure

PCI was performed with the intention to treat all lesions with a ≥50% diameter stenosis in vessels ≥1.5mm diameter. There was no mandated PCI technique; however, in bifurcation lesions final kissing balloon dilatation was recommended, and in chronic total occlusions the use of simultaneous injections was advised. The use of adjunctive devices was allowed. All PCI patients in the randomised group received TAXUS® Express (Boston Scientific Corporation, Natick, USA) paclitaxel eluting stents, whilst those patients in the registry group received a mixture of drug eluting and bare metal stents.

Procedural anticoagulation was achieved with unfractionated heparin 5000IU or 70-100IU/kg, whilst the use of glycoprotein IIb/IIIa inhibitors was left to the operator's discretion. Pre-procedure all patients enrolled into the study received ≥70 mg of aspirin, and ≥300mg clopidogrel. All patients were discharged on ≥70 mg of aspirin indefinitely, and clopidogrel 75mg for 6 months, although 71.1% of patients were still receiving clopidogrel at 12 months.

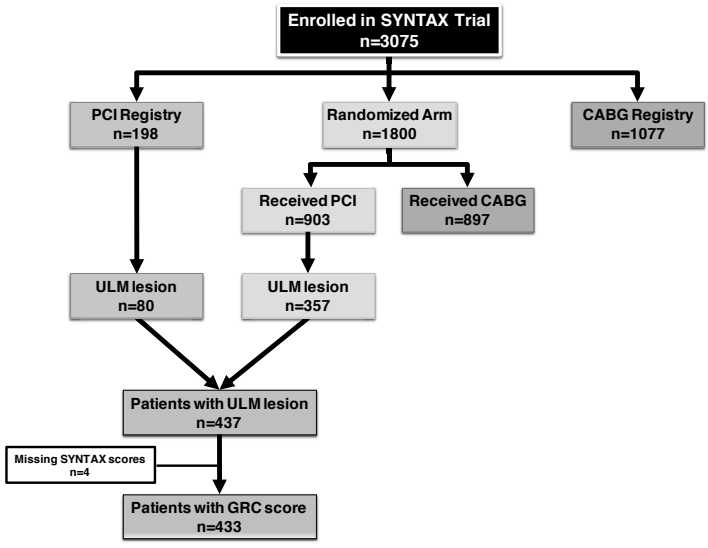
Risk Scores

The SXscore for each patient was calculated prospectively by scoring all coronary lesions with a diameter stenosis ≥50%, in vessels ≥1.5 mm, using the SXscore algorithm which is described in full elsewhere.[16-17,19] The SXscore were calculated for each diagnostic coronary angiogram at the time of the Heart Team conference by an interventional cardiologist and a cardiac surgeon and entered into a database at site prior to randomisation.[20] In addition, staff at the independent core laboratory, (Cardialysis, Rotterdam, The Netherlands), who were blinded to the investigator calculated score and treatment assignments, also calculated the SXscore; the core lab SXscores have been used in this analysis. The additive and logistic euroSCORE were calculated prospectively at the time of the Heart Team conference using previously described methodology.[21-22]

The GRC was calculated retrospectively as previously described[18] using tertiles of the SXscore, and historically accepted cut offs of the euroSCORE (low 0-2, intermediate 3-5, high ≥6).[21] In brief, patients were grouped into one of three GRC risk groups: GRC_{LOW} (euroSCORE <6 *AND* SXscore <33), GRC_{MID} (euroSCORE ≥6 *OR* SXscore ≥33) and GRC_{HIGH} (euroSCORE ≥6 *AND* SXscore ≥33).

For comparison the discriminatory ability of the GRC was compared with other risk models including the ACEF score,[23] the Mayo Clinic Risk Score (MCRS)[24] and Clinical SYNTAX Score (CSS).[25] The

Figure 1: Patient flow through the study. ULM, unprotected left main; PCI, percutaneous coronary intervention; CABG, coronary artery bypass surgery.



derivation of these models is described in the relevant primary manuscripts [23-25] and summarized in the Supplementary Appendix.

Definitions

All deaths were considered cardiac unless a clearly recognized non-cardiac cause was established. Stroke was defined as a focal, central neurological deficit lasting >72 hours which resulted in irreversible brain damage or body impairment. The definitions of MI, which was defined in relation to intervention status, and stent thrombosis, are provided in the Supplementary Appendix.

Endpoints

The primary endpoint of this *post hoc* sub-study was all-cause death at 24-months follow-up. Secondary endpoints included rates of 24-month cardiac death, stroke, MI, any repeat revascularisation, a composite safety endpoint of death/MI/stroke and major adverse cardiovascular and cerebrovascular events (MACCE), a composite of all-cause death, stroke, any MI and any repeat revascularization. An independent clinical events committee (CEC) adjudicated all MACCE events in the cohort of patients in the randomised PCI group. In the PCI registry MACCE events were 100% monitored, with all stent thrombosis events adjudicated by the CEC.

Statistical methods

All variables were stratified according to the GRC groups (low, mid, high). Discrete data were summarized as frequencies (%), whilst continuous data were expressed as mean±standard deviation test (SD). The Fisher exact (categorical variables), one way ANOVA test (parametric, continuous variables) and Kruskal-Wallis test (non-parametric, continuous variables) were used to analyze differences

Table 1. Baseline and procedural characteristics of patients

Variable (n,%) unless stated	GRC_{LOW} (n=186)	GRC_{MID} (n=177)	GRC_{HIGH} (n=70)	P Value
Baseline Characteristics				
Male gender	142 (76.3%)	121 (68.4%)	43 (61.4%)	0.04
Age, years (±SD)	61.4±8.7	68.0±9.5	77.3±6.9	<0.001
Body Mass Index, kg/m^2 (±SD)	28.5±5.2	27.9±5.2	28.0±5.0	0.52
Risk factors				
Previous Myocardial infarction	40 (21.6%)	56 (32.2%)	32 (45.7%)	0.001
Diabetes	37 (19.9%)	49 (27.7%)	21 (30.0%)	0.11
Requiring insulin	13 (7.0%)	13 (7.3%)	7 (10.0%)	0.71
Hypertension	129 (69.7%)	125 (70.6%)	57 (81.4%)	0.15
Hypercholesterolemia	156 (83.9%)	141 (79.7%)	45 (64.3%)	0.004
Family history ischaemic heart disease	57 (32.0%)	43 (25.1%)	8 (11.9%)	0.005
Current smoker	43 (23.1%)	26 (14.7%)	3 (4.3%)	0.001
Peripheral vascular disease	12 (6.5%)	30 (16.9%)	11 (15.7%)	0.004
Chronic obstructive airways disease	12 (6.5%)	20 (11.3%)	17 (24.3%)	0.001
Previous cerebrovascular accident	12 (6.5%)	18 (10.2%)	11 (15.7%)	0.08
Creatinine Clearance, ml/1.73m^2 (±SD)*	91.0±31.9	82.3±27.0	76.0±32.5	0.008
Indication for Treatment				
Stable angina	117 (62.9%)	90 (50.8%)	18 (25.7%)	<0.001
Unstable angina	34 (18.3%)	65 (36.7%)	44 (62.9%)	<0.001
Silent ischemia	21 (11.3%)	13 (7.3%)	3 (4.3%)	0.18
Risk Scores				
SYNTAX score	20.6±7.0	34.3±13.2	45.2±10.9	<0.001
Additive euroSCORE	2.4±1.5	4.9±2.8	8.2±2.2	<0.001
Logistic euroSCORE	1.9±0.9	5.3±7.1	12.2±9.3	<0.001
ACEF score†	1.03±0.28	1.21±0.42	1.53±0.40	<0.001
Mayo Clinic Risk score	2.9±1.1	3.5±1.4	5.2±1.4	<0.001
Clinical SYNTAX score ‡	23.2±14.1	52.3±35.2	97.0±55.4	<0.001
Left ventricular function (%)¶	61.1±12.7	59.7±11.9	54.5±12.4	0.01

SD for standard deviation;
* Available in 336 patients (GRC_{LOW}=155, GRC_{MID}=141, GRC_{HIGH} =40)
† Available in 212 patients (GRC_{LOW}=96, GRC_{MID}=90, GRC_{HIGH} =26)
‡ Available in 210 patients (GRC_{LOW}=96, GRC_{MID}=89, GRC_{HIGH}=25)
¶ Available in 258 patients (GRC_{LOW} =108, GRC_{MID}=106, GRC_{HIGH}=44)

between the groups. Event-free survival curves were generated by the Kaplan-Meier method, and survival between groups was compared using the log-rank test. A reclassification analysis was used to compare the SXscore with the GRC for the endpoints of death and MACCE as described in the Supplementary Methods. Receiver operator curves (ROC) were used to compare the discrimination of the SXscore, GRC, euroSCORE, ACEF score, MCRS and CSS. A 2-sided p value <0.05 was considered significant for all tests. All analyses were performed using SPSS 17.0.

Table 2. Angiographic and procedural characteristics of study population per patient

Variable (n,%) unless stated	GRC_{LOW} (n=186)	GRC_{MID} (n=177)	GRC_{HIGH} (n=70)	P Value
Extent of Disease				
Number of diseased lesions (±SD)	2.6±1.6	3.6±1.8	4.3±2.0	<0.001
Mean number of vessels diseased (±SD)	2.0±0.8	2.2±0.8	2.6±0.8	<0.001
Isolated LM disease	39 (21.0%)	11(6.2%)	2 (2.9%)	<0.001
LM + 1 vessel	46 (24.7%)	34 (19.2%)	3 (4.3%)	
LM + 2 vessels	49 (26.3%)	65 (36.7%)	21 (30.0%)	
LM + 3 vessels	52 (28.0%)	67 (37.9%)	70 (62.9%)	
Lesion Location				
Left anterior descending artery	116 (62.4%)	127 (71.8%)	65 (92.9%)	<0.001
Circumflex artery	92 (49.5%)	122 (68.9%)	60 (85.7%)	<0.001
Right coronary artery	92 (49.5%)	116 (65.5%)	52 (74.3%)	<0.001
Proximal LAD involvement	84 (45.2%)	96 (54.2%)	45 (64.3%)	0.02
Lesion Characteristics				
≥1Bifucation lesion	108 (58.1%)	105 (59.3%)	56 (80.0%)	0.002
≥1Trifurcation lesion	17 (9.1%)	31 (17.5%)	9 (12.9%)	0.06
≥1Tortuous lesion	84 (45.9%)	122 (68.9%)	59 (84.3%)	<0.001
≥1Total occlusion	17 (9.3%)	38 (21.5%)	22 (31.4%)	<0.001
≥1Calcified lesion	56(30.6%)	101 (57.1%)	50 (71.4%)	<0.001
≥1 Lesion >20mm in length	35 (19.1%)	78 (44.1%)	43 (61.4%)	<0.001
≥1Ostial lesion	61 (33.3%)	47 (26.6%)	22 (31.4%)	0.36
≥1Diffuse/small vessel disease	18 (9.7%)	27 (15.3%)	7 (10.0%)	0.28
≥1Lesion containing thrombus	4 (2.2%)	7 (4.0%)	2 (2.9%)	0.61
Procedural Characteristics				
Number of stents implanted (±SD)*	3.1±2.1	3.8±2.0	4.1±2.2	<0.001
Total stent length, mm (±SD)*	55.0±45.4	67.1±39.7	71.6±43.8	<0.001
Implantation >100mm stent	29/176 (16.5%)	33/175 (18.9%)	14/68 (20.6%)	0.69
Completeness of Revascularization	132/181 (72.9%)	97 (54.8%)	30/69 (43.5%)	<0.001
Use of glycoprotein IIb/IIIa inhibitors	20/181 (11.0%)	30 (16.9%)	10/69 (14.5%)	0.26
Procedure time, hours (±SD)	1.3±0.7	1.6±0.9	1.6±0.9	<0.001
Post procedural Hospital stay, days (±SD)	2.3±2.9	4.3±10.3	4.0±4.3	<0.001

SD, standard deviation; LM, left main; LAD, left anterior descending artery

* Available in 419 patients (GRC_{LOW}=176, GRC_{MID}=175, GRC_{HIGH}=68)

RESULTS

In total 437 (39.7%) of the 1101 patients enrolled in the randomized and registry PCI arms of the SYNTAX trial had an ULM lesion (**Figure 1**). The GRC, which was available in 433 (99.1%) patients (randomised 356, registry 77), was subsequently used to divide the population into three groups: GRC_{LOW} (n=186, 43.0%), GRC_{MID} (n=177, 40.9%), GRC_{HIGH} (n=70, 16.2%). The proportions of patients in the GRC_{LOW}, GRC_{MID}, and GRC_{HIGH} groups who were from the randomised arm of the study were 89.2%, 83.1% and 61.4%, respectively.

Table 3. Clinical Outcomes at Two Year Follow-up

Variable (n,%) unless stated	GRC_{LOW} (n=184)	GRC_{MID} (n=177)	GRC_{HIGH} (n=70)	P Value
Hierarchical				
Death	2 (1.1%)	16 (9.0%)	15 (21.4%)	<0.001
Cerebrovascular Accident	1 (0.5%)	1 (0.6%)	1 (1.4%)	
Myocardial Infarction	5 (2.7%)	10 (5.6%)	0 (0.0%)	
Death/Stroke/MI	8 (4.3%)	27 (15.3%)	16 (22.9%)	<0.001
Repeat Revascularization	21 (11.4%)	31 (17.5%)	8 (11.4%)	
CABG	6 (3.3 %)	5 (2.8%)	1 (1.4%)	
PCI	15 (8.2%)	26 (14.7%)	7 (10.0%)	
Any MACCE	29 (15.8%)	58 (32.8%)	24 (34.3%)	<0.001
Non-Hierarchical				
Cardiovascular death	1 (0.5%)	12 (6.8%)	9 (12.9%)	<0.001
Cerebrovascular Accident	1 (0.5%)	1 (0.6%)	2 (2.9%)	0.28
Myocardial Infarction	5 (2.7%)	17 (9.6%)	0 (0.0%)	0.001
Repeat Revascularization	24 (13.0%)	44 (24.9%)	10 (14.3%)	0.01
PCI	20 (10.9%)	38 (21.5%)	9 (12.9%)	0.02
CABG	6 (3.3%)	10 (5.6%)	1 (1.4%)	0.25
Stent thrombosis	2 (1.1%)	9 (5.5%)	1 (1.8%)	0.052

PCI, percutaneous coronary intervention
CABG, coronary artery bypass grafting
MACCE, major adverse cardiovascular and cerebrovascular events

Table 4: Comparison of the Predictive Ability of Different Risk Models.

Risk Score	Mortality*	Death/MI/CVA*	Repeat Revascularization*	MACCE*
	(n=431)	(n=431)	(n=431)	(n=431)
ACEF†	0.59	0.48	0.52	0.52
Clinical SYNTAX score‡	0.63	0.57	0.52	0.55
euroSCORE (Additive)	0.77 ¶	0.68 ¶	0.56	0.63¶
euroSCORE (Logistic)	0.77 ¶	0.68 ¶	0.56	0.63¶
Mayo Clinic Risk Score	0.66 ‖	0.59#	0.50	0.55
SYNTAX score	0.71 ¶	0.65 ¶	0.57	0.62¶
Global Risk Classification	0.77 ¶	0.68 ¶	0.55	0.63¶

All values non-significant unless indicated.
* C-statistics
†Available in 212 patients
‡Available in 210 patients
#p<0.05; ‖p<0.01; ¶p<0.001

Baseline Patients Characteristics

Baseline patient characteristics stratified according to GRC groups are shown in **Table 1**. Variables used in the calculation of the euroSCORE such as female gender, patient age, the presence of obstructive airways disease, impaired renal function and presentation with unstable symptoms were all significantly higher in GRC_{HIGH}. Notably, values for all other calculated risk models were also significantly higher in the $GRC_{HIGH.}$ group.

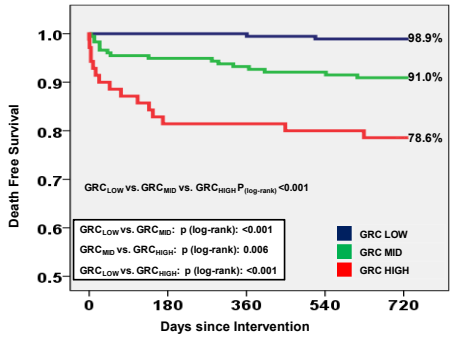
Baseline Angiographic Characteristics

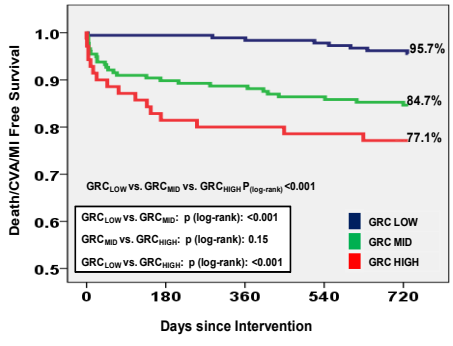
Baseline angiographic characteristics according to GRC groups are shown in **Table 2**. Markers reflecting the extent of CAD, such as the mean number of diseased vessels, and indicators of increased lesion complexity including the presence of bifurcation lesions and chronic occlusions were all significantly greater in the GRC_{HIGH} group reflecting the higher calculated SXscores in these patients. Consequently procedural variables (e.g., number of implanted stents, total stent length and incomplete revascularization) were also significantly higher in this group.

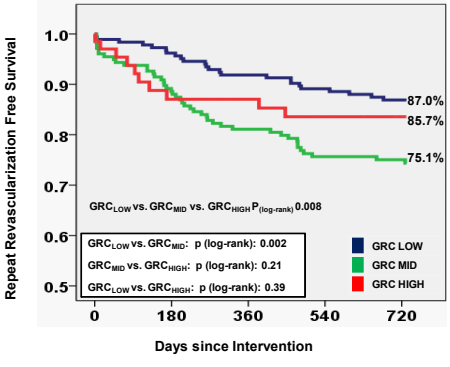
Clinical Outcomes

Clinical outcomes were available in 431 (99.5%) patients. Hierarchical and non-hierarchical outcomes stratified according to GRC groups are shown in **Table 3,** whilst cumulative survival curves are shown in **Figure 2**. The primary endpoint of all-cause death at 24-months was significantly higher in patients in GRC_{HIGH} group, with only one cardiovascular death occurring amongst those patients in the GRC_{LOW} group (cardiac death GRC_{LOW} 0.5%, GRC_{MID} 6.8%, GRC_{HIGH} 12.9%, p<0.001). Overall the rates of the composite endpoints of safety and MACCE were also significantly higher in the GRC_{HIGH}.

Figure 2: Kaplan Meier survival curves for (A) death, (B) the composite of death/myocardial infarction (MI)/ stroke (CVA), (C) repeat revascularization and (D) major adverse cardiovascular and cerebrovascular events (MACCE) a composite of death, MI, CVA and repeat revascularization.







GRC vs. SXscore

Reclassifications following the use of the GRC for mortality and MACCE are shown in **Supplementary Tables 1 and 2**. In total 33 patients died, of whom 1 and 9 were respectively reclassified into a higher (upward movement), and lower (downward movement) group with the use of the GRC. The net gain in reclassification was therefore -24.2%. Among the 398 patients who did not die, use of the GRC lead to 176 patients being downgraded and 36 patients upgraded. The net gain in reclassification was therefore 35.2%, and the overall net reclassification improvement for the GRC was 10.9% (p=0.13). Thus, when using mortality as an endpoint, 10.9% of patients in this study were appropriately reclassified by the use of the GRC. Conversely for MACCE, the use of the GRC resulted in an overall net reclassification improvement of -2.3% (p=0.37).

Table 4 shows the respective C-statistics for the GRC and other contemporary risk models including the SXscore for the endpoints of mortality, repeat revascularization, the safety composite of death/MI/stroke, and the composite of MACCE. As demonstrated the discriminatory ability of GRC was superior to the SXscore for all outcomes apart from repeat revascularization. In addition, when compared with other risk models, the discriminatory ability of the GRC was not inferior for any measured outcome.

DISCUSSION

This study represents the first validation to date of the Global Risk Classification in a population of patients with ULM lesions treated with PCI who had the SXscore and euroSCORE collected prior to treatment. The results demonstrate an overall superior ability of the GRC to stratify risk compared to the SXscore and other contemporary risk models. Moreover the GRC was able to identify a population of patients who had very low cardiovascular mortality following ULM PCI.

The importance of appropriately selecting patients to undergo percutaneous revascularization of ULM lesions is clearly indicated by results from prospective randomised trials such as the SYNTAX study,[3,12] and moreover is stipulated in the recent ACC/AHA/ESC/EACTS guidelines covering ULM revascularization.[8-10] Besides aiding patient selection, this risk stratification enables patients to be better informed of the potential risks of treatment; facilitates objective comparisons of clinical performance; and provides a vital measure of patient care which may identify future directions to further improve revascularisation outcomes using PCI. Despite these undeniable benefits, previous studies assessing risk models have failed to report standardized endpoints at comparable periods of follow-up, and therefore the optimal method of risk stratifying patients with ULM lesions remains to be established.[11]

Previous studies have identified the euroSCORE[3,14-15,26-27] and the SXscore[3,12-15] as having a definitive role in the assessment of patients with ULM lesions with both models being able to identify patients at highest risk of adverse outcomes. The absence of clinical variables has been considered a limitation to the sole use of the SXscore for determining outcomes, including mortality, which are

heavily influenced by pre-morbid characteristics. This limitation however does not detract from the importance of calculating the SXscore, as indicated by its additional ability to assist with the selection of treatment modality, with those patients having a SXscore greater than 32/34 being more optimally revascularised by CABG.[4,12] Importantly the combination of the SXscore with a clinical based score in the GRC aims to correct for these previous deficiencies.

The first assessment of the GRC, which reported outcomes from a retrospective population at 2-year follow-up demonstrated a superior discriminatory ability of the GRC compared to other risk models; in particular, an additive discriminatory benefit was seen for the GRC over the SXscore for mortality (GRC 0.76 vs. SXscore 0.75).[18] On the basis of the logistic euroSCORE (mean±SD 4.9±2.9 vs. 5.0±6.9) and the SXscore (24.8±10.6 vs. 30.2±13.9) the current study enrolled a more complex patient population than described in the first assessment of the GRC, and therefore it is encouraging to note the consistent results between both studies, and the larger additive benefit of the GRC compared to the SXscore for mortality (GRC 0.77 vs. SXscore 0.71).

The benefit of using the GRC over the SXscore was greater when assessing hard endpoints, such as mortality and safety than in the assessment of repeat revascularization. This serves to reinforce that 'softer' endpoints are harder to predict, which is likely to be a consequence of them also being influenced by additional factors including operator technique, operator competence and device performance.

Unrestricted registries report 2-year all-cause mortality rates of up to 24% for PCI of ULM lesions, reaffirming the potential risks associated with revascularization of these lesions.[15] Similarly, despite the overall all-cause mortality in the current study being considerably lower, at 7.7%, this was still higher than that seen in patients from the current cohort without ULM disease. It is therefore of great significance that the GRC was able to identify a sub-group of ULM patients who had respective rates of all-cause mortality and cardiovascular mortality of 1.1%, and 0.5% out to 2-year follow-up. The results from this group of patients, which comprised just under half of the study population, reiterate that with appropriate patient selection ULM lesions can be safely treated with PCI.

Of the other risk models assessed in the current study the inferior performance of the CSS when compared with the SXscore alone, is on first glance disappointing in view of the promising results seen in the initial assessment in patients without ULM lesions who were enrolled in the ARTS-II population.[25] These results are likely to be due to underpowered analyses given the relatively small number of patients with a calculated CSS which was the result of a large number of missing values for the serum creatinine and left ventricular ejection fraction. Further assessment is therefore required before definitive conclusions can be reached on the usefulness of the CSS in ULM patients.

In summary, this study provides important evidence to support the appropriate selection of patients for ULM PCI. Although this is not a new concept, the emergence of new risk models allows patient selection to be considerably more objective than before. With respect to the optimal method of risk stratifying patients with ULM lesions, the current results suggest that the GRC is a promising risk

model, however further research is needed. The forthcoming EXCEL study, the first dedicated study of ULM revascularization, will no doubt provide important data to explore these concepts further.

LIMITATIONS

The current study is limited by the relatively short period of follow-up. The SYNTAX study is scheduled to have follow-up out to 5-years, and results from the assessment of the GRC at later time points will be of particular interest. The highest risk group comprised under a fifth of the patient population which may account for the lack of statistically significant adverse outcomes in this group. The absence of quantitative values for the serum creatinine and left ventricular ejection fraction restricted the number of patients in whom the CSS could be calculated and thereby prevented a fair comparison between the two combined risk scores. Finally the study may be limited by the inherent restrictions of sub-group analysis such as under-powering and chance findings.

CONCLUSIONS

The SXscore and the euroSCORE can be combined in the Global Risk Classification to produce a risk model which can be used to effectively risk stratify patients receiving PCI for ULM lesions.

REFERENCES

1. Yusuf S, Zucker D, Peduzzi P, Fisher LD, Takaro T, Kennedy JW, Davis K, Killip T, Passamani E, Norris R, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet.* 1994;344(8922):563-570.
2. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med.* 2009;360(10):961-972.
3. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Stahle E, Colombo A, Mack MJ, Holmes DR, Torracca L, van Es GA, Leadley K, Dawkins KD, Mohr F. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. *Circulation.* 2010;121(24):2645-2653.
4. Capodanno D, Capranzano P, Di Salvo ME, Caggegi A, Tomasello D, Cincotta G, Miano M, Patane M, Tamburino C, Tolaro S, Patane L, Calafiore AM. Usefulness of SYNTAX score to select patients with left main coronary artery disease to be treated with coronary artery bypass graft. *JACC Cardiovasc Interv.* 2009;2(8):731-738.
5. Seung KB, Park DW, Kim YH, Lee SW, Lee CW, Hong MK, Park SW, Yun SC, Gwon HC, Jeong MH, Jang Y, Kim HS, Kim PJ, Seong IW, Park HS, Ahn T, Chae IH, Tahk SJ, Chung WS, Park SJ. Stents versus coronary-artery bypass grafting for left main coronary artery disease. *N Engl J Med.* 2008;358(17):1781-1792.
6. Park DW, Seung KB, Kim YH, Lee JY, Kim WJ, Kang SJ, Lee SW, Lee CW, Park SW, Yun SC, Gwon HC, Jeong MH, Jang YS, Kim HS, Kim PJ, Seong IW, Park HS, Ahn T, Chae IH, Tahk SJ, Chung WS, Park SJ. Long-term safety and efficacy of stenting versus coronary artery bypass grafting for unprotected left main coronary artery disease: 5-year results from the MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) registry. *J Am Coll Cardiol.* 2010;56(2):117-124.
7. Buszman PE, Kiesz SR, Bochenek A, Peszek-Przybyla E, Szkrobka I, Debinski M, Bialkowska B, Dudek D, Gruszka A, Zurakowski A, Milewski K, Wilczynski M, Rzeszutko L, Buszman P, Szymszal J, Martin JL, Tendera M. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. *J Am Coll Cardiol.* 2008;51(5):538-545.
8. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D, Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas PE, Widimsky P, Alfieri O, Dunning J, Elia S, Kappetein P, Lockowandt U, Sarris G, Vouhe P, von Segesser L, Agewall S, Aladashvili A, Alexopoulos D, Antunes MJ, Atalar E, Brutel de la Riviere A, Doganov A, Eha J, Fajadet J, Ferreira R, Garot J, Halcox J, Hasin Y, Janssens S, Kervinen K, Laufer G, Legrand V, Nashef SA, Neumann FJ, Niemela K, Nihoyannopoulos P, Noc M, Piek JJ, Pirk J, Rozenman Y, Sabate M, Starc R, Thielmann M, Wheatley DJ, Windecker S, Zembala M. Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2010;31:2501-2555.
9. Guidelines on myocardial revascularization. *Eur J Cardiothorac Surg.* 2010;38 Suppl:S1-S52.
10. Kushner FG, Hand M, Smith SC, Jr., King SB, 3rd, Anderson JL, Antman EM, Bailey SR, Bates ER, Blankenship JC,

Casey DE, Jr., Green LA, Hochman JS, Jacobs AK, Krumholz HM, Morrison DA, Ornato JP, Pearle DL, Peterson ED, Sloan MA, Whitlow PL, Williams DO. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2009;54(23):2205-2241.

11. Garg S, Stone GW, Kappetein AP, Sabik JF, 3rd, Simonton C, Serruys PW. Clinical and angiographic risk assessment in patients with left main stem lesions. *JACC Cardiovasc Interv.* 2010;3(9):891-901.

12. Serruys PW. Left Main Lessons from SYNTAX (Early Results and 2 Year Follow-up): Interventional Perspectives. Presentation Transcatheter Cardiovascular Therapeutics, 21st September 2009. [Available online: www.tctmd.com/txshow.aspx?tid=9390768&id=83938&trid=938634.].

13. Capodanno D, Di Salvo ME, Cincotta G, Miano M, Tamburino C, Tamburino C. Usefulness of the SYNTAX Score for Predicting Clinical Outcome After Percutaneous Coronary Intervention of Unprotected Left Main Coronary Artery Disease. *Circ Cardiovasc Intervent.* 2009;2(4):302-308.

14. Kim Y-H, Park D-W, Kim W-J, Lee J-Y, Yun S-C, Kang S-J, Lee S-W, Lee CW, Park S-W, Park S-J. Validation of SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) Score for Prediction of Outcomes After Unprotected Left Main Coronary Revascularization. *J Am Coll Cardiol Intv.* 2010;3(6):612-623.

15. Onuma Y, Girasis C, Piazza N, Garcia-Garcia HM, Kukreja N, Garg S, Eindhoven J, Cheng J-M, Valgimigli M, van Domburg R, Serruys PW, on behalf of Interventional Cardiologists at Thoraxcenter -. Long-Term Clinical Results Following Stenting of the Left Main Stem: Insights From RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) and T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) Registries. *J Am Coll Cardiol Intv.* 2010;3(6):584-594.

16. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Van Dyck N, Russell ME, Mohr F, Serruys P. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. *Eurointervention.* 2005;1:219-227.

17. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, Van Dyck N, Mack M, Holmes D, Feldman T, Morice MC, Colombo A, Bass E, Leadley K, Dawkins KD, van Es GA, Morel MA, Mohr FW. Assessment of the SYNTAX score in the Syntax study. *EuroIntervention.* 2009;5(1):50-56.

18. Capodanno D, Miano M, Cincotta G, Caggegi A, Ruperto C, Bucalo R, Sanfilippo A, Capranzano P, Tamburino C. EuroSCORE refines the predictive ability of SYNTAX score in patients undergoing left main percutaneous coronary intervention. *Am Heart J.* 2010;159(1):103-109.

19. SYNTAX working-group. SYNTAX score calculator: www.syntaxscore.com. Launched 19th May 2009.

20. Ong AT, Serruys PW, Mohr FW, Morice MC, Kappetein AP, Holmes DR, Jr., Mack MJ, van den Brand M, Morel MA, van Es GA, Kleijne J, Koglin J, Russell ME. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. *Am Heart J.* 2006;151(6):1194-1204.

21. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg.* 1999;16(1):9-13.

22. Roques F, Michel P, Goldstone AR, Nashef SAM. The logistic EuroSCORE. *Eur Heart J.* 2003;24(9):882-.

23. Ranucci M, Castelvecchio S, Menicanti L, Frigiola A, Pelissero G. Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony. *Circulation.* 2009;119(24):3053-3061.

24. Singh M, Rihal CS, Lennon RJ, Spertus J, Rumsfeld JS, Holmes DR. Bedside Estimation of Risk From Percutaneous Coronary Intervention: The New Mayo Clinic Risk Scores. *Mayo Clinic Proceedings*. 2007;82(6):701-708.

25. Garg S, Sarno G, Garcia-Garcia HM, Girasis C, Wykrzykowska J, Dawkins KD, Serruys PW. A New Tool for the Risk Stratification of Patients With Complex Coronary Artery Disease: The Clinical SYNTAX Score. *Circ Cardiovasc Interv*. 2010;3(4):317-326.

26. Kim YH, Ahn JM, Park DW, Lee BK, Lee CW, Hong MK, Kim JJ, Park SW, Park SJ. EuroSCORE as a predictor of death and myocardial infarction after unprotected left main coronary stenting. *Am J Cardiol*. 2006;98(12):1567-1570.

27. Rodes-Cabau J, Deblois J, Bertrand OF, Mohammadi S, Courtis J, Larose E, Dagenais F, Dery JP, Mathieu P, Rousseau M, Barbeau G, Baillot R, Gleeton O, Perron J, Nguyen CM, Roy L, Doyle D, De Larochelliere R, Bogaty P, Voisine P. Nonrandomized comparison of coronary artery bypass surgery and percutaneous coronary intervention for the treatment of unprotected left main coronary artery disease in octogenarians. *Circulation*. 2008;118(23):2374-2381.

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplementary Methods

Risk Score Calculations

• ACEF Score

The ACEF score was calculated as previous described[1] using the formula:

ACEF= [Age/Ejection fraction (%)] + [1 (if creatinine >2mg/dl)].

The left ventricular ejection fraction (LVEF) used was the value recorded prior to the index PCI, and in the event of multiple available values the lowest recorded figure. The serum creatinine value used was the value recorded prior to the index PCI.

• Mayo Clinic Risk Score (MCRS)

The MCRS was calculated using previously described methodology[2] and the variables: patient age, serum creatinine, LVEF, presence of peripheral vascular disease, and presentation with pre-procedural shock, myocardial infarction and congestive cardiac failure.

• Clinical SYNTAX score

The CSS was also calculated as previously described[3] using the formula: CSS= [SXscore] x [modified ACEF score]. The modified ACEF score was calculated retrospectively using the formula: age/ejection fraction+1 point for every 10ml/min reduction in creatine clearance below 60ml/min/1.73m^2 (up to a maximum of 6 points). The LVEF used was the value recorded prior to the index PCI, and in the event of multiple available values the lowest recorded figure. Creatinine clearance was calculated using the Cockcroft-Gault equation,[4] using the patient's age, weight, and serum creatinine recorded prior to the index PCI.

Definitions

MI was defined in relation to intervention status as follows:

(i) After allocation but before treatment: Q-wave (new pathological Q-waves in ≥2 leads lasting ≥0.04 seconds with CK-MB levels elevated above normal), and non-Q wave MI (elevation of CK levels >2 times the upper limit of normal [ULN] with positive CK-MB or elevation of CK levels to >2 times ULN without new Q-waves if no baseline CK-MB was available);

(ii) <7 days after intervention: new Q-waves and either peak CK-MB/total CK >10% or plasma level of CK-MB 5x ULN;

(iii) ≥7d after intervention: new Q-waves or peak CK-MB/total CK >10% or plasma level of CK-MB 5x ULN or plasma level of CK 5x ULN.

Stent thrombosis was defined as either: (i) clinical presentation of an acute coronary syndrome with documentation of a flow limiting thrombus or occlusion within or adjacent to a previously successfully treated artery; or (ii) a Q-wave MI in the territory of ≥1 treated vessels within the first 30 days.

Statistical Methods

Further to the statistical methods described in the main manuscript, the SXscore was compared to the GRC using previously described methodology.[5] Firstly, the net reclassification improvement was calculated for mortality using the GRC. Amongst patients experiencing an event, movement from a low to a high risk group was considered favourable, whilst movement from a high risk group to a lower risk group detrimental. Conversely amongst patients not experiencing an event, movement from a low to high group was detrimental, whilst movement form a high to low risk group beneficial. The net reclassification improvement was subsequently calculated by considering the difference between the proportion of patients who experienced an event and were reclassified, and the proportion of patients who did not experience an event and were reclassified.[5] Secondly, discrimination of the models was assessed using the C-statistic from the receiver operator curves (ROC).

SUPPLEMENTARY TABLES

Supplementary Table 1: 1-year all-cause mortality classified according to terciles of the SYNTAX score and Global Risk Classification Groups.

DEATH (number of patients)		**SYNTAX Score**		
		Tercile 1 (≤22)	Tercile 2 (>22-32)	Tercile 3 (≥33)
Global Risk Classification	Low	1	1	0
	Mid	1	7	8
	High	0	0	15

No DEATH (number of patients)		**SYNTAX Score**		
		Tercile 1 (≤22)	Tercile 2 (>22-32)	Tercile 3 (≥33)
Global Risk Classification	Low	99	83	0
	Mid	36	32	93
	High	0	0	55

Supplementary Table 2: 1-year MACCE classified according to terciles of the SYNTAX score and Global Risk Classification Groups.

MACCE (number of patients)		SYNTAX Score		
		Tercile 1 (≤22)	Tercile 2 (>22-32)	Tercile 3 (≥33)
Global Risk Classification	Low	15	14	0
	Mid	7	18	33
	High	0	0	24

No MACCE (number of patients)		SYNTAX Score		
		Tercile 1 (≤22)	Tercile 2 (>22-32)	Tercile 3 (≥33)
Global Risk Classification	Low	85	70	0
	Mid	30	21	68
	High	0	0	46

Supplementary References

1. Ranucci M, Castelvecchio S, Menicanti L, Frigiola A, Pelissero G. Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony. *Circulation.* 2009;119(24):3053-3061.
2. Singh M, Rihal CS, Lennon RJ, Spertus J, Rumsfeld JS, Holmes DR. Bedside Estimation of Risk From Percutaneous Coronary Intervention: The New Mayo Clinic Risk Scores. *Mayo Clinic Proceedings.* 2007;82(6):701-708.
3. Garg S, Sarno G, Garcia-Garcia HM, Girasis C, Wykrzykowska J, Dawkins KD, Serruys PW. A New Tool for the Risk Stratification of Patients With Complex Coronary Artery Disease: The Clinical SYNTAX Score. *Circ Cardiovasc Interv.* 2010;3(4):317-326.
4. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16(1):31-41.
5. Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat. Med.* 2008;27(2):157-172; discussion 207-112.

PART V

The Impact of Clinical Factors on Outcomes in Patients Treated with PCI

Chapter 5.1

Cardiovascular risk profile of patients included in stent trials: A meta-analysis of individual patient data from randomized clinical trials: Insights from 33 prospective stent trials in Europe

EuroIntervention. In press

Pascal Vranckx, Eric Boersma, Scot Garg, Marco Valgimigli, Gerrit-Anne van Es, Dick Goedhart, Patrick W. Serruys

ABSTRACT

Background: Few data document trends in cardiovascular (CV) risk-factors in patients with or without previous symptomatic CV-disease. We assessed the prevalence and trends in (non) modifiable CV risk-factors, and the use of cardio-protective therapies in patients enrolled in coronary stent trials.

Methods: This analysis included prospective data on 10253 predominantly European adults who were enrolled in 33 coronary stent studies between 1995 and 2006. Data were collected at the time of enrolment using a standardized patient clinical record form, and analysed by considering three consecutive time periods: 1995-1997 (I), 1998-2002 (II) and 2003-2006 (III) rendering approximately equal numbers per period.

Findings: Overall the proportion of active smokers remained constant (Period I to III: 28%, 27%, 21%, p=0.45), however the proportion increased in females under 50 years of age (about 2%/ year, R.R: 1.20, P=0.05 period III vs. I). Prevalent diabetes increased (16%, 17%, 25%; p=0.03). The prevalence of a body-mass index (BMI) ≥25 kg/m^2 was high, but no trend was observed (69%, 68%, 70%; p=0.24). The proportion of patients with elevated blood pressure (i.e. ≥140/90 mmHg, in diabetes ≥130/80 mmHg) remained unchanged (55%, 50%, 53%; p=0.22), despite an increase in the number of patients taking anti-hypertensive agents (84%, 89%, 90%; p=0.30). Conversely, the proportion of patients with elevated total cholesterol (≥4.5mmol/L) decreased (80%, 66%, 52%; p=0.002), which was consistent with the increase in patients taking lipid lowering drugs (32%, 62%, 69%; p=0.08). The portion of patients reaching therapeutic targets for blood lipids improved, but no improvement was seen in blood pressure control (p=0.29).

Interpretation: There is an unmet clinical need in primary and secondary CV prevention in Europe. Patients requiring PCI are an important target population in whom lifestyle changes and aggressive secondary preventative measures should be aimed. Ultimately PCI should open the door towards optimising secondary prevention.

Key Words: coronary artery disease, prognosis, risk stratification, percutaneous coronary intervention.

INTRODUCTION

Atherosclerosis and coronary thrombosis are a major cause of premature death worldwide, and are an important source of loss of disability-adjusted life years.[1-3] As its clinical consequences are highly relevant for patients and society, so are the benefits of prevention. Effective prevention involves a strategy based on the knowledge of a population's attributable risk, which itself is prone to variation as the prevalence of several risk factors may fluctuate within a population over time.[4]

Patients with established atherosclerotic cardiovascular disease (CVD) [coronary artery disease (CAD), cerebrovascular disease, and peripheral arterial disease (PAD)] are at particular risk of recurrent nonfatal and fatal cardiovascular (CV) events.[5]

The EUROASPIRE study group applied a cross-sectional design to assess trends in modifiable cardiovascular risk factors and medical treatment in CVD patients from 1995—96, 1999—2000, and 2006—07 in selected geographical areas and hospitals in Europe. The results were discouraging, and revealed a continuing gap between the standards set by guidelines on secondary cardiovascular risk prevention, and the results achieved in clinical practice.[6] As per design, the EUROASPIRE surveys focussed on secondary prevention in routine clinical practice patients. We aimed to support the EUROASPIRE findings in the clinical trial setting, together with simultaneously addressing the aspect of primary prevention.

The prevalence of baseline demographic and the CV-risk profile of patients included in stent investigations is influenced by specific study inclusion and exclusion criteria, changes in the prevalence of CV-risk factors and related therapy, and may or may not mirror trends reported in routine clinical practice. This information is important when considering differences between trial results and extrapolations with routine clinical practice.

We conducted a retrospective analysis of prospectively collected data from stent trials conducted mainly in Europe by an Academic Research Organization (ARO) over the last two decades focusing on modifiable CV risk factors and medical treatment. The aim of the present investigation was to analyze apparent variations in overall CV-risk over time in this specific patient population.

METHODS:

Study population and data collection:

We analysed the baseline data sets of 10253 patients, with angiographic proven obstructive atherosclerotic CAD, enrolled in one of 33 prospective, randomized native coronary stent trials conducted predominantly in Europe by a single independent ARO (CARDIALYSIS, Rotterdam, the Netherlands) between 1995 and 2006 (last patient in 10/2006) All trials except two were registered in the ClinicalTrials.gov database [ClinicalTrials.gov]. A summary of all trials included in the current analysis, together with their inclusion and exclusion criteria are presented in Appendices 1 and 2, respectively. Detailed

trial information and trial results are available elsewhere.[7-38] Individual databases were managed by CARDIALYSIS, Rotterdam, who conducted systematic audits and quality checks.

We addressed trends in the prevalence of diabetes and individual modifiable CV risk factors, together with the presence of established symptomatic atherosclerotic peripheral or cerebral arterial disease. Modifiable CV-risk factors considered in this analysis consisted of current smoking, systolic blood pressure (SBP), body mass index (BMI) and hypercholesterolemia. Patients were classified according to their gender and age (men: 65 years or older; women 70 years or older). The cut-offs for age were arbitrary set considering the relation between age and cardiovascular disease in men and women with or without diabetes.[39] The standard case record form (CRF) did not record the participants' level of physical activity.

The use of cardio-protective drugs such as cholesterol lowering medications (statins, fibrates), anti-platelet drugs (clopidogrel, ticlopidine, aspirin), anti-hypertensive agents (beta-blockers, calcium antagonists, angiotensin-converting enzyme [ACE] inhibitors/angiotensin receptor blockers, diuretics) and any diabetic treatment prior to randomization was systematically recorded. Information on contra-indications against the use or reasons for stopping or specific cardio-protective drugs could not be captured from the data base.

Each individual study was approved by the appropriate local regulatory and ethics committee of the participating trials. All participants provided informed consent before taking part in each of the individual studies.

Definitions:

Information about the patient's previous history of coronary or other atherosclerotic disease, reported medication, and baseline CV-risk factors were obtained via a standardized patient CRF used by the ARO in all stent trials, thus enabling the following definitions to be used in the current analysis:

Current smoking was defined as the consumptions of an average of ≥5 cigarettes per day within the month prior to enrolment.

Prevalent diabetes mellitus was defined as a fasting serum glucose level ≥ 7.0 mmol/l (126mg/dl), non-fasting glucose level ≥ 11.1 mmol/l (200mg/l), or a patient indicating a previous diagnosis of diabetes mellitus made by a physician, or the current use of diabetes medication. Diabetes treatment was specified: exercise/diet only, treatment with oral hypoglycaemic agents, or treatment with insulin.[40]

Prevalent hypertension was defined as a seated SBP ≥ 140mmHg and a diastolic (DBP) ≥ 90mmHg, (except among patients with diabetes in whom this was defined as BP >130/80mmHg). Patients were further stratified as "optimal" if mean SBP was <120 and diastolic pressure <80mmHg; as "normal" if mean SBP was <130 mm Hg/DBP was 80-84 mm Hg and "high normal" if SBP 130-139mmHg/DBP 85-89mmHg.[41] If the systolic and diastolic pressure readings belonged to different categories, the higher of the two readings was used to assign the blood-pressure category.

Body mass index was calculated as weight in kilograms divided by the square of height in meters. Patients were considered to be of normal weight, overweight or obese if their respective BMI's were <25, 25≤ and <30, or ≥30.[42]

Established, symptomatic CVD[5] consisted of 1 or more of the following criteria: history of unstable angina with documented obstructive CAD, history of percutaneous coronary intervention (PCI), history of coronary artery bypass grafting, or previous myocardial infarction (MI). Documented cerebrovascular disease consisted of a hospital or neurologist's report with the diagnosis of transient ischemic attack or ischemic stroke. Documented PAD consisted of a history of intermittent claudication together with a previous and related intervention, such as angioplasty, stenting, atherectomy, peripheral arterial bypass graft, or other vascular intervention including amputation.

Prior MI was defined as either a self-reported history of physician diagnosed MI, or a history of MI identified on the baseline electrocardiogram, which was characterized by the presence of a major Q-wave or a minor Q-wave with ischemic ST-T changes.

Statistics:

We considered three consecutive study periods: 1995-1997 (Period I), 1998-2002 (Period II) and 2003-2006 (Period III), rendering approximately equal numbers of patients per study period. The time period refers to the starting date of the study. We respected the time periods used in the EUROASPIRE program.[6]

Analyses were done applying the method of Generalized Estimated Equations (GEE) with a Poisson distribution, a logarithmic link, modelling the study period either as factor or as a covariate.[43] By taking the study level as a random factor, using patients as replicates, nested within the study we acknowledge patients within a study form a more homogeneous group than between studies. This model also allowed accommodation of 'ignorable' missing data.[44] An exchangeable working correlation matrix was used to apply the GEE methodology. For the purpose of this analysis baseline values from stent investigations, recorded in the database, were grouped into higher level terms. In the case that a patient scored positively on one of the lower level terms, he or she became member of the higher level term, otherwise the existence of one variable that showed that the patient did not belong to the higher level term was sufficient to exclude him/her from membership, even in the presence of missing data on other lower level terms. This strategy was used to minimise the loss of data, however, this may have lead to some under-estimation when calculating the prevalence percentages of these high level terms. [e.g. statins and fibrates were grouped into the class of lipid lowering drugs]. Patients were classified into using lipid lowering drugs when they reported to use at least one of the drugs. In the case that there was no information at all about any drug in this class they were classified as missing, in all other cases they were classified as using no lipid lowering drug at all. This strategy was used for all grouped variables. With this approach, the estimated regression coefficients were identical to those obtained using ordinary logistic regression, but the standard errors were adjusted to account for the clustered data structure. All tests were 2-sided, p-values were

not used to reject null-hypotheses, they are only shown to inform the reader of the probability level of a given outcome.

Results are summarized as relative risks for study periods 1998-2002 (RR_1) and 2003-2006(RR_2) both with respect to the 1995-1997 period. Trends are calculated by using the time period as a covariate into the GEE model. Statistical analyses and graphics were produced with assistance of a commercially available statistical software package (SAS version 8.2; SAS, Cary, NC, USA)

Role of the funding source

The sponsors of the individual trials had no role in this study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Between February 1995 and 2006, 10253 patients (male: 76%) were pooled from 33 coronary stent trials in patients with obstructive CAD. The mean age of patients included in the analysis was respectively 60.1, 60.6 and 62.0 years for time periods I, II, and III [***Table 1***]. ***Tables 2-4*** show the frequency and distribution of the modifiable CV risk factors over the study periods in relation to patient age, gender, medical history of CV disease, and treatment. Relative changes between consecutive time periods, taking Period I as a reference, are expressed as relative risks, and are shown in **Table 5**, together with trends over the 12 year study period.

Table 1: Prevalence of Cardiovascular risk factors expressed as counts and percentages*

		1995-1997	1998-2002	2003-2006	Total
Age	> 70 (Women), > 65 (Men)	1287 (29%)	684 (31%)	998 (34%)	2969
	≤ 70 (Women), ≤ 65 (Men)	3189 (71%)	1548 (69%)	1920 (66%)	6657
Sex	Men	3486 (78%)	2162 (76%)	2164 (74%)	7812
	Women	1010 (22%)	675(24%)	754 (26%)	2439
SBP (mmHg)	SBP <120	798 (28%)	909 (32%)	893 (31%)	2600
	120≤SBP<130	539 (19%)	518 (18%)	559 (19%)	1616
	130≤SBP<140	495 (17%)	544 (19%)	550 (19%)	1589
	SBP≥140	1043 (36%)	856 (30%)	898 (31%)	2797
Total cholesterol	≤ 4.5 mmol/L	2852 (63%)	1793 (63%)	2458 (84%)	7103
	> 4.5 mmol/L	1645(37%)	1045 (37%)	460 (16%)	3150
BMI	<18	9 (3%)	13 (5%)	10 (4%)	32
	18 ≤ BMI <25	870 (31%)	886 (32%)	836 (29%)	2592
	25≥ BMI <30	1356 (48%)	1290 (46%)	1375 (48%)	4021
	BMI ≥ 30	610 (21%)	598 (21%)	636 (22%)	1844
Diabetes melitus		701 (16%)	496 (17%)	732 (25%)	1929
Current smokers		1103 (28%)	769 (27%)	650 (22%)	2522

*Percentage relative to the study period

SBP: systolic blood pressure; BMI: body mass index

Table 2: Prevalence of current smoking, being overweight and/or obesity expressed as percentages (relative to the study period) by age, sex and history of established cardiovascular disease.

Subgroups			Current smoker > 5 sigarettes per day			Overweight and Obesity BMI > 25kg/m^2			Obesity BMI > 30kg/m^2		
			1995-1997	1998-2002	2003-2006	1995-1997	1998-2002	2003-2006	1995-1997	1998-2002	2003-2006
Age	**> 70 (Women) > 65 (Men)**		13.5%	12.2%	9.3%	63.7%	66.7%	66.6%	15.8%	19.1%	17.3%
	≤ 70 (Women) ≤ 65 (Men)		33.5%	33.4%	29.0%	71.4%	69.8%	72.3%	23.7%	22.4%	24.7%
Sex	**Men**		30.5%	28.4%	24.5%	71.0%	69.9%	71.5%	19.5%	19.4%	20.7%
	Women		18.7%	22.2%	15.9%	63.2%	65.4%	67.2%	27.1%	27.6%	26.7%
Established CVD	A	**Previous MI**	26.7%	30.3%	28.1%	68.3%	66.7%	68.8%	19.0%	20.8%	21.3%
	B	**Previous PCI or CABG**	20.2%	18%	12.1%	49.4%	41.4%	72.4%	14.0%	22.2%	26.8%
	C	**Previous Peripheral Vascular disease**	34.5%	33.1%	29.0%	62.8%	63.1%	65.4%	17.5%	22.0%	22.6%
	D	**Previous Stroke**	6.1%	13.0%	20.2%	77.6%	77.8%	66.6%	16.3%	25.9%	27.5%
		Any of A,B,C,D	26.2%	28.7%	25.1%	68.0%	67.2%	68.5%	19.1%	21.9%	22.1%

CVD: cardiovascular disease; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting
Previous stroke (of any kind) = cerebrovascular accident, transient ischaemic attack, reversible intermittent neurological deficit.

Table 3: Prevalence of hypertension, hypercholesterolemia and diabetes expressed as percentages (relative to the study period) by age, sex, history of established cardiovascular disease.

Subgroups			Hypertension BP>140/90mmHg non diabetes, >130/80mmHg Diabetes			Hypercholesterolaemia >4.5mmol/l (200mg/dl)			Diabetes		
			1995-1997	1998-2002	2003-2006	1995-1997	1998-2002	2003-2006	1995-1997	1998-2002	2003-2006
Age	> 70 (Women) > 65 (Men)		59.4%	57.0%	60.4%	77.3%	59.9%	48.6%	18.4%	19.6%	29.2%
	≤ 70 (Women) ≤ 65 (Men)		53.2%	47.5%	48.4%	81.1%	64.5%	53.0%	14.3%	16.3%	22.9%
Sex	Men		52.7%	47.5%	49.5%	79.2%	60.3%	48.5%	14.2%	16.0%	22.5%
	Women		62.6%	59.7%	61.1%	83.0%	71.5%	60.6%	20.2%	21.7%	32.5%
Established CVD	A	Previous MI	46.5%	45.3%	44.4%	78.7%	59.4%	41.5%	16.4%	18.3%	24.9%
	B	Previous PCI or CABG	52.6%	49.5%	54.2%	85.4%	48.1%	38.5%	19.6%	24.8%	32.6%
	C	Previous Peripheral Vascular disease	64.1%	64.3%	64.8%	80.8%	64.4%	56.3%	24.1%	22.4%	35.5%
	D	Previous Stroke	77.1%	68.5%	56.8%	77.8%	66.7%	30.8%	34.7%	33.3%	39.3%
		Any of A,B,C,D	48.9%	48.9%	48.8%	79.4%	60.2%	43.0%	16.8%	19.1%	26.2%

CVD: cardiovascular disease; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting

Previous stroke (of any kind) = cerebrovascular accident, transient ischaemic attack, reversible intermittent neurological deficit.

Table 3B: Prevalence of blood pressure categories expressed as percentages (relative to the study period) by age, sex, history of established cardiovascular disease.

Subgroups			Systolic Blood Pressure (mmHg)										
			1995-1997				1998-2002				2003-2006		
			<120	120-129	130-139	≥140	<120	120-129	130-139	≥140	<120	120-129	130-139	≥140
Age	**> 70 (Women) > 65 (Men)**		22.0%	17.2%	18.1%	42.7%	24..2%	17.2%	20.7%	38.0%	24.2%	17.9%	18.8%	39.1%
	≤ 70 (Women) ≤ 65 (Men)		30.3%	19.4%	16.9%	33.5%	34.9%	19.2%	18.4%	27.5%	34.3%	20.0%	19.0	28.7%
Sex	**Men**		28.9%	20.1%	17.9%	33.2%	33.6%	19.0%	19.2%	28.2%	33.0%	20.1%	18.9%	28.0%
	Women		24.4%	14.4%	15.2%	46.1%	25.2%	17%	18.9%	38.9%	24.4%	17.0%	19.2%	39.4%
Established CVD	A	**Previous MI**	35.6%	21.8%	16.4%	26.2%	37.5%	18.2%	17.9%	26.5%	38.2%	21.1%	15.7%	25.0%
	B	**Previous PCI or CABG**	23.7%	22.5%	19.7%	34.1%	34.7%	15.8%	18.8%	30.7%	27.5%	24.4%	14.5%	33.6%
	C	**Previous Peripheral Vascular disease**	20.1%	14.7%	21.2%	44.0%	19.6%	21.0%	12.6%	46.9%	19.4%	21.3%	19.0%	40.3%
	D	**Previous Stroke**	18.8%	6.3%	12.5%	62.5%	24.1%	9.3%	20.4%	46.3%	29.6%	16.0%	19.8%	34.6%
		Any of A,B,C,D	32.3%	21.4%	17.1%	29.1%	34.7%	18.3%	17.4%	29.6%	34.2%	20.7%	17.1%	27.9%

CVD: cardiovascular disease; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting

Previous stroke (of any kind) = cerebrovascular accident, transient ischaemic attack, reversible intermittent neurological deficit.

Table 4: Prevalence of cardiovascular treatment per drug category as percentages (relative to the study period) by age, sex, history of established cardiovascular disease and cardio-protective therapy.

			Cardio-protective drug treatment		
			1995-1997	1998-2002	2003-2006
			blood pressure lowering therapy		
Age	> 70 (Women), > 65 (Men)		80.1%	89.3%	91.4%
	≤ 70 (Women), ≤ 65 (Men)		85.7%	89.2%	89.7%
Sex	Men		84.0%	88.2%	89.7%
	Women		84.4%	92.6%	91.8%
Established CVD	A	Previous MI	90.0%	92.3%	94.1%
	B	Previous PCI or CABG	82.4%	92.0%	91.9%
	C	Previous Peripheral Vascular disease	84.5%	90.9%	96.0%
	D	Previous Stroke	75.6%	90.7%	89.3%
		Any of A,B,C,D	88.5%	91.9%	93.4%
			Lipid lowering treatment		
Age	> 70 (Women), > 65 (Men)		27.2%	54.6%	62.6%
	≤ 70 (Women), ≤ 65 (Men)		33.5%	64.5%	72.4%
Sex	Men		28.4%	61.5%	68.4%
	Women		42.9%	61.3%	70.9%
Established CVD	A	Previous MI	34.3%	69.5%	80.0%
	B	Previous PCI or CABG	19.6%	72.1%	78.5%
	C	Previous Peripheral Vascular disease	31.8%	70.7%	71.3%
	D	Previous Stroke	—	73.2%	69.0%
		Any of A,B,C,D	33.2%	68.7%	77.3%
			Anti platelet therapy		
Age	> 70 (Women), > 65 (Men)		89.1%	90.2%	92.0%
	≤ 70 (Women), ≤ 65 (Men)		91.6%	93.7%	93.4%
Sex	Men		91.2%	92.7%	93.4%
	Women		89.7%	92.4%	91.6%

			Cardio-protective drug treatment		
			1995-1997	1998-2002	2003-2006
Established CVD	A	Previous MI	93.2%	95.3%	96.5%
	B	Previous PCI or CABG	92.6%	92.7%	92.6%
	C	Previous Peripheral Vascular disease	87.2%	90.2%	96.0%
	D	Previous Stroke	89.8%	98.1%	89.3%
		Any of A,B,C,D	92.3%	94.5%	96.0%

CVD: cardiovascular disease; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting
Previous stroke (of any kind) = cerebrovascular accident, transient ischaemic attack, reversible intermittent neurological deficit.

Table 4B: Prevalence of statin use expressed as percentages (relative to the study period) by age, sex, history of established cardiovascular disease and cardio-protective therapy.

		STATIN USE		
		1995-1997	1998-2002	2003-2006
Age	**> 70 (Women), > 65 (Men)**	—	3.4%	56.6%
	≤ 70 (Women), ≤ 65 (Men)	—	3.0%	67.0%
Sex	**Men**	—	3.1%	64.0%
	Women	—	3.2%	65.3%
EstablishedCVD	**A Previous MI**	—	3.2%	58.7%
	B Previous PCI or CABG	—	4.0%	74.2%
	C Previous Peripheral Vascular disease	—	7.7%	66.4%
	D Previous Stroke	—	3.7%	60.7%
	Any of A,B,C,D	—	3.0%	71.9%
Antiplatelet treatment		—	3.2%	66.5%
Aspirin		—	3.2%	66.7%
Thienopyridine (ticlopidine or clopidogrel)		—	3.6%	68.4%
Any blood-pressure-lowering treatment		—	3.2%	67.1%
Beta-blockers		—	2.9%	69.8%
ACE-inhibitors and ARBs		—	4.0%	69.4%
Calcium Channel blockers		—	3.7%	64.3%
Diuretics		—	3.1%	61.8%
Any Lipid Lowering Drugs		—	7.2%	93.2%
Statins		—	100%	100%
Fibrates		—	7.2%	61.3%

Table 5: Relative risks for study periods 1998-2002 and 2003-2006 both with respect to the 1995-1997 period for the individual risk factors studied, cardio-protective drugs by class and concomitant disease. Trends are calculated by using the time period as a covariate.

	1998-2002 vs. <1997	>2002 vs. <1997	
	Relative Risk (95% Confidence Interval)	Relative Risk (95% Confidence Interval)	P Value
Risk factor			
Current smoking (>5 cigarettes/ day)	0.96 (0.80-1.15)	0.89 (0.71-1.11)	0.45
Obesity: BMI > 30kg/m^2	1.02 (0.86-1.21)	1.06 (0.91-1.25)	0.45
Overweight: BMI > 25kg/m^2	1.00 (0.94-1.07)	1.04 (0.98-1.11)	0.24
Hypertension[1]	0.84(0.68-1.04)	0.86 (0.69-1.07))	0.22
Raised cholesterol Concentration[2]	0.78 (0.69-0.88)	0.61 (0.54-0.70)	0.002
Diabetes Mellitus [3]	1.11 (0.96-1.28)	1.43 (1.17-1.75)	0.03
Blood pressure control treatment	1.04 (0.95-1.15)	1.06 (0.96-1.17)	0.30
Lipid lowering treatment	3.40 (0.86-13.44)	3.80 (0.98-14.77)	0.08
Cardioprotective drugs by class			
Antiplatelet treatment	1.03 (0.99-1.06)	1.04 (0.996-1.09)	0.09
Aspirin	1.02 (0.99-1.06)	1.03 (0.98-1.09)	0.23
Thienopyridine (clopidogrel, Ticlopidin)	1.24 (0.69-2.24)	1.82 (1.05-3.16)	0.04
β blockers	1.11 (1.01-1.22)	1.16 (1.06-1.27)	0.009
ACE-inhibitors and ARBs	0.77 (0.45-1.30)	1.06 (0.60-1.77)	0.86
Calcium-channel blockers	0.74 (0.62-0.89)	0.61 (0.54-0.67)	< 0.001
Diuretics	1.38 (1.07-1.78)	1.85 (1.48-2.30)	0.002
Statins	>2002 vs 1998-2002: 0.92 (0.88-0.97)		
Fibrates	3.45 (0.86-13.91)	1.14 (0.22-5.99)	0.23
Concomitant disease			
Peripheral vascular disease	0.84 (0.48-1.47)	0.67 (0.38-1.19)	0.54
Cerebrovascular disease	0.48 (0.21-1.13)	0.66 (0.27-1.61)	0.43
Congestive heart failure	0.40 (0.31-0.52)	0.55 (0.30-1.02)	0.55

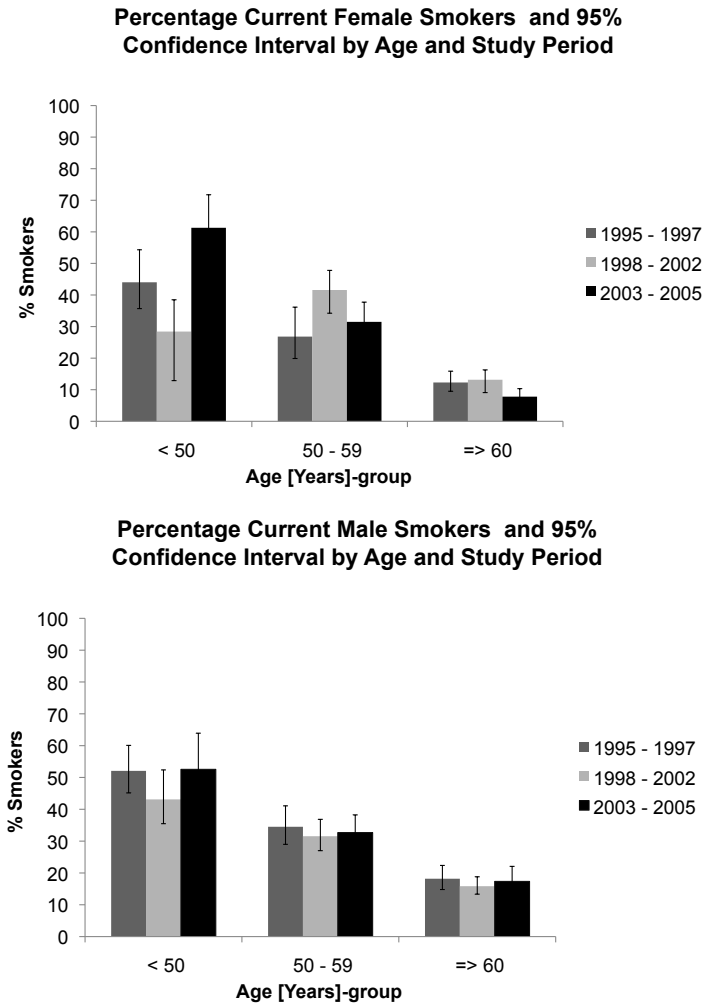
Non-diabetic: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90mmHg
Diabetic: systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥80mmHg
Total cholesterol ≥4.5 mmol/L
Diabetes: a fasting serum glucose level ≥ 7.0 mmol/l (126mg/dl), non-fasting glucose level ≥ 11.1 mmol/l (200mg/l), or participant report of a physician diagnosis of diabetes or current use of diabetes medication

ACE-inhibitors: angiotensin-converting enzyme inhibitors; ARB: angiotensin-receptor blockers

Overall the proportion current smokers did not differ between time periods (P_{TREND}=0.45), not even in the subgroup of patients with known CVD (P_{TREND}=0.43)[***Tables 2 and 5***]. There was a decrease in male smokers over time which was consistent in all age categories, however this trend was offset by an increase in the proportion of women smokers aged less than 50 years [***Figure 1***].

Mean body weight respectively was 78.3, 78.8, and 78.7 kilogram for Periods I, II and III. The overall proportion of obese and overweight patients did not show a trend over time, not even in the patient group with history of CV disease [***Table 5***]. There was a possible increase however, in the proportion of overweight women (P_{TREND}=0.15), whilst the proportion of obese women remained much the same [***Table 2***]. The proportion of obese women was higher than obese men throughout the study period.

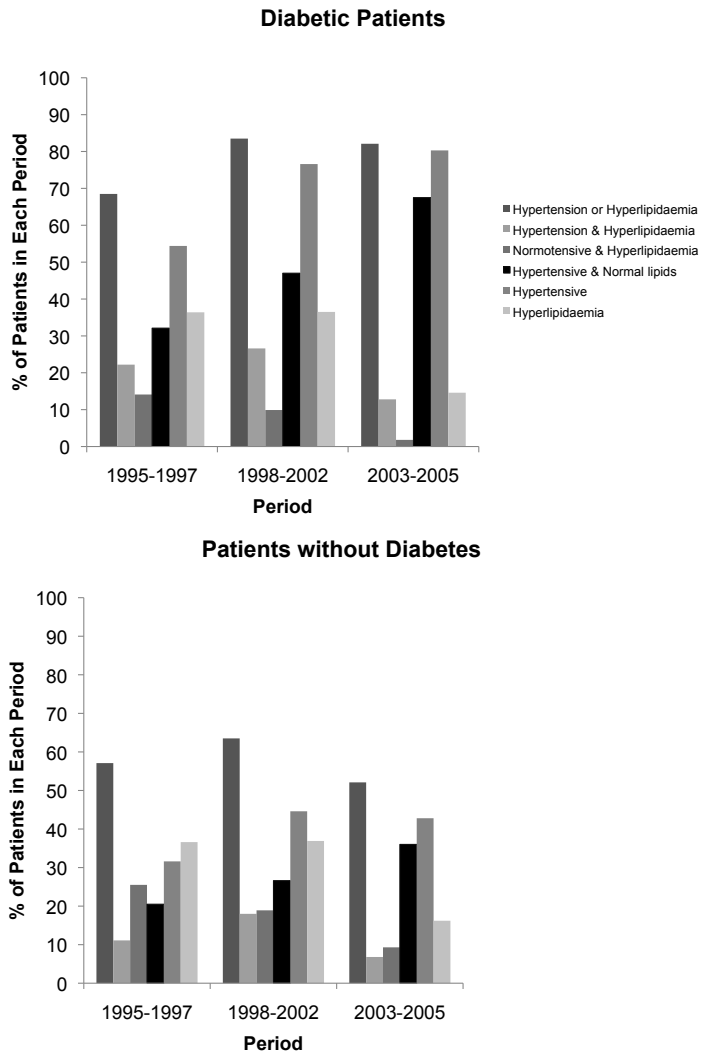
Figure 1 a-b



Only three-fifth of patients in all three periods had their BP below target levels [respectively: 55%, 50%, 53%], and most compelling this occurred in only half of the patients with established CVD [respectively: 51%, 52%., 51%; P_{TREND}=0.56] [***Tables 3, 3B and 5***] Of those patients taking BP lowering drugs, although not necessarily taken as anti-hypertensive treatment, the proportion that achieved the SBP target of <140/90 mm Hg (<130/80 mm Hg in patients with diabetes) did not differ over time (Period I: 47%, Period II:49%, Period III:47%; P=0.53; ***Tables 3 and 5***). The proportion of hypertensive patients not taking blood-pressure-lowering treatment declined over time (respectively: 19%, 10%, 9.0%; p=0.21).

Overall, the proportion of patients with a raised total blood cholesterol concentration decreased over the three time periods (P_{TREND}=0.002) [***Tables 3 and 5***], with a similar trend observed in the subgroup

Figure 2 a-b



of patients with established CVD (P_{TREND}<0.001). Although the proportion of patients taking lipid-lowering drugs (statins, fibrates) who achieved the cholesterol target of <4.5 mmol/L, was twice as high in Period III than in Period I [***Tables 3 and 5***], only 48% of patients receiving treatment in Period III achieved the target for optimal cholesterol control, a trend consistent with the increase in statin use [***Table 4;*** R.R= 9.7, P=0.02]. Of note, statin use was absent, or not specifically asked about in the CRF in Period I, and therefore the relative risk was calculated comparing Period III to II, and consequently no trend could be calculated.

The frequency of prevalent diabetes increased over time [P_{TREND}=0.03] and this increase was more prominent in men than in women [***Tables 3 and 5***]. There was a parallel, proportional increase in the concomitant use of lipid lowering and antihypertensive drugs in these patient groups. In the group of diabetics, the proportion of patients with hypertension increased, whilst those with a cholesterol level >4.5mmol showed a reverse trend [***Figure 2***].

The proportion of patients taking either statins, calcium channel blockers, β-blockers, diuretics and anti-platelet treatment increased over time and to the same extent considering age and gender, in secondary and primary prevention [***Table 4-5***].

DISCUSSION

The lack of improvement in modifiable behavioural risk factors in patients enrolled in stent investigations in Europe between 1995 and 2006 reflects similar evolutions in the general population.[6,45-47] Potential patient selection bias, reflecting the specific inclusion and exclusion criteria of the individual studies must be taken into account when putting the current results into perspective. This study emphasises the continuing gap between the standards set in guidelines on CV risk prevention, and the results achieved in clinical practice. Our results are the product of lifestyle, inadequate risk factor management, and the under-use of prophylactic drug therapies, even after the development of a potential life-threatening disease. Overall, these results call for action.

In our analysis the prevalence of smokers was systematically higher than in the corresponding time periods of the EUROASPIRE surveys, however similar trends appeared. Overall, there was a decrease in smoking over time in all age categories, although this trend was partially offset by an increase in the proportion of women smokers younger than 50 years. The high number of smokers in patients with previous symptomatic CV disease is worrisome. Promotion of smoking cessation is important at both a population and individual level, for both primary and secondary prevention.[48-49] The magnitude of the increase in CV-risk through smoking is closely, and linearly, related to the number of cigarettes smoked, with even low levels of smoking (e.g., five cigarettes per day) still being associated with an appreciable increased risk of acute MI.[50] A physician's advice to stop smoking is one of the most important first steps in the cessation process, but efforts need to be sustained over time, and more than likely will need to be complemented by pharmacological therapies to counteract nicotine dependence.[51-52]

The prevalence of obesity, systolic hypertension and to slightly lesser extent diabetes was lower in our analysis as compared to EUROASPIRE and a recent all-comers trial setting.[53] Most studies involved in our analysis only included patients with 'simple' coronary lesion morphology. Consequently, we potentially excluded from our analysis a patient cohort with high arterial atherosclerotic burden and hence patients with a high prevalence of obesity, hypertension and diabetes.

The frequency of overweight and obese patients included in elective stent studies was slightly lower when compared to the general population for the three time periods considered.[6] In EUROASPIRE, but not in our analysis, the distribution of BMI shifted in a skewed fashion such that the proportion of the population with morbid obesity increased by a greater extent than the proportion who were overweight. Still in Period III seven out of ten patients had a BMI ≥ 25 kg/m^2 and over one fifth were obese. The numbers of patients classified as overweight and/or obese has reached epidemic proportions, despite both being associated with numerous co-morbidities. More than 70% of overweight patients were on anti-hypertensive or lipid lowering drugs in our analysis. The maladaptive effects of excessive body weight on various CV risk factors, together with its adverse effects on CV structure and function, results in its propensity to reduce overall survival.[54-55] Weight reduction interventions, beyond bariatric surgery, involves lifestyle choices including dietary intervention and increased physical exercise.[56] In a stepwise approach approved prescription medications targeting the various systems that regulate eating behaviour and body weight can be a valid adjunct to behavioural changes. The long-term maintenance of weight reduction is difficult and needs sustained personal and family motivation, and long-term professional support.

The prevalence of diabetes in the current study is less than reported in the real world,[6] though there was a possible trend towards an increase in the proportion of diabetics, especially in women (P_{TREND}: 0.19) and the elderly (0.03) over time.

The prevalence of hypertension was relatively low, compared to the corresponding time periods in the EUROASPIRE surveys, and only showed a small time trend towards better management in the subgroup of younger patients (P_{TREND}: 0.18). Despite the increased number of patients with systolic hypertension taking one or more BP lowering drugs, there was no corresponding improvement in overall BP control. Moreover, the proportion of patients taking one or more anti-hypertensives that lowered their systolic BP within the normal range did not change. This failure to manage BP effectively was higher than reported in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) at both one and two years follow-up.[57] Potential explanations for this are the sub-optimal dosing and titration of medication and/or poor patient compliance. BP lowering is essential for CV disease prevention; in a previous large meta-regression analysis within-trial gradients in achieved systolic pressure almost completely accounted for the differences in cardiovascular outcomes, including stroke and MI.[58]

In contrast with BP, the management of blood lipid concentrations improved substantially, which is largely attributed to the increased use of statins from 1998 onwards. Despite this however, only about half of patients achieved the target cholesterol concentration of below 4.5mmol/L, set by the 2003 joint European societies guidelines on CV disease prevention.[59] Lipid control in patients taking lipid lowering drugs has improved, however, reaching the 2007 total cholesterol target of 4.0mmol/L

or less may prove to be an important challenge for patients and physicians.[60] Systematic reviews indicate that a reduction of total (and LDL) cholesterol by statins is associated with marked reductions in both fatal and non-fatal CV-events.[61] In the subgroup of patients with a history of CV-disease we noticed a reduction in the portion of patients using concomitant cardioprotective drugs, that remarkably paralleled the trend for those that did not reach the preset cut off threshold target of total cholesterol (≤4.5mmol/l) accepted for this analysis. Again, this might be an indication of lack of change in lifestyle, suboptimal prevention or both, in this subgroup of patients.

Even if drug treatment according to guidelines and blood lipid status substantially improved, the attainment of therapeutic targets for BP did not. Again this might, point to the fact that drug treatments alone are not sufficient, and must be combined with a professional lifestyle intervention. The recommendations for lifestyle management remain the foundation of preventive cardiology: to stop smoking, make healthy food choices, and become physically active. Moreover, the evidence for their effectiveness in cardiovascular disease prevention and rehabilitation programmes that address lifestyle is compelling.[62] The preset targets as recommended by clinical practice guidelines are not unrealistic. In the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, patients had high rates of adherence to the regimen of diet, regular exercise, and smoking cessation.[63]

An important strength of this analysis is that all baseline data were collected using a standardized CRF in an established network of participating sites across Europe by a single ARO. The findings of this analysis must be considered within the context of the studies' limitations. Our study results only apply to patients in need of PCI for symptomatic CAD, extrapolations to the general populations may not be valid. A selection bias towards the sickest patients, not receiving effective CV prevention cannot be excluded. Patients included in stent investigations were recruited in specialist cardiac centres and may not be a representative sample of all patients with CV disease requiring PCI and stenting in Europe. The reality of preventive therapy and lifestyle changes in non specialist centres may be considerably different. Our analysis included only those aged 25–84 year because of the limited data available in older patient groups. Moreover, elderly patients and women have been shown to be under-represented in many clinical trials and surveys in cardiovascular heart disease.[64]

Changes in the baseline characteristics of patients who were enrolled in these stent investigations between 1995-2005 most probably reflect the shift in the general patient population. However, we acknowledge the slight variation in individual inclusion and exclusion criteria among studies which may have had an impact on the results. On the other hand, our statistical analysis allows correction for a relatively large variation of some items between studies within (a) study period(s) with respect to the observed trend over time.

CONCLUSIONS

Patients requiring PCI are an important target population in whom lifestyle changes and aggressive secondary preventative measures should be aimed. PCI should open the door towards optimising secondary prevention.

Appendix Table 1: Studies included in the Cardialysis Stent Database

Study	Study Name	Number of patients
ACS329[7]	ACS Multilink® Radiation Coronary Stent System Project	31
ADVANCE[8]	Additional Value of NIR Stents for Treatment of Long Coronary Lesions	437
ARTS-I[9]	Arterial Revascularisation Therapies Part I	1205
ARTS-II[10]	Arterial Revascularisation Therapies Part II	607
BENESTENT-2[11]	Belgian Netherlands Stent-2	827
DIRECTOR[12]	DIRECT stenting with the ORBUS R Stent	30
DOMINO[13]	The Study to Compare Cypher Versus Cypher Select in Treating Coronary Artery Lesions	102
EUROSPAH[14]	European Sonotherapy Prevention of Arterial Hyperplasia	403
FINESS1[15]	First International New Intravascular Rigid-Flex Endovascular Stent Study	255
FINESS2[16]	First International New Intravascular Rigid-Flex Endovascular Stent Study-2	156
GRANITE[7]	Gamma Radiation to Athermatous Neointima using Intra Coronary Therapy in Europe	96
HEALING-II[17]	Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth	63
JO-stent[7]		115
MAGIC 5-L[7,18]	The relationship between Wallstent length and late clinical and angiographic results	276
MUST[19]	Multicentre Stents Ticlopidine	260
NIRTOP[20]	Comparison of the NIRFLEX and NIRFLEX Royal Stent Systems	158
NUGGET[21]	NIR ultra-gold gilded equivalency trial	603
NOBORI[22]	Nobori Stent Trial	120
PAIR[23]	Pullback Atherectomy for In-stent Restenosis Trial	52
PAMI[24]	Primary Angioplasty in Myocardial Infarction	900
Stent PAMI pilot study[25]	Primary Angioplasty in Myocardial Infarction – pilot study	101
RAVEL[26]	Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions	238
REALITY[27]	Comparison of the Cypher Sirolimus Eluting and the Taxus Paclitaxel Eluting Stent Systems Trial	1386
SCEPTER[28]	Study of the Controlled Elution of Paclitaxel for the Elimination of Restenosis	271
SICTO [29]	Sirolimus-eluting stent in chronic total occlusions	25
SIMPLE[30]	The safety and efficacy of the Infinnium paclitaxel eluting stent for the treatment of single de novo lesions	103
SPIRIT[31]	Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions	60
SOPHOS[32]	Study Of PHosphorylcholine coating On Stents	425
TAXUS III[33]	TAXUS stent trial	28
TESTER[34]	Terumo Stent Registry	100
VELVET-2[35]	Direct stenting with the Bx VELOCITY balloon-expandable stent mounted on the Raptor rapid exchange delivery system versus pre-dilatation in a European randomized Trial	401
Wellstent native study[36]	The safety and efficacy of the self-expanding Wallstent	105
WEST-1[37]	West European Stent Trial	102
WEST-2[38]	West European Stent Trial	165

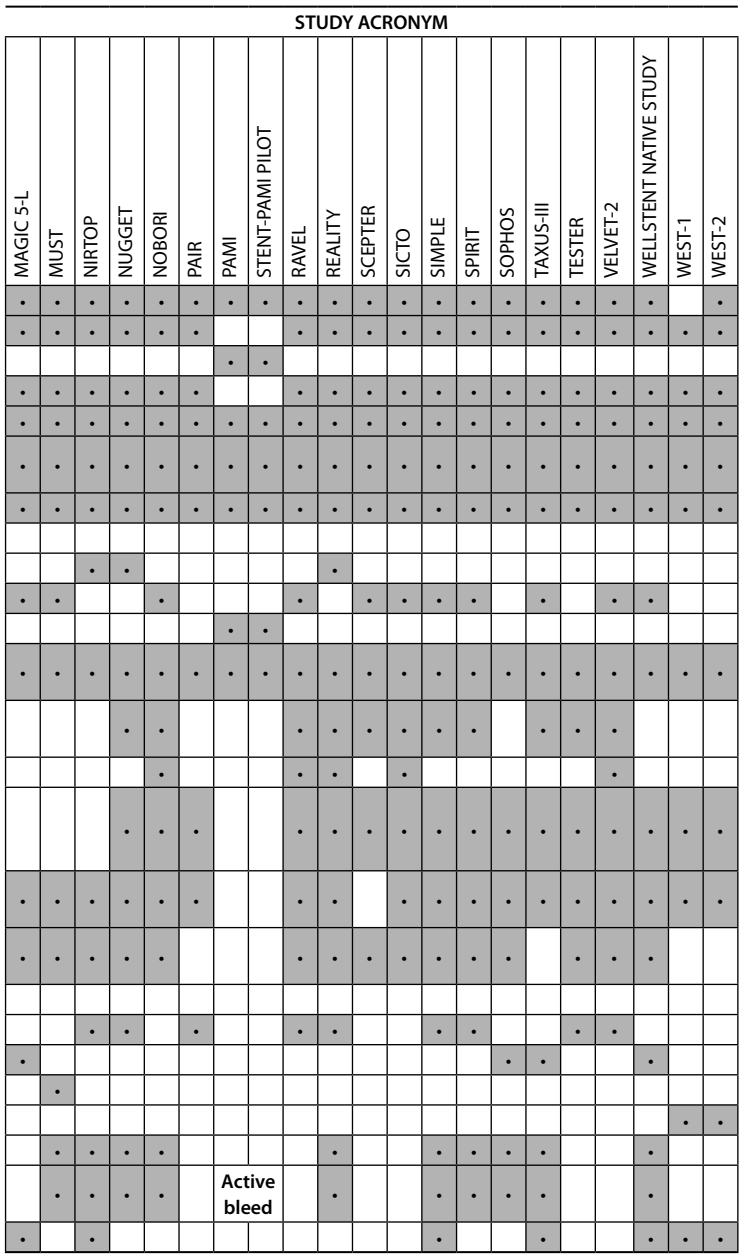
Appendix Table 2: Relevant clinical in-and exclusion criteria for trials included this analysis:

Inclusion Criteria	STUDY ACRONYM											
	ADVANCE	ARTS-I	ARTS-II	BENESTENT_II	DIRECTOR	DOMINO	EUROSPAH	FINESS-1	FINESS-2	GRANITE	HEALING-II	JO-stent
Age18 to 85 years	•	•	•	•	•	•	•	•	•	•	•	•
Stable and unstable angina.*	•	•	•	•	•	•	•	•	•	•	•	•
Myocardial infarction												
Eligible for PCI	•	•	•	•	•	•	•	•	•	•	•	•
Informed consent	•	•	•	•	•	•	•	•	•	•	•	•
Not pregnant and protected against pregnancy during the study	•	•	•	•	•	•	•	•	•	•	•	•
Participating in an investigational drug or another device study	•	•	•	•	•	•	•	•	•	•	•	•
Exclusion Criteria												
LV- EF ≤25%												
≤30%	•			•	•	•	•	•	•	•	•	•
Heart failure or CS		•	•									
Intolerance of aspirin, clopidogrel, ticlopidine, heparin, stainless steel, or contrast material.	•	•	•	•	•	•	•	•	•	•	•	•
Impaired renal function Creatinine >3.0 g/dl		•	•							•	•	
Creatinine clearance <50ml/kg/min		•	•	•	•	•	•	•		•	•	
Any significant condition which in the investigators opinion could interfere with the patient's optimal participation in the study.		•	•	•	•	•	•			•	•	
Known malignancy or life expectancy of less than the duration of the trial	•	•	•	•	•	•	•			•	•	•
Q-wave-MI in the territory supplied by the vessel to be stented and a large akinesia in the same region											•	•
MI <48 hours							•					
<72 hours									•	•	•	
<7days	•	•	•	•	•	•						
<14 days												
<30 days												
Stroke < 6 months	•	•	•	•	•	•	•	•	•		•	
GI bleed or peptic ulcer < 6months	•	•	•	•	•	•	•	•	•		•	
Hepatic failure		•	•	•	•	•	•				•	

CS: cardiogenic shock; GI: gastro-intestinal; HF: heart Failure; MI: myocardial infarction; PCI: percutaneous coronary intervention; LV-EF: Left ventricular ejection fraction

H denotes hours; D denotes days; M denotes months

*: Canadian Cardiology Society (I-IV) and Braunwald (B and C, I-III) classifications[65-66] or documented silent ischemia.


STUDY ACRONYM
MAGIC 5-L
MUST
NIRTOP
NUGGET
NOBORI
PAIR
PAMI
STENT-PAMI PILOT
RAVEL
REALITY
SCEPTER
SICTO
SIMPLE
SPIRIT
SOPHOS
TAXUS-III
TESTER
VELVET-2
WELLSTENT NATIVE STUDY
WEST-1
WEST-2
Active bleed

REFERENCES

1. Murray CJL, Lopez AD. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Boston: Harvard School of Public Health. 1996.
2. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation.* 2001;104:2746-2753.
3. Levi F, Lucchini F, Negri E, La Vecchia C. Trends in mortality from cardiovascular and cerebrovascular diseases in Europe and other areas of the world. *Heart.* 2002;88:119-124.
4. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, Lang CC, Rumboldt Z, Onen CL, Lisheng L, Tanomsup S, Wangai P, Jr., Razak F, Sharma AM, Anand SS. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet.* 2005;366:1640-1649.
5. Steg PG, Bhatt DL, Wilson PW, D'Agostino R, Sr., Ohman EM, Rother J, Liau CS, Hirsch AT, Mas JL, Ikeda Y, Pencina MJ, Goto S. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA.* 2007;297:1197-1206.
6. Kotseva K, Wood D, De Backer G, De Bacquer D, Pyorala K, Keil U. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. *Lancet.* 2009;373:929-940.
7. Data on file at Cardialysis.
8. Serruys PW, Foley DP, Suttorp MJ, Rensing BJ, Suryapranata H, Materne P, van den Bos A, Benit E, Anzuini A, Rutsch W, Legrand V, Dawkins K, Cobaugh M, Bressers M, Backx B, Wijns W, Colombo A. A randomized comparison of the value of additional stenting after optimal balloon angioplasty for long coronary lesions: final results of the additional value of NIR stents for treatment of long coronary lesions (ADVANCE) study. *J Am Coll Cardiol.* 2002;39:393-399.
9. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schonberger JP, Buller N, Bonser R, van den Brand MJ, van Herwerden LA, Morel MA, van Hout BA. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med.* 2001;344:1117-1124.
10. Serruys PW, Ong ATL, Morice M-C, Bruyne BD, Colombo A, Macaya C, Richardt G, Fajadet J, Hamm C, Dawkins K, O'Malley AJ, Bressers M, Dennis D, on behalf of the ARTS II Investigators. Arterial Revascularisation Therapies Study Part II - Sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. *Eurointervention.* 2005;1:147-156.
11. Serruys PW, van Hout B, Bonnier H, Legrand V, Garcia E, Macaya C, Sousa E, van der Giessen W, Colombo A, Seabra-Gomes R, Kiemeneij F, Ruygrok P, Ormiston J, Emanuelsson H, Fajadet J, Haude M, Klugmann S, Morel MA. Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). *Lancet.* 1998;352:673-681.
12. Knook AH, Wardeh AJ, Rensing BJ, Foley DP, Van Der Giessen WJ, Van Den Brand M, De Feyter PJ, Davis HR, Becker GJ, Serruys PW. Low rates of clinical restenosis with the new flexible stainless steel tube intracoronary stent: the R Stent. A six-month safety and feasibility study. *Int J Cardiovasc Intervent.* 2000;3:91-95.
13. DOMINO Study: The Study to Compare Cypher Versus Cypher Select in Treating Cornary Artery Lesions. Clinical Trial number: NCT00232791.
14. Serruys PW, Hoye A, Grollier G, Colombo A, Symons J, Mudra H. A European multi-center trial investigat-

ing the anti-restenotic effect of intravascular sonotherapy after stenting of de novo lesions (EUROSPAH: EUROpean Sonotherapy Prevention of Arterial Hyperplasia). *Int J Cardiovasc Intervent.* 2004;6:53-60.

15. Feld S, Almagor Y, Vaughn WK, Leon MB, Serruys PW. Predictors of clinical outcome following NIR stent implantation for coronary artery disease: analysis of the results of the First International New Intravascular Rigid-Flex Endovascular Stent Study (FINESS trial). *J Interv Cardiol.* 2002;15:1-6.

16. Rutsch W, Kiemeneij F, Colombo A, Macaya C, Guermonprez JL, Grip L, Hamburger J, Umans V, Gotsman M, Almagor Y, Morice MC, Garcia E, Chevalier B, Erbel R, Cobaugh M, Morel MA, Serruys PW. Clinical and angiographic results with the NIR stent: First International NIR Endovascular Stent Study (FINESS-II). *Int J Cardiovasc Intervent.* 2000;3:143-151.

17. Duckers HJ, Silber S, de Winter R, den Heijer P, Rensing B, Rau M, Mudra H, Benit E, Verheye S, Wijns W, Serruys PW. Circulating endothelial progenitor cells predict angiographic and intravascular ultrasound outcome following percutaneous coronary interventions in the HEALING-II trial: evaluation of an endothelial progenitor cell capturing stent. *EuroIntervention*. 2007;3:67-75.

18. Foley DP, Pieper M, Wijns W, Suryapranata H, Grollier G, Legrand V, de Scheerder I, Hanet C, Puel J, Mudra H, Bonnier HJ, Colombo A, Thomas M, Probst P, Morice M, Kleijne J, Serruys PW. The influence of stent length on clinical and angiographic outcome in patients undergoing elective stenting for native coronary artery lesions; final results of the Magic 5L Study. *Eur Heart J.* 2001;22:1585-1593.

19. Morice MC, Aubry P, Benveniste E, Bourdonnec C, Commeau P. The MUST Trial: Acute Results and Six-Month Clinical Follow-up. *J Invasive Cardiol.* 1998;10:457-463.

20. Kornowski R, Fort S, Almagor Y, Silber S, Lewis BS. Impact of vessel size, lesion length and diabetes mellitus on angiographic restenosis outcomes: insights from the NIRTOP study. *Acute Card Care.* 2008;10:104-110.

21. Reifart N, Morice MC, Silber S, Benit E, Hauptmann KE, de Sousa E, Webb J, Kaul U, Chan C, Thuesen L, Guagliumi G, Cobaugh M, Dawkins K. The NUGGET study: NIR ultra gold-gilded equivalency trial. *Catheter Cardiovasc Interv.* 2004;62:18-25.

22. Chevalier B, Serruys PW, Silber S, Garcia E, Suryapranata H, Hauptmann K, Wijns W, Schuler G, Fath-Ordoubadi F, Worthley S, Theusen L, Meredith I, Bressers M, Nagai H, Paunovic D. Randomised comparison of Nobori™, biolimus A9-eluting coronary stent with a Taxus®, paclitaxel-eluting coronary stent in patients with stenosis in native coronary arteries : the Nobori 1 trial. *EuroIntervention.* 2007;2:426-434.

23. O'Brien ER, Veinot J, Foley D. Pullback atherectomy for coronary artery in-stent restenosis: preliminary report from the PAIR trial on tissue histology [abstract]. . *Circulation.* 1999;100:I-307.

24. Grines CL, Cox DA, Stone GW, Garcia E, Mattos LA, Giambartolomei A, Brodie BR, Madonna O, Eijgelshoven M, Lansky AJ, O'Neill WW, Morice MC. Coronary angioplasty with or without stent implantation for acute myocardial infarction. Stent Primary Angioplasty in Myocardial Infarction Study Group. *N Engl J Med.* 1999;341:1949-1956.

25. Serruys P, Grines C, Stone G, Garcia E, Kiemeney F, Morice M, Sousa J, Hamm C, Costantini C, Probst P, Rutsch W, Penn I, Fernandez-Aviles F, Vandormael M, Bartorelli A, Bilodeau L, Eijgelshoven M. Stent implantation in acute myocardial infarction using a heparin-coated stent: a pilot study as a preamble to a randomized trial comparing balloon angioplasty and stenting. *Int J Cardiovasc Intervent.* 1998;1:19-27.

26. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med.* 2002;346:1773-1780.

27. Morice MC, Colombo A, Meier B, Serruys P, Tamburino C, Guagliumi G, Sousa E, Stoll HP. Sirolimus- vs

paclitaxel-eluting stents in de novo coronary artery lesions: the REALITY trial: a randomized controlled trial. *JAMA*. 2006;295:895-904.

28. Serruys P. The SCEPTER trial: A study of controlled elution of paclitaxel for the elimination of restenosis. Presentation at the European Society of Cardiology meeting, Stockholm, Sweden, September 4-7, 2005.

29. Lotan C, Almagor Y, Kuiper K, Suttorp MJ, Wijns W. Sirolimus-eluting stent in chronic total occlusion: the SICTO study. *J Interv Cardiol.* 2006;19:307-312.

30. Vranckx P, Serruys PW, Gambhir S, Sousa E, Abizaid A, Lemos P, Ribeiro E, Dani SI, Dalal JJ, Mehan V, Dhar A, Dutta AL, Reddy KN, Chand R, Ray A, Symons J. Biodegradable-polymer-based, paclitaxel-eluting Infinnium stent: 9-Month clinical and angiographic follow-up results from the SIMPLE II prospective multi-centre registry study. *EuroIntervention.* 2006;2:310-317.

31. Serruys PW, Ong AT, Piek JJ, Neumann FJ, van der Giessen WJ, Wiemer M, Zeiher A, Grube E, Haase J, Thuesen L, Hamm C, Otto-Terlouw PC. A randomized comparison of a durable polymer Everolimus-eluting stent with a bare metal coronary stent: The SPIRIT first trial. *EuroIntervention.* 2005;1:58-65.

32. Boland JL, Corbeij HA, Van Der Giessen W, Seabra-Gomes R, Suryapranata H, Wijns W, Hanet C, Suttorp MJ, Buller C, Bonnier JJ, Colombo A, Van Birgelen C, Pieper M, Mangioni JA, Londero H, Carere RG, Hamm CW, Bonan R, Bartorelli A, Kyriakides ZS, Chauhan A, Rothman M, Grinfeld L, Oosterwijk C, Serruys PW, Cumberland DC. Multicenter evaluation of the phosphorylcholine-coated biodivYsio stent in short de novo coronary lesions: The SOPHOS study. *Int J Cardiovasc Intervent.* 2000;3:215-225.

33. Tanabe K, Serruys PW, Grube E, Smits PC, Selbach G, van der Giessen WJ, Staberock M, de Feyter P, Muller R, Regar E, Degertekin M, Ligthart JM, Disco C, Backx B, Russell ME. TAXUS III Trial: in-stent restenosis treated with stent-based delivery of paclitaxel incorporated in a slow-release polymer formulation. *Circulation.* 2003;107:559-564.

34. Bonnier HJ, van den Heuvel P, Legrand V, Tanabe K, Vos J, Serruys PW. Clinical and angiographic outcomes after Tsunami coronary stent placement. *J Invasive Cardiol.* 2004;16:252-256.

35. Serruys PW, S IJ, Hout B, Vermeersch P, Bramucci E, Legrand V, Pieper M, Antoniucci D, Gomes RS, Macaya C, Boekstegers P, Lindeboom W. Direct stenting with the Bx VELOCITY balloon-expandable stent mounted on the Raptor rapid exchange delivery system versus predilatation in a European randomized Trial: the VELVET trial. *Int J Cardiovasc Intervent.* 2003;5:17-26.

36. Foley DP, Rensing BJ, Pieper M, Colombo A, Heyndrickx G, Macaya C, Amann FW, Suryapranata H, Mudra H, Hanet C, Meier B, W P. Clinical and quantitative angiographic outcomes following elective implantation of the self-expanding Wallstent for longer coronary artery lesions--final results of the Wellstent native study. *Int J Cardiovasc Intervent.* 1999;2:171-179.

37. Emanuelsson H, Serruys PW, van Der Giessen WJ, Dawkins K, Rutsch W, Katus H, Morel MA, Veldhof S, Wijns W, Sigwart U. Clinical and Angiographic Results with the Multi-Link feminine Coronary Stent System N The West European Stent Trial (WEST). *J Invasive Cardiol.* 1997;9:561-568.

38. Serruys PW, van Der Giessen W, Garcia E, Macaya C, Colombo A, Rutsch W, Vrints C, Bonnier H, Mudra H, Fleck E, Ormiston J, Figulla H, Seabra-Gomes R, Veldhof S, Morel MA. Clinical and Angiographic Results with the Multi-Link Stent Implanted under Intravascular Ultrasound Guidance (West-2 Study). *J Invasive Cardiol.* 1998;10 Suppl B:20B-27B.

39. Booth GL, Kapral MK, Fung K, Tu JV. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. *Lancet.* 2006;368:29-36.

40. Ryden L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de Boer MJ, Cosentino F, Jonsson B, Laakso M, Malmberg K, Priori S, Ostergren J, Tuomilehto J, Thrainsdottir I, Vanhorebeek I, Stramba-Badiale M, Lindgren P, Qiao Q, Priori SG, Blanc JJ, Budaj A, Camm J, Dean V, Deckers J, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo J, Zamorano JL, Deckers JW, Bertrand M, Charbonnel B, Erdmann E, Ferrannini E, Flyvbjerg A, Gohlke H, Juanatey JR, Graham I, Monteiro PF, Parhofer K, Pyorala K, Raz I, Schernthaner G, Volpe M, Wood D. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *Eur Heart J.* 2007;28:88-136.

41. Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, Levy D. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med.* 2001;345:1291-1297.

42. Preventing and Managing the Global Experience of Obesity. Report of the World Health Organisation Consultation on Obesity. WHO, Geneva June 1997.

43. Hardin JW, Hilbe JM, eds. *Generalized Estimating Equations. Boca Raton Fl: Chapman & Hall. 2007.*; 2007.

44. Little RJA, Rubin DB, (1987). Statistical analysis with missing data. John Wiley and Sons. New York NY

45. De Velasco JA, Cosin J, Lopez-Sendon JL, De Teresa E, De Oya M, Sellers G. [New data on secondary prevention of myocardial infarction in Spain. Results of the PREVESE II study]. *Rev Esp Cardiol.* 2002;55:801-809.

46. de Velasco JA, Cosin J, Lopez Sendon JL, de Teresa E, de Oya M, Carrasco JL, Navarro A. [Secondary prevention of myocardial infarction in Spain. The PREVERSE study]. *Rev Esp Cardiol.* 1997;50:406-415.

47. Danchin N, Hanania G, Grenier O, Vaur L, Amelineau E, Gueret P, Blanchard D, Ferrieres J, Genes N, Lablanche JM, Cantet C, Cambou JP. [Trends in discharge prescriptions for patients hospitalized for acute coronary syndromes in France from 1995 to 2000. Data from the Usik 1995, Prevenir 1, Prevenir 2 and Usic 2000 surveys.]. *Ann Cardiol Angeiol (Paris).* 2003;52:1-6.

48. Haddock CK, Poston WS, Taylor JE, Conard M, Spertus J. Smoking and health outcomes after percutaneous coronary intervention. *Am Heart J.* 2003;145:652-657.

49. Wilson K, Gibson N, Willan A, Cook D. Effect of smoking cessation on mortality after myocardial infarction: meta-analysis of cohort studies. *Arch Intern Med.* 2000;160:939-944.

50. Teo KK, Ounpuu S, Hawken S, Pandey MR, Valentin V, Hunt D, Diaz R, Rashed W, Freeman R, Jiang L, Zhang X, Yusuf S. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. *Lancet.* 2006;368:647-658.

51. Rigotti NA. Clinical practice. Treatment of tobacco use and dependence. *N Engl J Med.* 2002;346:506-512.

52. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. *JAMA.* 2003;290:86-97.

53. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Juni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet.* 2008;372:1163-1173.

54. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, Qizilbash N, Collins R, Peto R. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet.* 2009;373:1083-1096.

55. Strandberg TE, Strandberg AY, Salomaa VV, Pitkala KH, Tilvis RS, Sirola J, Miettinen TA. Explaining the obesity paradox: cardiovascular risk, weight change, and mortality during long-term follow-up in men. *Eur Heart J.* 2009;30:1720-1727.

56. Eckel RH. Clinical practice. Nonsurgical management of obesity in adults. *N Engl J Med.* 2008;358:1941-1950.

57. Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet.* 2005;366:895-906.

58. Staessen JA, Wang JG, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. *Lancet.* 2001;358:1305-1315.

59. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, Ebrahim S, Faergeman O, Graham I, Mancia G, Cats VM, Orth-Gomer K, Perk J, Pyorala K, Rodicio JL, Sans S, Sansoy V, Sechtem U, Silber S, Thomsen T, Wood D. European guidelines on cardiovascular disease prevention in clinical practice: third joint task force of European and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of eight societies and by invited experts). *Eur J Cardiovasc Prev Rehabil.* 2003;10:S1-S10.

60. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, Dallongeville J, De Backer G, Ebrahim S, Gjelsvik B, Herrmann-Lingen C, Hoes A, Humphries S, Knapton M, Perk J, Priori SG, Pyorala K, Reiner Z, Ruilope L, Sans-Menendez S, Op Reimer WS, Weissberg P, Wood D, Yarnell J, Zamorano JL, Walma E, Fitzgerald T, Cooney MT, Dudina A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Funck-Brentano C, Filippatos G, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Altiner A, Bonora E, Durrington PN, Fagard R, Giampaoli S, Hemingway H, Hakansson J, Kjeldsen SE, Larsen L, Mancia G, Manolis AJ, Orth-Gomer K, Pedersen T, Rayner M, Ryden L, Sammut M, Schneiderman N, Stalenhoef AF, Tokgozoglu L, Wiklund O, Zampelas A. European guidelines on cardiovascular disease prevention in clinical practice: full text. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *Eur J Cardiovasc Prev Rehabil.* 2007;14 Suppl 2:S1-113.

61. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet.* 2005;366:1267-1278.

62. McAlister FA, Lawson FM, Teo KK, Armstrong PW. Randomised trials of secondary prevention programmes in coronary heart disease: systematic review. *BMJ.* 2001;323:957-962.

63. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med.* 2007;356:1503-1516.

64. Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. *Arch Intern Med.* 2002;162:1682-1688.

65. Campeau L. Letter: Grading of angina pectoris. *Circulation.* 1976;54:522-523.

66. Braunwald E. Unstable angina. A classification. *Circulation.* 1989;80:410-414.

Chapter 5.2

Influence of age on the clinical outcomes of coronary revascularization for the treatment of patients with multivessel de novo coronary artery lesions. Sirolimus-eluting stents vs. coronary artery bypass surgery and bare metal stent. Insights from the multicenter randomised Arterial Revascularization Therapy Study Part I (ARTS-I) and Part II (ARTS-II)

EuroIntervention 2011; 6(7):838-845

Victor Legrand, Scot Garg, Patrick W. Serruys, Kari S Virtanen, Gunter Szurawitki, Vassilis Voudris, Alessandro Fontanelli, Knut Endersen, Igor Kranjec, Tessa Rademaker, Christodoulos I. Stefanidis, Kristel Wittebols

EuroIntervention

Influence of age on the clinical outcomes of coronary revascularisation for the treatment of patients with multivessel *de novo* coronary artery lesions: sirolimus-eluting stent vs. coronary artery bypass surgery and bare metal stent, insight from the multicentre randomised Arterial Revascularisation Therapy Study Part I (ARTS-I) and Part II (ARTS-II)

Victor M. Legrand[1], MD; Scot Garg[2], MD; Patrick W. Serruys[2]*, MD; Kari S. Virtanen[3], MD; Günter Szurawitzki[4], MD; Vassilis Voudris[5], MD; Alessandro Fontanelli[6], MD; Knut Endersen[7], MD; Igor Kranjec[8], MD; Tessa Rademaker[9], MSc; Christodoulos I. Stefanidis[10], MD; Kristel Wittebols[11], MSc

1. CHU Sart Tilman, Liège, Belgium; 2. Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands; 3. Helsinki University Central Hospital, Helsinki, Finland; 4. Elisabeth Krankenhaus, Essen, Germany; 5. Onassis Cardiac Surgery Center, Athens, Greece; 6. San Bortolo Hospital, Vincenza, Italy; 7. Riskhospital, Oslo, Norway; 8. Clinical Centre Ljubljana, Ljubljana, Slovenia; 9. Cardialysis BV, Rotterdam, The Netherlands; 10. Hippokratio Hospital, Athens, Greece; 11. Cordis, a Johnson & Johnson Company, Waterloo, Belgium

The authors have no conflict of interest to declare.

KEYWORDS
Ageing, coronary artery disease, revascularisation, bare metal stents, sirolimus-eluting stents, surgery

Abstract

Aims: We sought to evaluate the prognostic impact of age on the procedural results and subsequent clinical outcomes in patients with multivessel disease (MVD) treated either by coronary artery bypass surgery (CABG) or by percutaneous coronary intervention (PCI) with or without drug eluting stents, based on data of the Arterial Revascularisation Therapies Study (ARTS) part I and part II. The potential influence of age in determining the most appropriate revascularisation strategy for patients with MVD is largely unknown.

Methods and results: Three year clinical outcome of ARTS I patients randomised to PCI with bare metal stent (BMS) (n= 600) or CABG (n= 605), and matched patients treated by PCI with sirolimus-eluting stents (SES) in ARTS II (n= 607) were reviewed according to four age quartiles. Endpoints were measured in terms of major adverse cardiac and cerebrovascular events MACCE) during hospital stay and up to three years. The frequency of female, diabetes, hypertension, peripheral vascular disease, pulmonary disease, as well as lesion complexity increased with age. At three years, MACCE free survival was comparable between patients treated by CABG or SES PCI, regardless of age quartile. The incidence of MACCE was higher among ARTS I BMS treated patients in all but the second age quartile. This was primarily related to a higher need for repeat revascularisation among BMS treated patients. However, age, which emerged as a strong independent predictor of MACCE following CABG ($p<0.005$), was not predictive of adverse events following PCI. Conversely, diabetes was the strongest independent predictor of MACCE among PCI treated patients ($p<0.02$), but didn't affect three-year outcomes following CABG.

Conclusions: Age seems to influence the CABG outcome in-hospital but not PCI. PCI-SES could offer lower immediate risk in patients with MVD and comparable long-term outcome as CABG especially in older patients. The worst outcome of PCI-BMS group is primarily related to the need for repeat revascularisation. Diabetes is the most important predictor of MACCE following PCI.

** Corresponding author: Thoraxcenter, Ba 583, Dr. Molewaterplein 40, 3015 GD, Rotterdam, The Netherlands*
E-mail: p.w.j.c.serruys@erasmusmc.nl

Introduction

Coronary artery disease (CAD) is the leading cause of mortality worldwide. The prevalence of CAD increases with age, and this coupled with increasing life expectancy has led to a sharp rise in the number of elderly patients undergoing percutaneous coronary intervention (PCI) and coronary artery bypass grafting surgery (CABG).[1] In comparison to their younger counterparts, older patients with CAD usually present with more diffuse atherosclerosis and a higher plaque burden.[2] In addition non-cardiac co-morbidities such as renal insufficiency and impaired pulmonary function are also more prevalent with increasing age. This high risk profile of elderly CAD patients contributes to their increased complication rates, both after PCI[3] and CABG.[4] Consequently, numerous clinical studies have confirmed that a correlation exists between clinical outcomes from either method of revascularisation, and the patient's age.[5-9] On the other hand elderly patients have been shown to derive more benefit from invasive coronary revascularisation than from optimal medical therapy,[9-11] and one study[9] even concluded that elderly patients have a greater absolute risk reduction associated with revascularisation in comparison with younger patients. The most appropriate revascularisation procedure for older or younger patients remains controversial, primarily through the lack of clinical studies investigating a direct comparison of both treatment strategies.

The objective of the current investigation was to examine the prognostic impact of age on the procedural results, and subsequent early and late clinical outcomes in a contemporary cohort of patients with MVD treated by either CABG or PCI with or without drug eluting stents (DES).

Methods

Study population and protocol

The present study is a retrospective analysis of the ARTS I and II trials; the detailed protocols of both have been previously reported.[12,13]

Briefly, the study population includes the 1,205 patients from the ARTS-I study who were randomised to either bare metal stent (BMS) implantation (n=600) or CABG (n=605), and the 607 patients from the ARTS-II registry who were treated by sirolimus-eluting stent (SES) implantation. In order to obtain a population comparable to ARTS-I, patients in ARTS-II were stratified per clinical site in order to ensure that at least one third of the included patients had triple vessel disease. All inclusion and exclusion criteria were the same for both trials, including the upper age limit, which was 80 years old. Patients were enrolled irrespective of whether they had stable or unstable angina or silent ischaemia. They were required to have MVD and at least one other significant lesion (>50% diameter stenosis) in a different major epicardial artery suitable for stent implantation. Specific exclusion criteria included: patients with any prior coronary intervention, left main stem coronary disease, left ventricular ejection fraction of less than 30%, overt heart failure, history of a cerebrovascular accident, transmural myocardial infarction in the preceding week, severe hepatic or renal disease and the need for concomitant major surgery. All patients gave written informed consent.

The pooled population of ARTS-I and ARTS-II was divided into four equal quartiles of 453 subjects based on age at trial inclusion. The first, second, third and fourth quartiles (mean±SD) consisted of patients <54 years (48.8±4.8 years), 54-62 years (58.5±2.1 years), 62-68 years (65.6±1.9 years), and 68-83 years old (73.3±3.1 years) respectively. Five patients (3 in ARTS I and 2 in ARTS II) older than 80 years were included.

Data analysis and endpoints

Clinical outcomes in each subgroup were compared according to the assigned treatment, (CABG, PCI with BMS or PCI with SES) and analysis was performed on the outcome of each revascularisation procedure according to age quartiles. The primary endpoint was defined as the absence of any of the following major adverse cardiac and cerebral events (MACCE) within three years of inclusion in the trial: death (all-cause mortality), cerebrovascular accident, non-fatal myocardial infarction (MI), or any repeat revascularisation (either PCI or CABG).[12,14,15] MACCE rate during hospital stay and at three years is assessed according to hierarchical classification. In hierarchical classification, only the worst event was counted as an event. Single adverse events are reported in a non-hierarchical way. Events for the present report were counted from the time of procedure for all the three arms. Complete three-year follow-up was available for all of the 1,812 study patients.

Statistical analysis

Statistical analysis was performed with SAS 6.12 software (SAS Institute Inc., Chicago, IL, USA). Continuous variables are expressed as mean±standard deviation (SD) and compared with use of Student's unpaired *t*-test. Categorical variables were reported as counts and percentages and compared using the Fisher's exact test for pair wise variables or the Chi-square for trend to examine the impact of age. Longitudinal event rates were evaluated using Kaplan-Meier estimates and compared with the log-rank test. To examine the impact of age in each treatment strategy, Cox Proportional Hazard models in SAS V8.2 was used. Both the age and the treatment subgroups were tested for interaction with predictor variables. This analysis was restricted to the MACCE. For the interaction tests between predictor variables and age group or treatment group, a likelihood ratio test was used by subtracting the summed -2log(L) of the "by group" analysis from the -2log(L) of the stratified (by age and by treatment) analysis, and comparing the outcome with a Chi-square distribution with the correct number of degrees of freedom. In case of a p-value <0.05 for the interaction, the "by group" analysis regression parameters were used.

Results

Baseline characteristics

Three patients died while waiting for surgery, and were subsequently excluded from the clinical outcome evaluation. Six patients initially assigned to BMS implantation were instead treated by surgery, and 19 patients initially assigned to surgery were instead treated with BMS. One patient assigned to stenting, and four patients assigned to surgery received only medical treatment. All patients assigned to SES implantation were treated according to protocol.

The patient population between both trials was not matched, and consequently the mean age of patients in the ARTS-II trial which was 63±10 years is slightly higher than that of the patients in the ARTS-I trial, whose mean ages were 61±9 years and 61±10 years for CABG and PCI, respectively. The patients included in the ARTS-II registry had more complex lesions and anatomy as has been previously reported.[16]

Table 1 shows the baseline demographic and clinical characteristics of the enrolled patients. Increasing age is associated with an increased prevalence of diabetes mellitus, hypertension, peripheral artery disease, previous carotid artery surgery or cerebrovascular events, and chronic obstructive pulmonary disease. Conversely, the incidence of hypercholesterolaemia, obesity, family history of MI or sudden death, previous MI and current smoking, as well as the percentage of males in the population were found to decrease with advanced age. In all quartiles, the majority of patients presented with stable angina.

Procedural characteristics are depicted in Table 2. As patients included in ARTS had to be amenable for PCI or CABG, it is not surprising that the number of lesions treated was not influenced by age and was similar in patients assigned to CABG or stent implantation. The left anterior descending artery was equally revascularised within each age subgroups and more complex lesions were noted in older patients.

Based on the clinical and demographic data the calculated logistic EuroSCORE for each subgroup was 1.27±0.58, 1.33±0.58, 2.07±1.10 and 3.58±1.95, respectively. Finally, the average hospital stay increased with age and was longer among patients treated surgically.

Table 1. Demographics and patient characteristics (N=1,812 patients).

	Q1 30-54y N=453	Q2 54-62y N=453	Q3 62-68y N=453	Q4 68-83y N=453	*p*-value (trend)
Men	87.2%	81.7%	73.1%	64.2%	<0.001
Age (mean±sd)	48.8±4.8	58.5±2.1	65.6±1.9	73.3±3.1	<0.001
BMI (mean±sd)	27.7±3.9	27.6±3.7	27.3±3.6	26.8±4.0	<0.001
Current smoking	44.4%	25.2%	17.9%	9.8%	<0.001
Diabetes mellitus	14.8%	19.6%	22.5%	24.1%	<0.001
Hypertension	40.6%	51.2%	56.7%	60.7%	<0.001
Hypercholesterolaemia	66.7%	63.7%	64.1%	58.3%	0.014
Family history	50.6%	42.2%	35.7%	27.5%	<0.001
PVD	3.1%	4.4%	7.3%	8.6%	<0.001
CVA	0.4%	0.7%	1.1%	1.8%	0.034
Previous MI	49.0%	40.2%	35.8%	36.0%	<0.001
Previous CABG	0.0%	0.0%	0.0%	0.0%	N/A
Previous PCI	0.9%	1.3%	2.0%	1.5%	0.29
Carotid surgery	0.0%	0.7%	1.1%	2.0%	0.002
COPD	1.5%	3.8%	6.9%	5.7%	<0.001
Silent ischaemia	7.3%	7.1%	7.3%	6.6%	0.74
Stable angina	54.3%	57.6%	57.0%	54.5%	1.00
Unstable angina	38.4%	35.3%	35.8%	38.9%	0.86
1 vessel disease	2.9%	2.7%	1.8%	3.2%	0.97
2 vessel disease	63.5%	60.7%	58.2%	58.1%	0.08
3 vessel disease	33.6%	36.6%	40.0%	38.7%	0.07
LVEF (%) (mean±sd)	59.2±12.1	61.1±12.3	61.6±12.3	60.1±12.7	0.21
Lipid lowering agent	54.0%	54.3%	53.8%	52.8%	0.69
Beta blockers	67.8%	66.8%	59.0%	63.5%	0.04
ACE inhibitors	27.8%	26.3	33.9%	34.5	0.004

BMI: body mass index; PVD: peripheral vascular disease; CVA: cerebrovascular accident; MI: myocardial infarction; CABG: coronary artery bypass surgery; PCI: percutaneous coronary intervention; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; ACE: angiotensin converting enzyme

Table 2. Angiographic and procedural characteristics (N=1,778 patients, N=5,404 lesions).

	Q1 30-54y N=453	Q2 54-62y N=453	Q3 62-68y N=453	Q4 68-83y N=453	*p*-value (trend)
No. of treated lesions (mean±sd)	2.8±1.1	2.8±1.0	2.9±1.0	2.9±1.1	0.30
Location of lesions:					
RCA	32.9%	29.4%	28.6%	28.5%	0.013
LM	0.0%	0.1%	0.0%	0.1%	0.54
LAD	40.0%	40.9%	41.6%	40.7%	0.65
LCX	27.1%	29.7%	29.9%	30.8%	0.047
Lesion length					
Discrete <10 mm	65.0%	64.2%	65.1%	63.6%	0.58
Tubular 10-20 mm	26.6%	26.5%	26.9%	26.7%	0.90
Diffuse >20 mm	8.4%	9.3%	8.0%	9.7%	0.46
Bifurcation or SB	33.2%	33.9%	33.7%	33.2%	0.96
Lesion classification					
Type A/B1	37.2%	32.5%	31.6%	31.8%	0.003
Type B2/C	62.8%	67.5%	68.4%	68.2%	0.003
Randomised to					
ARTS-I CABG	33.3%	35.1%	33.3%	31.8%	0.52
ARTS-I BMS	38.4%	31.3%	33.1%	29.6%	0.012
ARTS-II SES	28.3%	33.6%	33.6%	38.6%	0.002
In-hospital stay					
Post PCI (days±sd)	3.5±2.8	3.3±2.6	4.0±4.2	3.8±3.0	0.037
Post CABG (days±sd)	8.6±3.9	8.8±3.4	10.2±5.2	10.9±6.5	<0.001

In-hospital clinical outcome

In-hospital death and MACCE for each assigned treatment are presented in Table 3 according to age quartile. There was an age related increase in mortality and MACCE in patients treated surgically. The in-hospital mortality observed in these patients was comparable to the predicted mortality estimated by the EuroSCORE. Conversely, age had no significant influence on the in-hospital outcomes of patients assigned to percutaneous treatment, either with BMS or DES. In the youngest quartile (Q1) of patients assigned to BMS there was an excess MACCE as compared to SES PCI, which was primarily due to the increased repeat revascularisations, and myocardial infarctions in the BMS subgroup (p=0.016). However, we may speculate that this observation is related to improvements in ARTS-II PCI techniques and medical management. In the oldest quartile (Q4) patients treated by SES PCI had less MACCE as compared to surgically treated patients (2.3% vs. 9.0%, p=0.011); which was predominantly driven by a reduction in mortality (0.0% vs. 3.5%, p=0.018).

Three-year clinical outcome

Patient mortality increased with age and this trend was significant for patients assigned to CABG and SES PCI (Table 4). A trend noted only

Table 3. In-hospital events (hierarchical MACCE and non hierarchical events up to hospital discharge, per patient) counted since date of procedure.

	Q1 30-54y	Q2 54-62y	Q3 62-68y	Q4 68-83y	*p*-value (trend)
ARTS-I CABG	N=150[n]	N=158[n]	N=150[n]	N=144	
MACCE % (n)	2.0 (3)	5.1 (8)	7.3 (11)	9.0 ¶(13)	0.007
Death % (n)	0.0 (0)	0.6 (1)	1.3 (2)	3.5 *(5)	0.009
CVA % (n)	0.0 (0)	2.5 (4)	0.0 (0)	1.4 (2)	0.68
MI% (n)	2.0 (3)	2.5 (4)	4.7 (7)	3.5 (5)	0.30
CABG % (n)	0.0 (0)	0.0 (0)	0.7 (1)	0.7 (1)	0.19
PCI% (n)	0.0 (0)	0.6 (1)	0.7 (1)	0.7 (1)	0.41
ARTS-I BMS	N=174	N=142	N=150	N=134	
MACCE % (n)	6.3 *(11)	5.6 (8)	10.7 ¶(16)	5.2 (7)	0.78
Death % (n)	0.6 (1)	1.4 (2)	1.3 (2)	0.7 (1)	0.84
CVA % (n)	0.6 (1)	0.7 (1)	0.0 (0)	1.5 (2)	0.54
MI% (n)	3.4 (6)	2.8 (4)	4.0 ¶(6)	0.7 (1)	0.28
CABG % (n)	2.3 (4)	0.7 (1)	6.7 *(10)	0.7 (1)	0.74
PCI% (n)	4.0 (7)	1.4 (2)	1.3 (2)	2.2 (3)	0.26
ARTS-II SES	N=128	N=152	N=152	N=175	
MACCE % (n)	0.8 (1)	2.0 (3)	3.3 (5)	2.3 (4)	0.31
Death % (n)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	N/A
CVA % (n)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	N/A
MI% (n)	0.0 (0)	1.3 (2)	0.0 (0)	1.1 (2)	0.49
CABG % (n)	0.0 (0)	0.7 (1)	1.3 (2)	1.7 (3)	0.11
PCI% (n)	0.8 (1)	0.7 (1)	2.0 (3)	0.0 (0)	0.60

*p<0.02, ¶p<0.015 vs. ARTS-II SES; [n] one patient died before CABG and was not included; MACCE: major adverse cerebral and cardiovascular event; CVA: cerebrovascular accident; MI: myocardial infarction; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention

Table 4. Clinical endpoints at three years (hierarchical MACCE and non hierarchical events up to 1,080 days, per patient) counted since date of procedure.

	Q1 30-54y	Q2 54-62y	Q3 62-68y	Q4 68-83y	*p*-value (trend)
ARTS-I CABG	N=150[n]	N=158[n]	N=150[n]	N=144	
MACCE % (n)	7.3 (7)	17.1 (27)	18.7 (28)	21.5 (31)	0.001
Death % (n)	1.3 (1)	3.2 (5)	4.7 (7)	8.3 (12)	0.003
CVA % (n)	0.0 (0)	5.1 (8)	4.0 (6)	3.5 (5)	0.15
MI% (n)	2.7 (3)	3.8 (6)	7.3 (11)	6.3 (9)	0.07
CABG % (n)	0.7 (1)	1.3 (2)	1.3 (2)	1.4 (2)	0.57
PCI% (n)	4.0 (2)	8.2 (13)	4.7 (7)	6.9 (10)	0.56
ARTS-I BMS	N=174	N=142	N=150	N=134	
MACCE % (n)	32.2 *(56)	28.9 (41)	40.0 *(60)	35.1 §(47)	0.25
Death % (n)	2.9 (5)	3.5 (5)	4.7 (7)	5.2 (7)	0.25
CVA % (n)	1.7 (3)	0.7 (1)	2.7 (4)	9.0 (12)	<0.001
MI% (n)	8.6 §(15)	4.9 (7)	8.7 (13)	4.5 (6)	0.34
CABG % (n)	9.2 ¶(16)	7.0 (10)	12.7 #(19)	7.5 §(10)	0.94
PCI% (n)	20.7 §(36)	19.0 (27)	20.0 ¶(30)	18.7 (25)	0.72
ARTS-II SES	N=128	N=152	N=152	N=175	
MACCE % (n)	13.3 (17)	20.4 (31)	17.8 (27)	24.0 (42)	0.042
Death % (n)	1.6 (2)	1.3 (2)	2.0 (3)	6.3 (11)	0.01
CVA % (n)	0.0 (0)	0.7 (1)	2.6 (4)	6.3 (11)	0.001
MI% (n)	0.8 (1)	4.6 (7)	3.3 (5)	4.0 (7)	0.63
CABG % (n)	2.3 (3)	2.6 (4)	3.3 (5)	2.3 (4)	0.4
PCI% (n)	10.9 (14)	16.4 (25)	9.9 (15)	12.0 (21)	0.72

* P<0.001; ¶P<0.02; #P<0.01; §P<0.05 vs. ARTS-II SES; MACCE: major adverse cerebral and cardiovascular event; CVA: cerebrovascular accident; MI: myocardial infarction; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention

in those patients having PCI was the increasing incidence of cerebrovascular accidents with increasing age. Not surprisingly, the need for repeat revascularisation was higher among PCI treated patients in all age quartiles when compared to surgery. However, the need for repeat PCI and CABG was dramatically reduced in ARTS-II SES treated patients by 60.8%, 26.9%, 59.6% and 45.4% in Q1, Q2, Q3 and Q4, respectively, as compared to ARTS-I BMS treated patients. The need for repeat revascularisation was not age-dependent.

The 3-year event free survival in each treatment arm is depicted in Figure 1 according to age quartile. In brief, there was no significant difference in MACCE rate between patients allocated to CABG or SES PCI with similar outcomes noted for each age group. Conversely, the increased need for repeat revascularisation, specifically during the first year, resulted in a worse event free survival for ARTS-I BMS treated patients.

Impact of age on event free survival

A multi-variable analysis was conducted to determine the influence of age on outcome at three-years follow-up. Age together with hypertension and multiple long diffuse lesions were independent predictors of MACCE amongst surgically treated patients. In patients treated with SES PCI the presence of diabetes was the strongest independent predictor of MACCE, together with the absence of hypertension, a small number of lesions treated, and procedural duration (Table 5). Age was not found to be an independent predictor of three-year outcomes amongst patients treated by PCI either with SES or BMS.

Table 5. Predictors of MACCE.

	CABG		SES	
	P	Hazard ratio	*P*	Hazard ratio
Age group	0.005	1.46	0.152	1.22
Sex (female=0, male=1)	0.398	0.78	0.303	1.41
Diabetes	0.324	1.37	0.018	1.90
Hypertension	0.047	1.73	0.042	0.57
Hypercholesterolaemia	0.585	0.86	0.785	1.09
Family history	0.519	0.84	0.841	0.95
Previous vascular disease	0.057	2.21	0.458	0.64
Previous MI	0.804	1.07	0.384	0.78
Current smoker	0.403	1.31	0.060	0.40
Angina (stab/unstab/silent)	0.089	0.67	0.764	0.94
No. of diffuse lesions (> 20 mm)	0.001	2.35	0.394	0.83
No. of calcified lesions	0.216	0.78	0.621	1.06
No. of lesions double guidewire	0.451	0.86	0.470	1.11
No. of lesions type B2/C	0.246	0.82	0.069	1.32
No. of lesions in LAD	0.883	0.97	0.170	1.36
Duration of procedure (min.)	0.493	1.00	0.008	1.01
No. of treated lesions	0.680	1.06	<.0001	0.53

Discussion

The current investigation is the first to evaluate long-term outcomes of similar patients with MVD studied according to their age. Specifically, we assessed whether PCI with BMS, PCI with SES, or

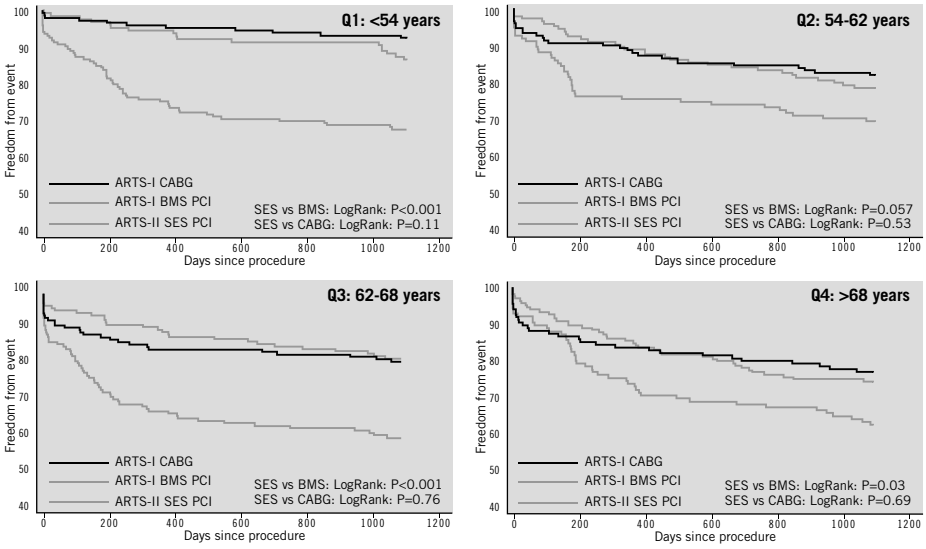


Figure 1. Kaplan-Meier curve to three years showing freedom from major adverse cardiac and cerebrovascular event (MACCE) according to age quartile in patients assigned to coronary artery bypass surgery (CABG), percutaneous coronary angioplasty with bare metal stent (BMS) and percutaneous coronary angioplasty with sirolimus-eluting stent (SES).

CABG is safer and/or more effective in particular age groups. In contrast to clinical registries, patients enrolled in the ARTS trials had less comorbidity, and a higher proportion of complete revascularisation.

At present the influence of age on long-term survival after PCI and CABG has not been adequately studied. Most of the data are derived from observational registries which doesn't allow for a direct comparison between PCI and CABG, as elderly patients referred to one or the other revascularisation technique have different baseline characteristics. However a recent registry, which corrected for baseline differences, has shown a trend towards a better survival following surgery, despite the less invasive nature of PCI, and the lower initial morbidity.[17,18]

There is a limited amount of data available from randomised trials on the influence of age on patient outcome after revascularisation. The BARI and SoS trial showed that survival was better with CABG compared with PCI irrespective of age.[19,20] Conversely, a systematic review has shown that long term survival after PCI or CABG is similar among patients over the age of 65 when compared to those younger than 65.[21]

Increasing age is associated with a lower three years survival among patients enrolled in CABG or SES arms of ARTS trials. However, neither PCI vs. CABG nor DES vs. BMS have a significant impact on survival up to three years, within each age quartiles.

This study has reiterated that important clinical and angiographic characteristics are age related. Older patients are more likely to be female, and when compared to their younger counterparts they are more likely to have comorbidities such as diabetes and hypertension.[1-4] Furthermore, the elderly have more diffuse and complex coronary lesions on angiography.[22,23] Therefore, in real-world clinical practice, when myocardial revascularisation is required, these important clinical characteristics are used on a case-by-case basis to make a clinical decision, without any well-established criteria for identifying those elderly patients more likely to benefit from PCI or CABG. Currently elderly patients with significant comorbidities tend to be treated by PCI, not only because it is less invasive, but also based on the results from the AWESOME randomised trial which demonstrated similar survival outcomes in patients >70 years of age following either PCI or CABG.[24]

The data from the ARTS-I trial confirms a gradual increase of both mortality (p=0.003) and morbidity (p=0.001) with age amongst patients referred for CABG. Although the death rate also increased with increasing age among ARTS-II patients (p=0.01), age (as assessed per quartile) was not an independent predictor of MACCE following PCI (p=0.15), whilst it did emerge as an important independent predictor of MACCE following surgery (p=0.005). The selection of patients without severe comorbidities, with preserved left ventricular function and amenable to (near) complete revascularisation by PCI is the most likely explanation of the excellent results observed after stenting, particularly amongst those treated with SES. Those patients having surgery also had similar baseline characteristics, and were low surgical risk based on their

calculated EuroSCORE. Therefore this study demonstrates that the impact of age on the outcomes after coronary revascularisation for MVD is significantly more important after surgery than after PCI. Our data show that the risk from surgery is highest during the in-hospital phase. Notably, the eldest patients (>68 years) undergoing surgery had a higher mortality rate than their counterparts treated by SES PCI. The in-hospital mortality observed in ARTS-I among surgically treated patients is in line with their predicted mortality based on the EuroSCORE. For patients included in the fourth quartile, the EuroSCORE predicted in-hospital mortality was of 3.58%, which is almost identical to that actually observed in this study (3.5%). For the younger age groups, the observed in-hospital mortality was slightly lower than that predicted by the EuroSCORE (0.0% vs. 1.27%, 0.6% vs. 1.33% and 1.3% vs. 2.07% for Q1, Q2 and Q3). These results are in keeping with recent evidence which suggests that the logistic EuroSCORE over estimates mortality, and requires recalibration.[25] The SYNTAX trial has also shown that early outcomes after PCI are related to initial lesion characteristics, however new evidence also suggests that these early outcomes after PCI can be influenced by adverse patient characteristics as assessed by the EuroSCORE.[26,27]

Clearly, the late outcomes after PCI are determined by the need for repeat revascularisation. At three-year follow-up, 173, 39 and 89 repeat revascularisations with PCI and/or surgery were performed in the ARTS-I PCI, ARTS-I CABG and ARTS-II PCI patients, respectively. Consistent with other trials of DES the use of SES lead to a dramatic improvement in the results of PCI in MVD as compared to BMS PCI.[28] This improvement has now been shown in our study to be independent of age. Despite the significantly lower repeat intervention rates with SES, CABG still remains associated with the lowest re-intervention rates in any age group quartile. Previous studies have shown that diabetes is a strong predictor of adverse outcome among patients treated by PCI, most notably for those with MVD.[29,30] Our results confirm that diabetes is the most important clinical risk factor for MACCE in patients treated by SES PCI. In the surgical group diabetes was not associated with MACCE, which is in contrast to previous observational studies which have shown diabetes to be an independent predictor of mortality.[31-33] The relative safety and efficacy of CABG decreases with increasing age, and this is independent of a patient's diabetic status. This data therefore suggests that young patients with diabetes benefit the most from surgery, and conversely, elderly patients without diabetes have a better outcome following SES PCI, compared to CABG. This implies that in diabetic patients with MVD, amenable to both PCI and CABG, a patient's age should be considered when deciding the most appropriate method of revascularisation. In view of the paucity of evidence this subject needs to be accurately assessed in a specifically designed clinical trial in diabetic patients. Currently there are no published randomised studies of revascularisation specifically in diabetics; previous data have all been derived from *post hoc* subgroup analysis. Recently the early results of the CARDia trial, the first dedicated randomised trial of revascularisation in diabetics, showed no difference in outcome between diabetic patients with MVD treated with PCI or CABG,[34] although no age distributions have yet been released. The full publication of CARDia is awaited, together with the results of the ongoing FREEDOM trial with the specific aim to clarify the role of CABG and PCI in diabetic patients with MVD. In the BARI 2D trial, Frye et al[35] reported that for many patients with both diabetes and coronary artery disease, optimal medical therapy rather than any intervention is an excellent first-line strategy, notably for those with less severe disease. When revascularisation by PCI is indicated, five year MACE free survival is not affected by the initial treatment strategy (medical or revascularisation). However, when revascularisation by CABG is deemed the more appropriate revascularisation strategy, MACE free survival is better in patients initially randomised to surgery. This trial also indicates that treatment strategy must be individualised for specific patients, based on the most appropriate evidence-based treatment recommendations.

Study limitations

Firm conclusions regarding the advisability of SES PCI in the oldest patients with multivessel disease cannot be drawn from the comparative evaluation of the ARTS-I and ARTS-II trials. Moreover, these data refer to selected patients with low co-morbidities, who were amenable to complete revascularisation with either PCI or CABG; importantly very old patients (octogenarians) were excluded from this study.

This study combines results of a randomised trial (ARTS I) and a registry (ARTS-II). Population of the registry was comparable (in term of inclusion criteria) but "not matched" besides a similar 2/3 MVD ratio. We sought that age-corrected or propensity analysis would not be appropriate for the pooled ARTS-I and II population analysis. We therefore aimed to compare outcomes according to age quartile. However, using this approach, clinical and anatomical differences between patient's arms of each quartile are not fully compensated.

An important limitation to consider is the long time lag between the enrolment of patients in ARTS-I and ARTS-II, which may have influenced outcomes. The development of new surgical techniques and increasing use of arterial conduits may of lead to improved surgical outcomes if the CABG patients had been enrolled at the same time as ARTS-II SES patients. Conversely the patients in ARTS-II had a worse baseline and procedural risk profile compared to those included in ARTS-I, however better stent design, improved PCI technique and equipment, as well as the increased use of anti-platelet agents probably account for the improved procedural success in these patients.

Clinical implications

Increasing age has an adverse prognosis in MVD patients treated by CABG which is not observed following percutaneous revascularisation. The use of SES has improved the results of PCI such that they are now as good as those of surgery for any age quartile, furthermore this use of SES is not associated with an excess in post discharge death or MI as compared to BMS. At present multivessel PCI with SES in elderly patients is a valuable alternative to surgery, particular in the absence of diabetes. Whether SES PCI is equivalent to CABG, or even superior in elderly patients

without diabetes, needs to be formally demonstrated in a head to head randomised trial, with long-term follow-up to help define the optimal treatment of these patients.

Conclusions

Age seems to influence the CABG outcome in-hospital but not PCI. PCI-SES could offer lower immediate risk in patients with MVD and comparable long-term outcome as CABG especially in older patients. The worst outcome of PCI-BMS group is primarily related to the need for repeat revascularisation. Diabetes is the most important predictor of MACCE following PCI.

References

1. Peterson ED, Alexander KP, Malenka DJ, Hannan EL, O'Conner GT, McCallister BD, Weintraub WS, Grover FL. Multicenter experience in revascularization of very elderly patients. *Am Heart J* 2004;148:486-92.

2. Weintraub WS. Coronary operations in octogenarians: can we select the patients? *Ann Thorac Surg* 1995;60:875-6.

3. Batchelor WB, Anstrom KJ, Muhlbaier LH, Grosswald R, Weintraub WS, O'Neill WW, Peterson ED. Contemporary outcome trends in the elderly undergoing percutaneous coronary interventions: results in 7,472 octogenarians. National Cardiovascular Network Collaboration. *J Am Coll Cardiol* 2000;36:723-30.

4. Alexander KP, Anstrom KJ, Muhlbaier LH, Grosswald RD, Smith PK, Jones RH,Peterson ED. Outcomes of cardiac surgery in patients >or=80 years: results from the National Cardiovascular Network. *J Am Coll Cardiol* 2000;35:731-8.

5. Mullany CJ, Mock MB, Brooks MM, Kelsey SF, Keller NM, Sutton-Tyrrell K,Detre KM, Frye RL. Effect of age in the Bypass Angioplasty Revascularization Investigation (BARI) randomized trial. *Ann Thorac Surg* 1999;67:396-403.

6. Legrand VM, Serruys PW, Lindeboom WK, Vrolix MD, Fransen GM, Materne PH,Dekoster G, Seabra-Gomes R, Queiroz E Melo J. Influence of Age on the Outcomes of Percutaneous and Surgical Treatment of Multivessel Coronary Artery Disease Patients: Results from the Multicentre Randomized Arterial Revascularization Therapy Study. *Geriatrics & Aging* 2002;5:9-16.

7. Garza JJ, Gantt DS, Van Cleave H, Riggs MW, Dehmer GJ. Hospital disposition and long-term follow-up of patients aged >/=80 years undergoing coronary artery revascularization. *Am J Cardiol* 2003;92:590-2.

8. Liistro F, Angioli P, Falsini G, Ducci K, Baldassarre S, Burali A, Bolognese L. Early invasive strategy in elderly patients with non-ST elevation acute coronary syndrome: comparison with younger patients regarding 30 day and long term outcome. *Heart* 2005;91:1284-8.

9. Graham MM, Ghali WA, Faris PD, Galbraith PD, Norris CM, Knudtson ML. Survival after coronary revascularization in the elderly. *Circulation* 2002;105:2378-84.

10. Trial of invasive versus medical therapy in elderly patients with chronic symptomatic coronary-artery disease (TIME): a randomised trial. *Lancet* 2001;358:951-7.

11. Pfisterer M, Buser P, Osswald S, Allemann U, Amann W, Angehrn W, Eeckhout E, Erne P, Estlinbaum W, Kuster G, Moccetti T, Naegeli B, Rickenbacher P. Outcome of elderly patients with chronic symptomatic coronary artery disease with an invasive vs optimized medical treatment strategy: one-year results of the randomized TIME trial. *Jama* 2003;289:1117-23.

12. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schonberger JP,Buller N, Bonser R, van den Brand MJ, van Herwerden LA, Morel MA, van Hout BA. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med* 2001;344:1117-24.

13. Serruys PW, Ong AT, Morice MC, De Bruyne B, Colombo A, Macaya C,Richardt G, Fajadet J, Hamm C, Dawkins K, O'Malley J, Bressers M, Dohonoe D on behalf of the ARTS II investigators. Arterial Revascularisation Therapies Study Part II - Sirolimus-eluting stents for the treatment of patients with Multivessel *de novo* coronary artery lesions. *EuroIntervention* 2005;1:147-156.

14. Legrand VM, Serruys PW, Unger F, van Hout BA, Vrolix MC, Fransen GM,Nielsen TT, Paulsen PK, Seabra Gomes R, de Queiroz e Melo JMG, Marques dos Santos Neves JP, Lindeboom W, Backx B. Three-year outcome after coronary stenting versus bypass surgery for the treatment of multivessel disease. *Circulation* 2004;109:1114-20.

15. Serruys PW, Ong AT, van Herwerden LA, Sousa JE, Jatene A, Bonnier JJ, Schönberger JPMA, Buller N, Bonser R, Disco C, Backx B, Hugenholtz PG, Firth BG, Unger F. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. *J Am Coll Cardiol* 2005;46:575-81.

16. Serruys PW, Daemen J, Morice MC, DeBruyne B, Colombo A, Macaya C, Richardt G, Fajadet J, Hamm C, Dawkins KD, Vranckx P, Bressers M, van Domburg R, Schuijer M, Wittebols K, Pieters M, Stoll HP. Three-year follow-up of the ARTS-II - sirolimus-eluting stents for the treatment of patients with multivessel coronary artery disease. *EuroIntervention* 2008;3:450-459.

17. Rodes-Cabau J, Deblois J, Bertrand OF, Mohammadi S, Courtis J, Larose E,Dagenais F, Déry JP, Mathieu P, Rousseau M, Barbeau G, Baillot R, Gleeton O, Perron J, Nguyen CM, Roy L, Doyle D De Larochellière R, Bogaty P, Voisine P. Nonrandomized comparison of coronary artery bypass surgery and percutaneous coronary intervention for the treatment of unprotected left main coronary artery disease in octogenarians. *Circulation* 2008;118:2374-81.

18. Kimura T, Morimoto T, Furukawa Y, Nakagawa Y, Shizuta S, Ehara N,Taniguchi R, Doi T, Nishiyama K, Ozasa N, Saito N, Hoshino K, Mitsuoka H, Abe M, Toma M, Tamura T, Haruna Y, Imai Y, Teramukai S, Fukushima M, Kita T. Long-term outcomes of coronary-artery bypass graft surgery versus percutaneous coronary intervention for multivessel coronary artery disease in the bare-metal stent era. *Circulation* 2008;118(14 Suppl):S199-209.

19. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. *N Engl J Med* 1996;335:217-25.

20. Zhang Z, Mahoney EM, Spertus JA, Booth J, Nugara F, Kolm P, Stables RH, Weintraub WS. The impact of age on outcomes after coronary artery bypass surgery versus stent-assisted percutaneous coronary intervention: one-year results from the Stent or Surgery (SoS) trial. *Am Heart J* 2006;152:1153-60.

21. Bravata DM, Gienger AL, McDonald KM, Sundaram V, Perez MV, Varghese R, Kapoor JR, Ardehali R, Owens DK, Hlatky MA. Systematic Review: The Comparative Effectiveness of Percutaneous Coronary Interventions and Coronary Artery Bypass Graft Surgery. *Annals of Internal Medicine* 2007;147:703-9.

22. Shirani J, Alaeddini J, Roberts WC. Comparison of modes of death and cardiac necropsy findings in fatal acute myocardial infarction in men and women >75 years of age. *Am J Cardiol* 2000;86:1010-2,A8,A10.

23. Hirsch H, Lazar J, Marzo KP, Steingart RM. Percutaneous revascularization for unstable angina in the elderly. *Coron Artery Dis* 2000;11:315-22.

24. Ramanathan KB, Weiman DS, Sacks J, Morrison DA, Sedlis S, Sethi G, Henderson WG. Percutaneous intervention versus coronary bypass surgery for patients older than 70 years of age with high-risk unstable angina. *Ann Thorac Surg* 2005;80:1340-6.

25. Bhatti F, Grayson AD, Grotte G, Fabri BM, Au J, Jones M, Bridgewater B. The logistic EuroSCORE in cardiac surgery: how well does it predict operative risk? *Heart* 2006;92:1817-1820.

26. Romagnoli E, Burzotta F, Trani C, Siviglia M, Biondi-Zoccai GG, Niccoli G,Leone AM, Porto I, Mazzari MA, Mongiardo R, Rebuzzi AG, Schiavoni G, Crea F. EuroSCORE as predictor of in-hospital mortality after percutaneous coronary intervention. *Heart* 2009;95:43-8.

27. Serruys PW. The Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery: The SYNTAX Study. Primary Endpoint Results at One Year in the Randomized Cohort- TCT presentation, Washington. 2008.

28. Stettler C, Wandel S, Allemann S, Kastrati A, Morice MC, Schomig A, Pfisterer ME, Stone GW, Leon MB, de Lezo JS, Goy JJ, Park SJ, Sabaté M, Suttorp MJ, Kelbaek H, Spaulding C, Menichelli M, Vermeersch P, Dirksen MT, Cervinka P, Petronio AS, Nordmann AJ, Diem P, Meier B, Zwahlen M, Reichenbach S, Telle S, Windecker S, Jüni P. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet* 2007;370:937-48.

29. The final 10-year follow-up results from the BARI randomized trial. *J Am Coll Cardiol* 2007;49:1600-6.

30. Daemen J, Kuck KH, Macaya C, LeGrand V, Vrolix M, Carrie D, Sheiban I, Suttorp MJ, Vrancks P, Rademaker T, Goedhart D, Schuijer M, Wittebols K, Macours N, Stoll HP, Serruys PWl. Multivessel coronary revascularization in patients with and without diabetes mellitus 3-year follow-up of the ARTS-II (Arterial Revascularization Therapies Study-Part II) trial. *J Am Coll Cardiol* 2008;52:1957-67.

31. Adler DS, Goldman L, O'Neil A, Cook EF, Mudge GH, Jr., Shemin RJ, DiSesa V, Cohn LH, Collins JJ. Long-term survival of more than 2,000 patients after coronary artery bypass grafting. *Am J Cardiol* 1986;58:195-202.

32. Thourani VH, Weintraub WS, Stein B, Gebhart SS, Craver JM, Jones EL, Guyton RA. Influence of diabetes mellitus on early and late outcome after coronary artery bypass grafting. *Ann Thorac Surg* 1999;67:1045-52.

33. Herlitz J, Wognsen GB, Emanuelsson H, Haglid M, Karlson BW, Karlsson T, Albertsson P, Westberg S. Mortality and morbidity in diabetic and nondiabetic patients during a 2-year period after coronary artery bypass grafting. *Diabetes Care* 1996;19:698-703.

34. Kapur A. Coronary Artery Revascularisation in Diabetes. The CARDia trial. Presentation at European Society of Cardiology meeting September 1st 2008.

35. The BARI 2D Study Group. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 2009;360: 2503-15.

Chapter 5.3

The impact of body mass index on the one year outcomes of patients treated by PCI with biolimus- and sirolimus-eluting stents in the LEADERS trial. Does the obesity paradox exist?

Am J Cardiol 2010; 105(4):475-479

Giovanna Sarno, Scot Garg, Yoshinobu Onuma, Pawel Buszman, Axel Linke, Thomas Ischinger, Volker Klauss, Franz Erbeli, Roberto Corti, William Wijns, Marie-Claude Morice, Carlo DiMario, Robert Jan van Geuns, Pedro Eerdmans, Hector M. Garcia-Garcia, Gerrit-Anne van Es, Dick Goedhart, Ton de Vries, Peter Juni, Bernhard Meier, Stephan Windecker, Patrick W. Serruys

The Impact of Body Mass Index on the One Year Outcomes of Patients Treated by Percutaneous Coronary Intervention With *Biolimus*- and *Sirolimus*-Eluting Stents (from the LEADERS Trial)

Giovanna Sarno, MD, PhD[a], Scot Garg, MB ChB, MRCP[a], Yoshinobu Onuma, MD[a], Pawel Buszman, MD, PhD[b], Axel Linke, MD, PhD[c], Thomas Ischinger, MD, PhD[d], Volker Klauss, MD, PhD[e], Franz Eberli, MD[f], Roberto Corti, MD[g], William Wijns, MD, PhD[h], Marie-Claude Morice, MD[i], Carlo di Mario, MD, PhD[j], Robert Jan van Geuns, MD, PhD[a], Pedro Eerdmans, MD, PhD[k], Hector M. Garcia-Garcia, MD, PhD[l], Gerrit-Anne van Es, PhD[l], Dick Goedhart, PhD[l], Ton de Vries, MSc[l], Peter Jüni[m,o], Bernhard Meier, MD[n], Stephan Windecker, MD, PhD[m,n], and Patrick Serruys, MD, PhD[a,*]

The aim of this analysis was to assess the effect of body mass index (BMI) on 1-year outcomes in patients enrolled in a contemporary percutaneous coronary intervention trial comparing a sirolimus-eluting stent with a durable polymer to a biolimus-eluting stent with a biodegradable polymer. A total of 1,707 patients who underwent percutaneous coronary intervention were randomized to treatment with either biolimus-eluting stents (n = 857) or sirolimus-eluting stents (n = 850). Patients were assigned to 1 of 3 groups according to BMI: normal (<25 kg/m^2), overweight (25 to 30 kg/m^2), or obese (>30 kg/m^2). At 1 year, the incidence of the composite of cardiac death, myocardial infarction, and clinically justified target vessel revascularization was assessed. In addition, rates of clinically justified target lesion revascularization and stent thrombosis were assessed. Cox proportional-hazards analysis, adjusted for clinical differences, was used to develop models for 1-year mortality. Forty-five percent of the patients (n = 770) were overweight, 26% (n = 434) were obese, and 29% (n = 497) had normal BMIs. At 1-year follow-up, the cumulative rate of cardiac death, myocardial infarction, and clinically justified target vessel revascularization was significantly higher in the obese group (8.7% in normal-weight, 11.3% in overweight, and 14.5% in obese patients, p = 0.01). BMI (hazard ratio 1.47, 95% confidence interval 1.02 to 2.14, p = 0.04) was an independent predictor of stent thrombosis. Stent type had no impact on the composite of cardiac death, myocardial infarction, and clinically justified target vessel revascularization at 1 year in the 3 BMI groups (hazard ratio 1.08, 95% confidence interval 0.63 to 1.83, p = 0.73). In conclusion, BMI was an independent predictor of major adverse cardiac events at 1-year clinical follow-up. The higher incidence of stent thrombosis in the obese group may suggest the need for a weight-adjusted dose of clopidogrel. **(Am J Cardiol 2010;105:475–479)**

The purpose of this study was to assess the effect of body mass index (BMI) on the clinical outcomes of patients who participated in the Limus Eluted From a Durable vs Erodable Stent Coating (LEADERS) trial,[1] which randomized patients to percutaneous coronary intervention (PCI) with either a sirolimus-eluting stent (with a durable polymer) or a biolimus-eluting stent (with a biodegradable polymer).

Methods

The LEADERS trial was a multicenter European trial that enrolled a total of 1,707 patients, who were randomized to PCI with a biolimus-eluting stent (n = 857) with a biodegradable polymer or a sirolimus-eluting stent (n = 850) with a durable polymer from November 27, 2006, to May 18, 2007. Details of the study have been described previously.[1]

Briefly, selection criteria were broad, reflecting routine clinical practice. Patients with chronic stable coronary ar-

[a]Department of Interventional Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands; [b]Medical University of Silesia, Katowice, Poland; [c]Herzzentrum Leipzig, Leipzig; [d]Department of Cardiology, Hospital Bogenhausen, Munich; [e]Department of Cardiology, University Hospital Munich, Innenstadt, Germany; [f]Department of Cardiology, Triemli Spital; [g]Department of Cardiology, University Hospital Zurich, Zurich, Switzerland; [h]Department of Cardiology, Onze Lieve Vrouw Ziekenhuis, Aalst, Belgium; [i]Institut Jacques Cartier, Massy, France; [j]Department of Cardiology, Royal Brompton Hospital, London, United Kingdom; [k]Biosensors Europe SA, Morges, Switzerland; [l]Cardialysis BV, Rotterdam, The Netherlands; [m]CTU Bern and [n]Department of Cardiology, Bern University Hospital; and [o]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland. Manuscript received August 18, 2009; revised manuscript received and accepted September 22, 2009.

*Corresponding author: Tel: 31-10-7035260; fax: 31-10-4369154.
E-mail address: p.w.j.c.serruys@erasmusmc.nl (P. Serruys).

0002-9149/10/$ – see front matter
doi:10.1016/j.amjcard.2009.09.055

tery disease or acute coronary syndromes, including ST elevation myocardial infarction (MI), were eligible for enrollment if they had ≥1 lesion with ≥50% diameter stenosis and reference vessel diameters of 2.25 to 3.5 mm. There were no limits to the numbers of treated lesions or vessels or to lesion length and no exclusion of patients on the basis of co-morbidities or age. Specific exclusion criteria included known allergy to acetylsalicylic acid, clopidogrel, heparin, stainless steel, sirolimus, biolimus, or contrast material; planned surgery within 6 months of PCI, unless dual-antiplatelet therapy could be maintained throughout the perisurgical period; pregnancy; participation in another trial before reaching the primary end point; and inability to provide informed consent. The study complied with the Declaration of Helsinki and was approved by all institutional ethics committees. All patients provided written informed consent for participation in this trial. Before or at the time of the procedure, patients were given ≥75 mg of acetylsalicylic acid, a 300- to 600-mg loading dose of clopidogrel, and unfractionated heparin in a dose of ≥5,000 IUs, or 70 to 100 IU/kg. The use of glycoprotein IIb/IIIa antagonists was left to the discretion of the operator. All patients were discharged on acetylsalicylic acid ≥75 mg/day for life and clopidogrel 75 mg/day for ≥12 months. In the case of intercurrent revascularization procedures needing stent implantation, treating cardiologists were encouraged to use study stents.

The primary end point of this post hoc analysis was the composite of cardiac death, MI, and clinically justified target vessel revascularization (TVR) at 12 months. The definition of cardiac death included any death due to an immediate cardiac cause (e.g., MI, low-output heart failure, fatal arrhythmia); procedure-related deaths, including those related to concomitant treatment; unwitnessed death; and death of unknown cause. MI was defined according to the electrocardiographic criteria of the Minnesota code manual or by a measured level of creatinine kinase 2 times the upper limit of normal, with a positive concentration of either creatine kinase-MB or troponin I or troponin T. TVR was defined as any repeat percutaneous intervention or surgical bypass of any segment within the entire major coronary vessel proximal and distal to a target lesion, including upstream and downstream branches and the target lesion itself. Target lesion revascularization was defined as a repeat revascularization due to a stenosis within the stent or within a 5-mm border proximal or distal to the stent. Stent thrombosis was defined according to the Academic Research Consortium definitions.[2]

A revascularization was regarded as clinically justified if the stenosis of the treated lesion was ≥50% of the luminal diameter on the basis of quantitative coronary angiography in the presence of ischemic signs or symptoms or if the diameter stenosis was ≥70% irrespective of the presence or absence of ischemic signs or symptoms.

The National Heart, Lung, and Blood Institute and the World Health Organization have introduced a weight classification for BMI that is calculated by dividing a patient's weight in kilograms by that patient's height in square meters. According to this classification, patients with BMIs of 18.5 to 24.9 kg/m^2 were considered normal, those with BMIs of 25 to 30 kg/m^2 were considered overweight, and those with BMIs >30 kg/m^2 were considered obese. Patients enrolled in the sirolimus- and biolimus-eluting stent arms of the LEADERS trial were stratified into 3 subgroups according to their BMIs: normal (BMI <25 kg/m^2), overweight (BMI 25 to 30 kg/m^2), and obese (BMI >30 kg/m^2).

Table 1
Baseline characteristics (n = 1,701)

Variable	BMI (kg/m^2)			p Value
	<25 (n = 497)	25–30 (n = 770)	>30 (n = 434)	
Women	142 (29%)	170 (22%)	117 (27%)	0.49
Mean BMI (kg/m^2)	23.0 ± 1.7	27.4 ± 1.4	33.1 ± 3.0	NA
Age (years)	65.9 ± 10.9	64.6 ± 10.5	63.1 ± 10.8	<0.05
Acute coronary syndromes	288 (58%)	412 (53%)	240 (55%)	0.38
Stable angina pectoris	157 (32%)	274 (36%)	156 (36%)	0.15
Previous PCI	163 (33%)	298 (39%)	163 (38%)	0.12
Previous MI	153 (31%)	265 (34%)	135 (31%)	0.86
Hypertension (≥165/95 mm Hg)	324 (65%)	565 (73%)	357 (82%)	<0.05
Diabetes mellitus	73 (15%)	181 (23%)	160 (37%)	<0.05
Peripheral vascular disease	45 (9%)	54 (7%)	34 (8%)	0.46
Hypercholesterolemia (>190 mg/dl)	299 (60%)	525 (68%)	316 (73%)	<0.05
Current smokers	134 (27%)	162 (21%)	122 (28%)	0.79

Data are expressed as number (percentage) or as mean ± SD.
NA = not applicable.

Continuous variables are expressed as mean ± SD and categorical variables as absolute and relative values. Comparisons among groups were performed by analysis of variance for independent samples; for variables measured repeatedly within a patient, the covariance structure was taken into account by the use of PROC MIXED in SAS (SAS Institute Inc., Cary, North Carolina). The Cochran-Armitage test for trend was used for comparisons of categorical data. For variables measured repeatedly within a patient, the covariance structure was taken into account by the use of PROC GENMOD.

The Kaplan-Meier method was used to estimate the event-free survival rate, and the differences among groups were assessed using the log-rank test. Cox proportional-hazards analysis, adjusted for clinical differences, was used to develop models for 30-day and 1-year mortality. The following variables were included in the models: BMI, diabetes, multivessel disease, stent type, age, hypertension, and dyslipidemia. A collinearity test on the explanatory variables included in the models was performed. Statistical analysis was performed using SAS by a dedicated statistician. All p values are 2 sided, and $p < 0.05$ was considered statistically significant.

Results

Data on 1,701 patients who underwent PCI with biolimus-eluting stents (n = 854) and sirolimus-eluting stents (n = 847) were available for complete analysis. Forty-five percent of the patients (n = 770) were overweight, 26% (n = 434) were obese, and 29% (n = 497) had normal BMIs. Baseline clinical characteristics of all patients are

Table 2
Baseline angiographic characteristics (n = 1,701)

Variable	BMI (kg/m^2)			p Value
	<25 (n = 497)	25–30 (n = 770)	>30 (n = 434)	
Left anterior descending	241 (48%)	382 (50%)	198 (46%)	0.41
Left circumflex	156 (31%)	253 (33%)	151 (35%)	0.27
Right	195 (39%)	296 (38%)	163 (38%)	0.60
Left main	7 (1%)	21 (3%)	6 (1%)	0.95
Coronary total occlusion	89 (18%)	147 (19%)	107 (25%)	<0.05
In-stent restenosis	8 (8%)	19 (13%)	6 (7.%)	0.95
Lesion length (mm)	14.7 (13.8–15.6)	14.5 (13.8–15.2)	16.0 (15.0–16.9)	0.06
Minimal luminal diameter (mm)	0.94 (0.91–0.98)	0.95 (0.92–0.98)	0.87 (0.82–0.91)	<0.05
Stenosis (%)	63 (62–65)	63 (62–64)	67 (65–69)	<0.05
SYNTAX score	13.6 ± 8.9	13.4 ± 8.4	12.8 ± 8.9	0.18
No. of treated lesions	1.44 ± 0.71	1.49 ± 0.73	1.39 ± 0.67	0.41
No. of stents	1.93 ± 1.21	1.91 ± 1.17	1.88 ± 1.21	0.53

Data are presented as number (percentage), median (range), or mean ± SD.

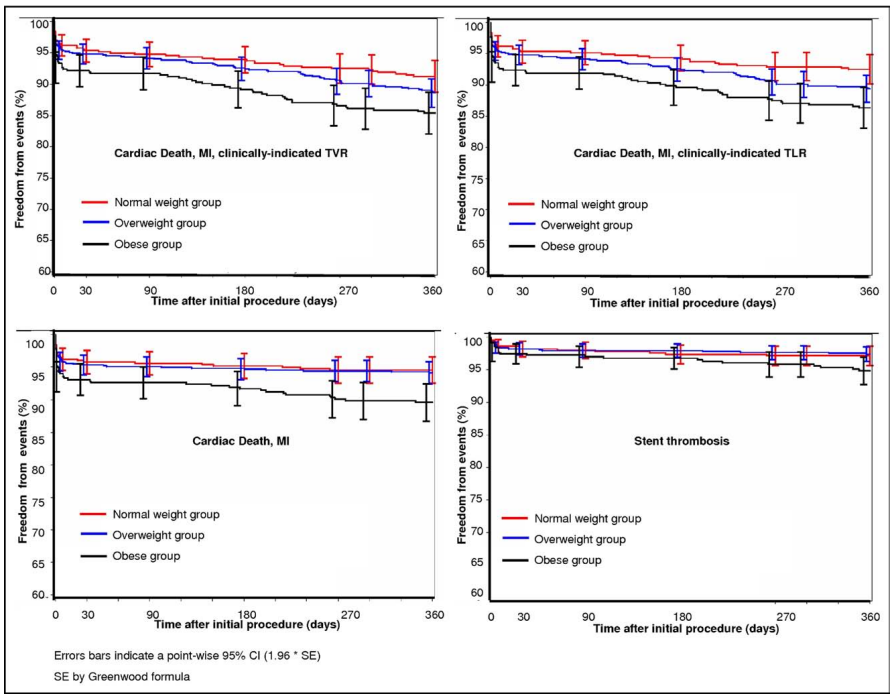


Figure 1. One year Kaplan-Meier survival curves. TLR = target lesion revascularization.

listed in Table 1. Of note, there was a significantly higher incidence of diabetes, hypertension, and dyslipidemia in the overweight and obese groups compared to the normal BMI group. The collinearity analysis showed no significant interrelations among the clinical variables (condition index <30).

Angiographic baseline and periprocedural characteristics are listed in Table 2. The rate of total occlusions was significantly higher in the obese patients. The Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score was not significantly different among the 3 BMI groups.

Table 3
Adjusted hazard ratios for adverse events in the body mass index subgroups

Variable	BMI (kg/m^2)			HR	95% CI	p Value
	<25 (n = 497)	25–30 (n = 770)	>30 (n = 434)			
Death	15 (3%)	22 (2.9%)	18 (4.1%)	1.23	0.85–1.78	0.27
Cardiac death	11 (2.2%)	14 (1.8%)	16 (3.7%)	1.4	0.91–2.16	0.13
Myocardial infarction	21 (4.2%)	35 (4.5%	33 (7.6%)	1.36	1.01–1.82	<0.05
Q-wave myocardial infarction	4 (0.8%)	3 (0.4%)	4 (0.9%)	1.25	0.55–2.84	0.6
Non-Q-wave myocardial infarction	18 (3.6%)	32 (4.2%)	29 (6.7%)	1.34	0.98–1.83	0.07
All revascularizations	33 (6.6%)	77 (9.9%)	43 (9.9%)	1.25	0.98–1.59	0.07
Percutaneous	25 (5%)	70 (9.1%)	40 (9.2%)	1.27	1.0–1.62	<0.05
Surgical	9 (1.8%)	11 (1.4%)	6 (1.4%)	0.71	0.42–1.22	0.22
All target vessel revascularization	32 (6.4%)	76 (9.9%)	43 (9.9%)	1.17	0.93–1.46	0.18
Percutaneous target vessel revascularization	25 (5%)	70 (9.1%)	40 (9.2%)	1.27	1.0–1.62	<0.05
Surgical target vessel revascularization	8 (1.6%)	10 (1.3%)	6 (1.4%)	0.77	0.44–1.35	0.36
Clinically justified target vessel revascularization	21 (4.2%)	56 (7.3%)	33 (7.6%)	1.24	0.95–1.62	0.11
Clinically justified percutaneous target vessel revascularization	18 (3.6%)	54 (7%)	31 (7.1%)	1.3	0.99–1.71	0.06
Clinically justified surgical target vessel revascularization	4 (0.8%)	4 (0.5%)	5 (1.2%)	0.97	0.45–2.08	0.93
All target lesion revascularization	22 (4.4%)	62 (8.1%)	35 (8.1%)	1.24	0.96–1.60	0.10
Percutaneous target lesion revascularization	19 (3.8%)	59 (7.7%)	33 (7.6%)	1.29	0.99–1.68	0.06
Surgical target lesion revascularization	4 (0.8%)	7 (0.9%)	5 (1.2%)	0.97	0.49–1.94	0.94
Clinically justified target lesion revascularization	15 (3%)	50 (6.5%)	28 (6.5%)	1.3	0.97–1.73	0.08
Clinically justified percutaneous target lesion revascularization	14 (2.8%)	48 (6.2%)	26 (6%)	1.32	0.98–1.77	0.07
Clinically justified surgical target lesion revascularization	2 (0.4%)	3 (0.4%)	5 (1.2%)	1.3	0.52–3.24	0.57
Composite of cardiac death, myocardial infarction, and clinically justified target vessel revascularization	43 (8.7%)	87 (11.3%)	63 (14.5%)	1.28	1.05–1.57	<0.05
Composite of cardiac death, myocardial infarction, and clinically justified target lesion revascularization	37 (7.4%)	81 (10.5%)	59 (13.6%)	1.33	1.08–1.63	<0.05
Composite of death, myocardial infarction, and clinically justified target vessel revascularization	47 (9.5%)	92 (11.9%)	65 (15%)	1.25	1.03–1.52	<0.05
Composite of death and myocardial infarction	31 (6.2%)	51 (6.6%)	47 (10.8%)	1.37	1.07–1.75	<0.05
Composite of cardiac death and myocardial infarction	27 (5.4%)	45 (5.8%)	45 (10.4%)	1.44	1.11–1.87	<0.05

Table 4
Adjusted hazard ratios for stent thrombosis in the 3 body mass index subgroups according to the Academic Research Consortium definition

Variable	BMI (kg/m^2)			HR	95% CI	p Value
	<25 (n = 497)	25–30 (n = 770)	>30 (n = 434)			
Stent thrombosis	14 (2.8%)	20 (2.6%)	22 (5.1%)	1.47	1.02–2.14	<0.05
Definite stent thrombosis	8 (1.6%)	14 (1.8%)	12 (2.8%)	1.34	0.83–2.16	0.22
Definite early stent thrombosis	6 (1.2%)	13 (1.7%)	9 (2.1%)	1.36	0.81–2.3	0.25
Definite late stent thrombosis	2 (0.4%)	1 (0.1%)	4 (0.9%)	1.47	0.5–4.3	0.49
Possible stent thrombosis	3 (0.6%)	6 (0.8%)	7 (1.6%)	1.91	0.94–3.89	0.08
Possible early stent thrombosis	0	0	0			
Possible late stent thrombosis	3 (0.6%)	6 (0.8%)	7 (1.6%)	1.91	0.94–3.89	0.08
Probable stent thrombosis	5 (1%)	1 (0.1%)	3 (0.7%)	0.77	0.3–1.98	0.58
Probable early stent thrombosis	4 (0.8%)	1 (0.1%)	2 (0.5%)	0.71	0.24–2.1	0.53
Probable late stent thrombosis	1 (0.2%)	0	1 (0.2%)	0.95	0.14–6.59	0.96

At 1-month clinical follow-up, BMI was an independent predictor of clinically justified percutaneous TVR (hazard ratio [HR] 1.83, 95% confidence interval [CI] 1.09 to 3.09, p = 0.04) and target lesion revascularization (HR 1.75, 95% CI 1.03 to 2.96, p = 0.04). The cumulative incidence of cardiac death, MI, and clinically justified TVR at 1 month was higher in obese patients (4.6% in normal-weight patients, 5.2% in overweight patients, and 7.8% in obese patients, p = 0.04).

One-year Kaplan-Meier survival curves are shown in Figure 1. The 1-year cumulative rate of cardiac death, MI, and clinically justified TVR was significantly higher in the obese group (8.7% in normal-weight patients, 11.3% in overweight patients, and 14.5% in obese patients, p = 0.01). The 1-year cumulative rate of MI was significantly higher in the obese group (4.2% in normal-weight patients, 4.5% in overweight patients, 7.6% in obese patients, p = 0.04) (Table 3).

BMI (HR 1.47, 95% CI 1.02 to 2.14, p = 0.04) and age (HR 1.04, 95% CI 1.02 to 1.07, p = 0.001) were independent predictors of stent thrombosis at 1 year. The 1-year cumulative rate of stent thrombosis according to the Academic Research Consortium definitions is displayed in Table 4. Stent type had no impact on the composite of cardiac death, MI, and clinically justified TVR at 1 year among the 3 BMI groups (HR 0.88, 95% CI 0.67 to 1.16, p = 0.38), and it was not a predictive factor of an increased risk for stent thrombosis (HR 1.08, 95% CI 0.63 to 1.83, p = 0.78).

Discussion

The main finding of this study is that BMI is an independent predictive factor of the composite of cardiac death, MI, and clinically justified TVR, as well as stent thrombosis at 1-year clinical follow-up.

Large population studies have shown an association between increased BMI and cardiac death.[3–5] Despite this, some studies have paradoxically shown a protective effect of obesity on clinical outcomes after PCI.[6–8]

The presence of obesity is closely linked to insulin resistance and metabolic risk factors such as hyperlipidemia and hypertension, which characterize the metabolic syndrome.[9,10] In this study population, the incidence of hypertension, hyperlipidemia, and diabetes was higher in the obese group, but no statistically significant relation was found between these risk factors and BMI by a collinearity test.

Despite a similar overall anatomic complexity of coronary artery disease among the 3 BMI groups as assessed by the SYNTAX score, obese patients had a higher rate of total occlusions. However, the rate of major adverse clinical events was not significantly different between obese patients with and without total occlusion (data not shown).

Therefore, these findings do not indicate a mere synergistic effect of multiple risk factors but rather suggest that obesity itself triggers physiopathologic mechanisms leading to more adverse events in this population. This is in line with previous reports[10–12] showing that obesity is associated with a greater inflammatory state, as reflected by increased levels of C-reactive protein as well as abnormalities of coagulation, platelet function, and fibrinolysis.

In this study, the higher incidence of stent thrombosis in obese patients could be potentially explained by a lower inhibition of platelet aggregation in this group. Previous studies[13,14] showed that higher BMI is an independent factor of clopidogrel resistance, and weight-adjusted long-term treatment has been suggested, although no clear recommendations have been established. Angiolillo et al[13,14] found increased platelet aggregation and a higher prevalence of inadequate clopidogrel responders in overweight patients after a clopidogrel loading dose of 300 mg. Furthermore, recent studies[15] have shown that the effect of BMI on platelet function persists even when a higher 600-mg loading dose is administered.

The relation between obesity and impaired response to antiplatelet therapy is difficult to explain. It is unclear whether the latter phenomenon is simply an issue of inadequate dosing of medication or whether the increased inflammatory state intrinsic to obesity leads to increased platelet activation. Obesity may activate platelet aggregation through a number of different pathways and as a result impair the response to antiplatelet therapy. Obesity, in particular abdominal adiposity, plays an important role in the modulation of C-reactive protein levels. Adipocytes produce interleukin-6, which in turn promotes CRP production by the liver and subsequent proinflammatory state.[10]

This subgroup analysis is limited by its post hoc nature. This study should be considered hypothesis generating, primarily because of the absence of any assessment of platelet function, which may have been important in view of the results.

1. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Juni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet* 2008;372:1163–1173.
2. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;115:2344–2351.
3. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med* 1999;341:1097–1105.
4. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation* 1983; 67:968–977.
5. Wang ZJ, Zhou YJ, Liu YY, Yu M, Shi DM, Zhao YX, Guo YH, Cheng WJ, Nie B, Ge HL, Jia DA, Yang SW, Yan ZX. Obesity and cardiovascular thrombotic events in patients undergoing percutaneous coronary intervention with drug-eluting stents. *Heart* 2009;95:1587–1592.
6. Gruberg L, Weissman NJ, Waksman R, Fuchs S, Deible R, Pinnow EE, Ahmed LM, Kent KM, Pichard AD, Suddath WO, Satler LF, Lindsay J Jr. The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: the obesity paradox? *J Am Coll Cardiol* 2002;39:578–584.
7. Powell BD, Lennon RJ, Lerman A, Bell MR, Berger PB, Higano ST, Holmes DR Jr, Rihal CS. Association of body mass index with outcome after percutaneous coronary intervention. *Am J Cardiol* 2003;91:472–476.
8. Gurm HS, Brennan DM, Booth J, Tcheng JE, Lincoff AM, Topol EJ. Impact of body mass index on outcome after percutaneous coronary intervention (the obesity paradox). *Am J Cardiol* 2002;90:42–45.
9. Rana JS, Nieuwdorp M, Jukema JW, Kastelein JJ. Cardiovascular metabolic syndrome—an interplay of, obesity, inflammation, diabetes and coronary heart disease. *Diabetes Obes Metab* 2007;9:218–232.
10. Lee YH, Pratley RE. Abdominal obesity and cardiovascular disease risk: the emerging role of the adipocyte. *J Cardiopulm Rehabil Prev* 2007;27:2–10.
11. Mills R, Bhatt DL. The yin and yang of arterial inflammation. *J Am Coll Cardiol* 2004;44:50–52.
12. Schneider DJ. Abnormalities of coagulation, platelet function, and fibrinolysis associated with syndromes of insulin resistance. *Coron Artery Dis* 2005;16:473–476.
13. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Ramirez C, Sabate M, Hernandez-Antolin R, Moreno R, Escaned J, Alfonso F, Banuelos C, Macaya C. Is a 300 mg clopidogrel loading dose sufficient to inhibit platelet function early after coronary stenting? A platelet function profile study. *J Invasive Cardiol* 2004;16:325–329.
14. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Barrera Ramirez C, Sabate M, Fernandez C, Hernandez-Antolin R, Escaned J, Alfonso F, Macaya C. Platelet aggregation according to body mass index in patients undergoing coronary stenting: should clopidogrel loading-dose be weight adjusted? *J Invasive Cardiol* 2004;16:169–174.
15. Sibbing D, von Beckerath O, Schomig A, Kastrati A, von Beckerath N. Impact of body mass index on platelet aggregation after administration of a high loading dose of 600 mg of clopidogrel before percutaneous coronary intervention. *Am J Cardiol* 2007;100:203–205.

PART VI

The Impact of Coronary Anatomy on Clinical Outcomes in Patients Treated with PCI

Chapter 6.1

Value of the SYNTAX score (SX) for risk assessment in the "all-comers" population of the randomized multicenter LEADERS trial

J Am Coll Cardiol 2010; 56(4):272-277

Joanna Wykrzykowska, Scot Garg, Chris Girasis, Ton de Vries, Marie-Angèle Morel, Gerrit-Anne van Es, Pawel Buszman, Axel Linke, Thomas Ischinger, Volker Klauss, F Eberli, Roberto Corti, William Wijns, Marie-claude Morice, Carlo di Mario, Robert-Jan van Geuns, Peter Juni, Stephan Windecker, Patrick W. Serruys

Interventional Cardiology

Value of the SYNTAX Score for Risk Assessment in the All-Comers Population of the Randomized Multicenter LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) Trial

Joanna J. Wykrzykowska, MD,* Scot Garg, MBChB, MRCP,* Chrysafios Girasis, MD,* Ton de Vries, MSc,† Marie-Angele Morel, BSc,† Gerrit-Anne van Es, PhD,† Pawel Buszman, MD,‡ Axel Linke, MD,§ Thomas Ischinger, MD,‖ Volker Klauss, MD,¶ Roberto Corti, MD,# Franz Eberli, MD, PhD,# William Wijns, MD,** Marie-Claude Morice, MD,†† Carlo di Mario, MD, PhD,‡‡ Robert Jan van Geuns, MD, PhD,* Peter Juni, MD, PhD,§§ Stephan Windecker, MD, PhD,‖‖ Patrick W. Serruys, MD, PhD*

Rotterdam, the Netherlands; Katowice, Poland; Leipzig and Munich, Germany; Zurich, Switzerland; Aalst, Belgium; Massy, France; London, United Kingdom; and Bern, Switzerland

Objectives We aimed to assess the predictive value of the SYNTAX score (SXscore) for major adverse cardiac events in the all-comers population of the LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial.

Background The SXscore has been shown to be an effective predictor of clinical outcomes in patients with multivessel disease undergoing percutaneous coronary intervention.

Methods The SXscore was prospectively collected in 1,397 of the 1,707 patients enrolled in the LEADERS trial (patients after surgical revascularization were excluded). Post hoc analysis was performed by stratifying clinical outcomes at 1-year follow-up, according to 1 of 3 SXscore tertiles.

Results The 1,397 patients were divided into tertiles based on the SXscore in the following fashion: SXscore ≤8 (SXlow) (n = 464), SXscore >8 and ≤16 (SXmid) (n = 472), and SXscore >16 (SXhigh) (n = 461). At 1-year follow-up, there was a significantly lower number of patients with major cardiac event–free survival in the highest tertile of SXscore (SXlow = 92.2%, SXmid = 91.1%, and SXhigh = 84.6%; $p < 0.001$). Death occurred in 1.5% of SXlow patients, 2.1% of SXmid patients, and 5.6% of SXhigh patients (hazard ratio [HR]: 1.97, 95% confidence interval [CI]: 1.29 to 3.01; $p = 0.002$). The myocardial infarction rate tended to be higher in the SXhigh group. Target vessel revascularization was 11.3% in the SXhigh group compared with 6.3% and 7.8% in the SXlow and SXmid groups, respectively (HR: 1.38, 95% CI: 1.1 to 1.75; $p = 0.006$). Composite of cardiac death, myocardial infarction, and clinically indicated target vessel revascularization was 7.8%, 8.9%, and 15.4% in the SXlow, SXmid, and SXhigh groups, respectively (HR: 1.47, 95% CI: 1.19 to 1.81; $p < 0.001$).

Conclusions The SXscore, when applied to an all-comers patient population treated with drug-eluting stents, may allow prospective risk stratification of patients undergoing percutaneous coronary intervention. (LEADERS Trial Limus Eluted From A Durable Versus ERodable Stent Coating; NCT00389220). (J Am Coll Cardiol 2010;56:272–7)

From the *Department of Interventional Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands; †Cardialysis B.V., Rotterdam, the Netherlands; ‡Medical University of Silesia, Katowice, Poland; §Herzzentrum Leipzig, Leipzig, Germany; ‖Department of Cardiology, Hospital Bogenhausen, Munich, Germany; ¶Department of Cardiology, University Hospital Munich (Innenstadt), Munich, Germany; #Department of Cardiology, University Hospital, Zurich, Switzerland; **Department of Cardiology, Onze Lieve Vrouw Ziekenhuis, Aalst, Belgium; ††Institut Cardiovasculaire, Paris-Sud, Massy, France; ‡‡Department of Cardiology, Royal Brompton Hospital, London, United Kingdom; and the §§CTU Bern and ‖‖Department of Cardiology, Bern University Hospital, Bern, Switzerland. Dr. Eberli is currently working at Triemlispital, Zurich, Switzerland. Funding for this paper was received from Biosensors Europe SA, Switzerland. Dr. Linke is a consultant for Medtronic. Dr. Windecker receives lecture and consulting fees from Abbott, Boston Scientific, Biosensors, Cordis, and Medtronic. Dr. di Mario's institution has received a research grant from Biosensors. Dr. Eberli is a consultant for the Cordis Company, and has received research grants from Biosensors, Medtronic, and Abbott Vascular.

Manuscript received November 30, 2009; revised manuscript received March 22, 2010, accepted March 23, 2010.

The SYNTAX score (SXscore) is a comprehensive angiographic scoring system that is derived entirely from the coronary anatomy and lesion characteristics (1–3). It was initially designed to quantify lesion complexity; however, it is also able to predict major adverse cardiac events (MACE) after percutaneous revascularization in patients with multivessel coronary artery disease (4–6) and/or left main disease (7). More recent data indicate its ability to predict periprocedural myocardial infarction (MI) in patients undergoing elective percutaneous coronary intervention (8). In this substudy of the LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial, in which the SXscore was collected prospectively in 1,397 all-comer patients, we assessed its prognostic value for MACE at 1-year follow-up.

Methods

Study population. LEADERS was a multicenter European noninferiority trial comparing the safety and efficacy of the BioMatrix Flex biolimus-eluting stent with a biodegradable polymer (Biosensors, Morges, Switzerland) with the Cypher Select sirolimus-eluting stent with a durable polymer (Cordis, Bridgewater, New Jersey) in 1,707 all-comer patients. Detailed study protocol can be found in the main report (9). The study complied with the Declaration of Helsinki and was approved by all institutional ethics committees. All patients provided written informed consent for participation in the trial.

SXscore and angiographic analysis. From the baseline diagnostic angiogram, each coronary lesion producing ≥50% diameter stenosis in vessels ≥1.5 mm was scored separately and added together to provide the overall SXscore, which was calculated prospectively using the SXscore algorithm (described in full elsewhere) (1–3). All angiographic variables pertinent to SXscore calculation were computed by blinded core laboratory analysts (Cardialysis B.V., Rotterdam, the Netherlands). The SXscore is not currently validated in patients with acute MI or previous percutaneous coronary intervention and coronary artery bypass graft. Core laboratory analysts were blinded to all clinical data, and therefore patients with occluded infarct–related arteries were scored as occlusions of unknown duration in a similar manner to any chronically occluded artery. Those patients with in-stent restenosis lesions were scored in the same manner as if the lesion was a de novo lesion.

Study end points. Definitions of all end points are provided elsewhere (9). The primary end point of this substudy was MACE, defined as the composite of cardiac death, MI, and clinically indicated target vessel revascularization (TVR) within 9 months. Secondary end points were any target lesion revascularization (both clinically and nonclinically indicated), any TVR, cardiac death, death from any cause, MI, stent thrombosis (defined according to the Academic Research Council [10]), device success, and lesion success.

The pre-specified principal outcome of the angiographic substudy was the in-stent percentage of diameter stenosis. Secondary angiographic outcomes were the in-segment percentage of diameter stenosis, minimal lumen diameter, late lumen loss, and binary restenosis.

Abbreviations and Acronyms

CI = confidence interval
HR = hazard ratio
MACE = major adverse cardiac event(s)
MI = myocardial infarction
SXhigh = SYNTAX score >16
SXlow = SYNTAX score ≤8
SXmid = SYNTAX score >8 and ≤16
SXscore = SYNTAX score
TVR = target vessel revascularization

Statistical analysis. A stratified post hoc analysis of clinical and angiographic outcomes was performed according to the tertiles of the SXscore (4,5). Dedicated software and visual coronary angiography served to determine the SXscore (1,2). All randomized patients without previous surgical revascularization (1,397 of 1,707) were included in the analysis. Angiographic outcomes were analyzed using SAS version 8 (SAS Institute, Cary, North Carolina) Proc Mixed for continuous and Proc Genmod for binominal outcomes, taking into account the within-patient correlation structure of these data. The Cox proportional hazards model was used to compare clinical outcomes among the groups. All analyses were performed using SAS version 8.02 by a dedicated statistician. All p values and confidence intervals (CIs) were 2-sided. Multivariate model included SXscore, diabetes, beta-blocker use, stent type, and the presence of acute coronary syndrome as covariates. Testing for (linear) trend was done by using generalized linear models with SYNTAX class as a covariable for continuous variables and the Cochran-Armitage test for trend in categorical data.

Results

SXscore and baseline characteristics. The SXscore was collected prospectively in 1,397 of the 1,707 patients (81.8%) enrolled in the LEADERS trial. The score ranged from 0 to 49, with a mean ± SD of 13.5 ± 8.7 and a median of 12 (interquartile range 7 to 19). In this post hoc analysis, the SXscore tertiles were defined as SXlow (SXscore ≤8) (n = 464), SXmid (SXscore >8 and ≤16) (n = 472), and SXhigh (SXscore >16) (n = 461). Baseline clinical and angiographic characteristics of the patients are listed in Tables 1 and 2.

1-year outcomes. The SXscore significantly predicted the rate of MACE at 360 days (Table 3, Figs. 1 to 4). There was a lower number of patients with MACE-free survival in the highest tertile of the SXscore (SXlow = 92.2%, SXmid = 91.1%, and SXhigh = 84.6%; $p < 0.001$). Death occurred in 1.5% of patients with SXlow, 2.1% of patients with SXmid, and 5.6% of patients with SXhigh (hazard ratio [HR]: 1.97, 95% CI: 1.29 to 3.01; $p = 0.002$). The rate of MI tended to be

Table 1 Baseline Clinical Characteristics

Baseline Clinical Variables	SXlow (n = 464)	SXmid (n = 472)	SXhigh (n = 461)	p Value on Trend (2-Sided)
Age >65 yrs	210 (45.3)	224 (47.5)	239 (51.8)	0.048
Male	346 (74.6)	344 (72.9)	340 (73.8)	0.79
Diabetes	93 (20.0)	117 (24.8)	111 (24.1)	0.15
Current smoking	134 (28.9)	121 (25.6)	126 (27.3)	0.61
Hypertension	353 (76.1)	353 (74.8)	324 (70.3)	0.048
Hypercholesterolemia	314 (67.7)	314 (66.5)	285 (61.8)	0.06
Family history of coronary artery disease	201 (43.3)	188 (39.8)	168 (36.4)	0.034
Renal insufficiency	17 (3.7)	21 (4.5%)	28 (6.1)	0.09
Previous MI	132 (28.5)	145 (30.7)	137 (29.7)	0.69
Previous PCI	179 (38.6)	165 (35.0)	147 (31.9)	0.036
PVD	26 (5.6)	36 (7.6)	31 (6.7)	0.51
Previous stroke	13 (2.8)	19 (4.0)	16 (3.5)	0.59
Clinical presentation				
Stable	146 (31.5)	154 (32.6)	108 (23.4)	0.008
Unstable	127 (27.4)	89 (18.9)	88 (19.1)	0.002
STEMI	46 (9.9)	90 (19.1)	128 (27.8)	<0.0001
Non-STEMI	90 (19.4)	90 (19.1)	97 (21.0)	0.54
Silent ischemia	55 (11.9)	49 (10.4)	40 (8.7)	0.12

Values shown are n (%).
MI = myocardial infarction; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; STEMI = ST-segment elevation myocardial infarction; SXhigh = SYNTAX score >16; SXlow = SYNTAX score <8; SXmid = SYNTAX score >8 and ≤16.

higher in patients with SXhigh (MI HR: 1.2, 95% CI: 0.9 to 1.61; p = 0.22). TVR was 11.3% in the SXhigh group compared with 6.3% and 7.8% in the SXlow and SXmid groups, respectively (HR: 1.38, 95% CI: 1.1 to 1.75; p = 0.006). Composite of cardiac death, MI, and clinically indicated TVR was 7.8%, 8.9%, and 15.4% in the SXlow, SXmid, and SXhigh groups, respectively (HR: 1.47, 95% CI: 1.19 to 1.81; p < 0.001).

Multivariate model. In a multivariate model, SXscore remained a significant predictor of MACE and mortality. Patients in the SXhigh group had a 50% greater chance of the composite of cardiac death, MI, and clinically indicated TVR than patients in the SXmid group (p < 0.001), which was comparable to the 51% higher composite event rate among diabetic patients (p = 0.022). Use of the biolimus-eluting stent tended to reduce the composite event rate by 26% (p = 0.07).

Stent thrombosis rates. The rates of definite stent thrombosis were 0.9%, 2.1%, and 3.5% in the SXlow, SXmid, and SXhigh groups, respectively.

Table 2 Baseline Angiographic Characteristics

Angiographic Variables	SXlow	SXmid	SXhigh	p Value
No. of diseased lesions per patient (based on SYNTAX application)	1.47 ± 0.66	2.37 ± 1.00	3.45 ± 1.44	<0.001
No. of treated lesions per patient (as defined by the core laboratory)	1.2 ± 0.46	1.47 ± 0.7	1.69 ± 0.86	<0.001
Ratio of diseased to treated lesions	1.22	1.61	2.04	N/A
Coronary artery treated				
LAD	162 (34.9)	242 (51.3)	296 (64.2)	<0.001
LCX	140 (30.2)	144 (30.5)	164 (35.6)	0.079
RCA	216 (46.6)	209 (44.3)	174 (37.7)	0.007
2-vessel disease	49 (10.6)	102 (21.6)	138 (29.9)	<0.001
3-vessel disease	3 (0.7)	13 (2.8)	23 (5.0)	<0.001
Stent type				
Biolimus-eluting	229 (49.3)	235 (49.8)	239 (51.8)	0.45
Sirolimus-eluting	235 (50.7)	237 (50.2)	222 (48.2)	0.45
No. of implanted stents	1.47 ± 0.8	1.90 ± 1.12	2.33 ± 1.39	<0.001
Total stent length/patient, mm	25.9 ± 16.5	34.2 ± 21.7	42.9 ± 26.2	<0.001
Chronic total occlusion	6 (1.3)	10 (2.1)	19 (4.1)	0.006
Moderate to severe calcification	23 (5.1)	96 (20.3)	184 (39.9)	<0.001
Bifurcation lesion	57 (12.3)	161 (34.1)	184 (39.9)	<0.001
Use of glycoprotein IIb/IIIa inhibitor	80 (17.2)	113 (23.9)	154 (33.4)	<0.001

Values are mean ± SD or n (%).
LAD = left anterior descending artery; LCX = left circumflex artery; N/A = not applicable; RCA = right coronary artery; other abbreviations as in Table 1.

Table 3 Clinical Outcomes at 360 Days After Index PCI Based on Tertiles of SXscore

Type of Event	Risk Factors Used	SXlow (%)	SXmid (%)	SXhigh (%)	p Value SYNTAX	HR, SYNTAX	Lower Limit HR, SYNTAX	Upper Limit HR, SXscore
Death	SYNTAX class, DM, STEMI	1.5	2.1	5.6	0.002	1.97	1.29	3.01
Stent thrombosis	SYNTAX class, DM, STEMI	1.1	3	6.1	<0.001	2.13	1.4	3.24
MI	SYNTAX class, DM, STEMI, beta-blockers, and treatment (BES vs. SES)	4.3	4.9	5.9	0.22	1.2	0.9	1.61
All TVR	SYNTAX class, DM, STEMI, beta-blockers, and treatment (BES vs. SES)	6.3	7.8	11.3	0.006	1.38	1.1	1.75
All TLR	SYNTAX class, DM, STEMI, beta-blockers, and treatment (BES vs. SES)	4.7	6.1	8.7	0.019	1.37	1.05	1.79
Composite of cardiac death, MI, clinically indicated TVR	SYNTAX class, DM, STEMI, beta-blockers, and treatment (BES vs. SES)	7.8	8.9	15.4	<0.001	1.47	1.19	1.81

BES = biolimus-eluting stent(s); DM = diabetes mellitus; HR = hazard ratio; PCI = percutaneous coronary intervention; SES = sirolimus-eluting stent(s); TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table 1.

Discussion

Complexity of disease and lesion characteristics are well recognized predictors of periprocedural complications (8) and long-term mortality (11–13). The SXscore was developed to comprehensively assess lesion characteristics and is based on the combination of classifications from the American Heart Association/American College of Cardiology, modified BARI classification, chronic total occlusion and bifurcation scores, and Leaman classification (1). It has previously been applied in both the SYNTAX trial and the ARTS II (Arterial Revascularization Therapies Study II), both of which demonstrated the good predictive value of the SXscore in patients with multivessel disease, with the highest tertile patients having significantly more MACE during short-term (4,5) and long-term (6) follow-up.

This study is the first to report the utility of the SXscore as a predictor of MACE, including cardiac death, in an all-comers population including patients with acute coronary syndromes. Overall, this patient population had much lower SXscores than the SYNTAX trial population; however, despite this, the SXscore still appears to have good discriminatory power for risk assessment.

Study limitations. The limitation of the SXscore is that it does not incorporate clinical patient characteristics. Patients who underwent previous coronary artery bypass graft surgery have not been included because the SXscore algorithm is only currently available for patients with de novo disease. Modifications to the SXscore for risk stratification in patients after coronary artery bypass graft surgery are currently being developed. The SXscore of patients who presented with acute MI or had previous percutaneous

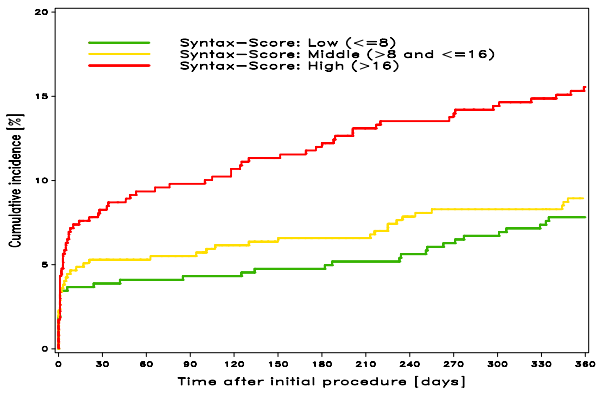


Figure 1 Kaplan-Meier Curves for MACE at 360 Days According to the SYNTAX Tertiles

Patients in the highest tertile of the SYNTAX score have an increased major adverse cardiac events (MACE) event rate (p = 0.0002).

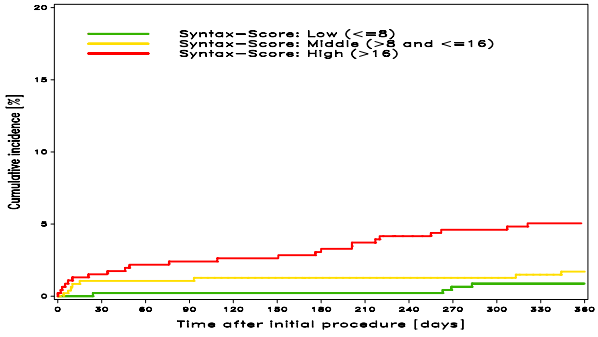


Figure 2 **Kaplan-Meier Curves for Cardiac Death at 360 Days According to the SYNTAX Score Tertiles**

Patients in the highest tertile of the SYNTAX score have a higher cardiac death rate ($p < 0.0001$).

coronary intervention were included in this analysis, despite no previous validation in these patients. Scoring of the infarct-related vessel as a chronic total occlusion may confound the results and have complex effects on the SXscore. There is the danger of overestimating the SXscore if all ST-segment elevation MIs with an occluded infarct–related vessel are taken as chronic total occlusions, particularly because the lesion is likely to be easier to treat due to the soft nature of plaque as opposed to an occlusion, which has calcified organized old thrombus and plaque (chronic occlusion). Alternatively, there is the danger of underestimating the SXscore because the underlying lesion complexity will not be accounted for because the vessel beyond the occlusion is not seen due to the occlusion. This is the subject of an ongoing study. This study may have limitations inherent to subgroup analysis (chance findings and underpowering) (14–16).

Conclusions

This study demonstrates that the prognostic value of the SXscore is valid for all patients with de novo coronary artery disease undergoing percutaneous revascularization.

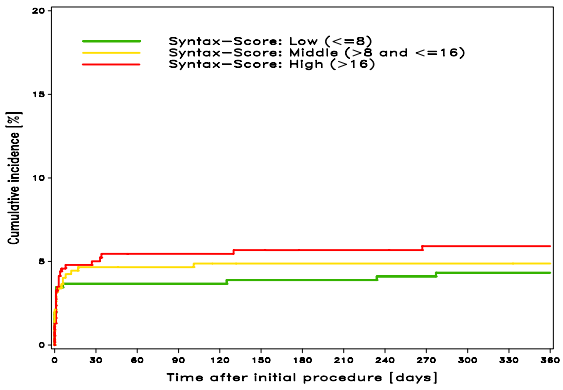


Figure 3 **Kaplan-Meier Curves for All Myocardial Infarctions at 360 Days According to the SYNTAX Score Tertiles**

There is no difference in the rate of overall myocardial infarctions across the tertiles of SYNTAX score ($p = 0.548$ [NS]).

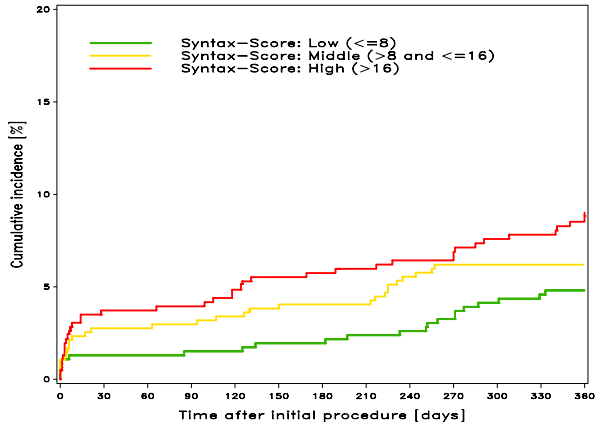


Figure 4 **Kaplan-Meier Curves for Target Lesion Revascularization at 360 Days According to the SYNTAX Score Tertiles**

Patients in the highest tertile of the SYNTAX score have an increased risk of target lesion revascularization (p = 0.036).

Reprint requests and correspondence: Dr. Patrick W. Serruys, Interventional Cardiology, Thoraxcenter, Erasmus Medical Center, 's Gravendijkwal 230 Bd 412, 3015CE Rotterdam, the Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl.

REFERENCES

1. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. Eurointervention 2005;1:219–27.
2. Serruys P, Onuma Y, Garg S, et al. Assessment of the SYNTAX score in the Syntax study. Eurointervention 2009;5:50–6.
3. SYNTAX Working Group. SYNTAX score calculator. Available at: http://www.syntaxscore.com. Accessed November 2009.
4. Valgimigli M, Serruys PW, Tsuchida K, et al. Cyphering the complexity of coronary artery disease using the syntax score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. Am J Cardiol 2007;99:1072–81.
5. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.
6. Serruys P, Onuma Y, Garg S, et al. 5-year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. J Am Coll Cardiol 2010;55:1093–101.
7. Capodanno D, Di Salvo ME, Cincotta G, Miano M, Tamburino C, Tamburino C. Usefulness of the SYNTAX Score for predicting clinical outcome after percutaneous coronary intervention of unprotected left main coronary artery disease. Circ Cardiovasc Interv 2009;2:302–8.
8. van Gaal WJ, Ponnuthurai FA, Selvanayagam J, et al. The Syntax score predicts peri-procedural myocardial necrosis during percutaneous coronary intervention. Int J Cardiol 2009;135:60–5.
9. Windecker S, Serruys PW, Wandel S, et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet 2008;372:1163–73.
10. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
11. Meier B, Gruentzig AR, Hollman J, Ischinger T, Bradford JM. Does length or eccentricity of coronary stenoses influence the outcome of transluminal dilatation? Circulation 1983;67:497–9.
12. Ischinger T, Gruentzig AR, Meier B, Galan K. Coronary dissection and total coronary occlusion associated with percutaneous transluminal coronary angioplasty: significance of initial angiographic morphology of coronary stenoses. Circulation 1986;74:1371–8.
13. Ellis SG, Roubin GS, King SB 3rd, et al. Angiographic and clinical predictors of acute closure after native vessel coronary angioplasty. Circulation 1988;77:372–9.
14. Lagakos SW. The challenge of subgroup analyses—reporting without distorting. N Engl J Med 2006;354:1667–9.
15. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine—reporting of subgroup analyses in clinical trials. N Engl J Med 2007;357:2189–94.
16. Pfeffer MA, Jarcho JA. The charisma of subgroups and the subgroups of CHARISMA. N Engl J Med 2006;354:1744–6.

Key Words: biodegradable polymer ■ biolimus-eluting stent ■ major adverse cardiac event ■ prognostic value ■ sirolimus-eluting stent ■ target vessel revascularization ■ SYNTAX score.

Chapter 6.2

The prognostic utility of the SYNTAX score for risk assessment in patients undergoing coronary revascularization with second generation drug eluting stents: A sub-study of the randomized RESOLUTE All Comers trial

J Am Coll Cardiol Intv. In press

Scot Garg, Patrick W. Serruys, Sigmund Silber, Joanna Wykrzykowska, Robert Jan van Geuns, Gert Richardt, Pawel E. Buszman, Henning Kelbæk, Adrianus Johannes van Boven, Sjoerd H. Hofma, Axel Linke, Volker Klauss, William Wijns, Carlos Macaya, Philippe Garot, Carlo DiMario, Ganesh Manoharan, Ran Kornowski, Thomas Ischinger, Antonio Bartorelli, Marco Bressers, Eric van Remortel, Jacintha Ronden, Stephan Windecker

ABSTRACT

Background: The SYNTAX score (SXscore) can identify patients treated with percutaneous coronary intervention (PCI) who are at highest risk of adverse events.

Objectives: This study assessed the ability of the SXscore to stratify risk in patients treated with PCI who received zotarolimus-eluting or everolimus-eluting stents.

Methods: The SXscore was calculated prospectively in 2,033 of the 2,292 patients enrolled in the RESOLUTE All-Comers study. Clinical outcomes in terms of a patient orientated composite endpoint (POCE) of all-cause death, MI and repeat revascularization; the individual components, of POCE; target lesion failure (TLF, a composite of cardiac death, target-vessel MI and clinically-driven target lesion revascularisation), and stent thrombosis were subsequently stratified according to SXscore tertiles: $SXscore_{LOW} \leq 9$(n=698), $9 < SXscore_{MID} \leq 17$ (n=676); $SXscore_{HIGH} > 17$ (n=659).

Results: At 12-month follow-up, rates of POCE, MI, repeat revascularization, TLF and the composite of death/MI, were all significantly higher in patients in the highest SXscore tercile. Rates of stent thrombosis were all highest in the $SXscore_{HIGH}$ tertile ($p>0.05$). After multivariate adjustment, the SXscore was identified as an independent predictor of POCE, MI, repeat revascularisation and TLF ($p<0.05$ for all). At 12-months follow-up the SXscore, ACEF score and Clinical SXscore had respective C-statistics of 0.57, 0.78, 0.67 for mortality and 0.62, 0.56, 0.63 for POCE. No significant between-stent differences were observed for TLF or POCE in any of the SXscore tertiles.

Conclusions: The SYNTAX score is able to stratify risk amongst an all-comers population treated with PCI using second generation DES; however improvements can be made with the inclusion of clinical variables.

INTRODUCTION

The SYNTAX score (SXscore) is a comprehensive scoring system made up of angiographic variables (1-2). It was originally developed to quantify the complexity of coronary artery disease (CAD), however subsequent studies have demonstrated its ability to identify patients treated by percutaneous coronary intervention (PCI) who are at highest risk of adverse events (3-8).

Currently, prospective studies assessing its use in patients treated with PCI are limited to the SYNTAX study (4), which only enrolled patients with complex CAD (three vessel and/or left main disease), and the LEADERS study (3), which was more reflective of everyday clinical practice through its all-comers design. Of note, other than the 703 patients treated with the biolimus-eluting stent with a biodegradable polymer in the LEADERS SXscore sub-study(3), all other studies evaluating the SXscore have assessed outcomes in patients treated with first generation drug-eluting stents (DES) (4-9). Second generation DES were developed on the background of safety concerns with these first generation devices, and early data suggest significantly improved outcomes (10-12), however the effect of this on the benefits of using the SXscore to stratify risk remains to be established.

The RESOLUTE All Comers study(13) randomized 2292 patients to treatment with the Resolute zotarolimus-eluting stent (R-ZES, Medtronic CardioVascular, Santa Rosa, California) or the Xience V everolimus-eluting stent (EES, Abbott Vascular, Santa Clara, California). Results demonstrated that R-ZES was non-inferior to EES with respect to the 12-month primary clinical endpoint of target lesion failure (TLF, R-ZES 8.2% vs. EES 8.3%, $P_{non\text{-}inferiority}<0.001$), a composite of cardiac death, target-vessel myocardial infarction (MI) and clinically-driven target lesion revascularization (TLR), and the 13-month secondary angiographic endpoint of in-stent diameter stenosis (R-ZES 21.65±14.42% vs. EES 19.76±14.64%, $P_{non\text{-}inferiority}=0.035$). In this sub-study of the RESOLUTE All Comers trial the prognostic value of the SXscore was assessed in isolation, and in comparison with the ACEF score(14-15) and the Clinical SYNTAX score (CSS),(16) in an all-comers population treated with second generation DES.

METHODS

Study population

The methods of the RESOLUTE All Comers study have been published previously (13). In brief, the studied applied an all-comers approach to recruit 2292 patients with chronic stable CAD or acute coronary syndromes (ACS) including ST-elevation myocardial infarction (STEMI), who were eligible for enrolment if they had at ≥1 lesion with diameter stenosis (DS) ≥50% and a reference vessel diameter (RVD) between 2.25 and 4.0mm. No restriction was placed on the number of lesions or vessels treated or the number of stents implanted. Principal exclusion criteria were: allergy to study medication, metal alloys or contrast media; planned surgery within 6 months of PCI unless the dual anti-platelet therapy could be maintained throughout the peri-operative period, pregnancy, participation in another trial before reaching the primary endpoint and lastly inability to give informed

consent. The study complied with the Declaration of Helsinki and was approved by all institutional ethics committees. All patients provided written, informed consent for participation in the trial.

Randomization and Procedures

Patients were randomly allocated on a 1:1 basis to treatment with R-ZES or EES, and to 12-month clinical follow-up only, or in addition active angiographic follow-up at 13-months, on a 1:4 basis with a factorial design. A blinded independent clinical events committee (CEC) adjudicated all endpoints, and independent study monitors verified all case reports from data on-site. The operators were by necessity aware of the assigned study stent during PCI and angiographic follow-up, but patients and staff involved in follow-up assessment were blinded to the allocated stent type.

R-ZES were available in diameters of 2.25-4.0 mm and in lengths of 8-30 mm, whilst EES were available in diameters of 2.25-4.0 mm and in lengths of 8-28 mm. Balloon angioplasty and stent implantation were performed according to standard technique, and direct stenting was allowed. The aim was to obtain full lesion coverage with one or several stents. No mixture of DES was permitted within a given patient, unless the operator was unable to insert the study stent, in which case crossover to another non-study device of the operator's choice was possible.

Procedural anticoagulation was achieved with unfractionated heparin 5000IU or 70-100IU/kg, whilst the use of glycoprotein IIb/IIIa inhibitors was left to the operator's discretion. Pre-procedure all patients enrolled into the study received ≥75 mg of acetylsalicylic acid, whilst the 300-600 mg loading dose of clopidogrel was only given if no clopidogrel had been administrated in the previous seven days. All patients were discharged on ≥75 mg of acetylsalicylic acid indefinitely, and clopidogrel 75mg for >6 months following the index procedure. In the case of inter-current revascularization procedures needing stent implantation, treating cardiologists were encouraged to use study stents.

Follow up

Adverse events were assessed in hospital, and clinical follow up was performed at 1, 6, and 12 months. Additional clinical follow-up is planned at yearly intervals to 5 years. One in five patients was asked to return for angiographic follow-up at 13-months.

SYNTAX Score

The SXscore for each patient was calculated prospectively by scoring all coronary lesions with a DS≥50%, in vessels ≥1.5 mm, using the SXscore algorithm which is described in full elsewhere (1-2), and available at www.syntaxscore.com.(17) All angiographic variables pertinent to SXscore calculation were computed by two core laboratory analysts (Cardialysis B.V., Rotterdam, The Netherlands), who were blinded to all clinical data, presentation and outcomes. In the event of disagreement, the opinion of a third analyst was sought, and the final decision was established by consensus. Patients with occluded infarct related arteries were scored as occlusions of unknown duration in a similar

manner as any chronically occluded artery. In addition those patients with lesions due to restenosis or in-stent restenosis, were scored in the same manner as if the lesion were a *de novo* lesion. Although this methodology was not described in the original description of the SXscore, it has previously been applied to other all-comers (3,6), and STEMI populations.(9)

ACEF Score and CSS

The ACEF score was calculated using the combination of the patient's age, left ventricular ejection fraction (LVEF) and serum creatinine as described elsewhere.(14) Similarly, the CSS was calculated using the combination of the SXscore and the patient's age, LVEF and creatinine clearance as described in the primary manuscript.(16)

Study Endpoints

The primary endpoint of this analysis was a patient oriented composite endpoint (POCE) of all cause death, any MI, and any repeat revascularization. Secondary endpoints included the individual components of the patient oriented composite endpoint, together with 1-year rates of cardiac death, target vessel MI, clinically-indicated TLR, a safety composite of death/MI, TLF (a composite of cardiac death, target-vessel MI, and TLR) and definite, definite/probable and any stent thrombosis (ST).

Definitions

Definitions of all endpoints are provided in the primary manuscript (13). All deaths were considered cardiac unless an undisputed non-cardiac cause was present. MI was defined according to an extended historical protocol definition and according to Academic Research Consortium (ARC) definitions (18-19). A Q-wave MI required, in the absence of cardiac enzyme data, a history of chest pain or other acute symptoms consistent with myocardial ischemia together with new pathological Q waves in ≥2 contiguous ECG leads as assessed by the core lab or CEC. In the presence of elevated cardiac enzymes, new pathological Q waves in ≥2 contiguous ECG leads as assessed by the core lab or CEC were sufficient to diagnose a Q-wave MI. In the absence of an ECG, a Q-wave MI could be adjudicated on the basis of the clinical scenario and appropriate cardiac enzyme data.

A TLR was considered clinically indicated if angiography during follow-up showed a DS≥50% (core laboratory quantitative coronary angiography [QCA] assessment) and if one of the following occurred: (1) a positive history of recurrent angina pectoris, presumably related to the target vessel; (2) objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent), presumably related to the target vessel; (3) abnormal results of any invasive functional diagnostic test (e.g. fractional flow reserve); (4) a TLR with a DS≥70% even in the absence of the above mentioned ischemic signs or symptoms. ST was defined according to the ARC definitions (18).

Statistical Methods

All patients with a calculated SXscore were included in the analysis. All variables were stratified according to SXscore tertiles. Discrete data were summarized as frequencies (%), whereas continuous data were expressed as mean±standard deviation (SD). Testing for (linear) trends was done by using generalized linear models with SYNTAX tertiles as a co-variable for continuous variables, and

the Cochran-Armitage test for trend in categorical data. The Fisher's exact test was used to analyze differences in outcome between stents. Survival curves were constructed for time-to-event variables using Kaplan-Meier estimates, and compared by the log-rank test. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. A Cox multi-variate model was performed using the co-variates gender, age >65, presence of diabetes, presentation with acute MI, stent type and SXscore. C-statistics from receiver operator characteristic curves were used to compare the discrimination of the SXscore, ACEF score, and CSS score. A p value of <0.05 was considered significant, and all tests were two-tailed. Data were analyzed using SAS version 9.2 software (SAS, Carey, North Carolina) by a dedicated statistician.

Results

The SXscore was available for 2,033 (88.7%) of 2,292 patients enrolled in the study, with the presence of coronary artery bypass grafts (224 patients) the major reason for inability to calculate the score. The SXscore ranged from 0 to 54.5, with a mean±SD of 14.6±9.2, and a median of 13.0 (inter-quartile range 7 to 20). In this analysis patients were categorized according to tertiles of the SXscore defined as: $SXscore_{LOW} \leq 9$ (n=698), $9 < SXscore_{MID} \leq 17$ (n=676); $SXscore_{HIGH} > 17$ (n=659).

Table 1. Baseline clinical characteristics

Variable %, (n)	SXscore ≤9 (N=698)	9<SXscore≤17 (N=676)	SXscore>17 (N=659)	P Value
Baseline Characteristics				
Male gender	71.2% (497)	76.9% (520)	78.8% (519)	0.001
Age, years (±SD)	63.0±10.9	63.0±10.8	65.5±11.0	<0.001
Risk factors				
Previous MI	26.5% (182)	24.8% (164)	28.7% (185)	0.37
Diabetes mellitus	19.3% (135)	23.2% (157)	24.7% (163)	0.02
Arterial hypertension	70.6% (493)	71.3% (482)	68.3% (450)	0.35
Hypercholesterolemia	65.6% (458)	64.1% (433)	59.8% (394)	0.03
Premature CAD in first degree relative	36.0% (214)	37.7% (218)	30.7% (169)	0.07
Current smoker	25.5% (178)	29.3% (198)	29.1% (192)	0.13
Previous PCI	31.2% (218)	26.6% (180)	29.9% (197)	0.57
Creatinine clearance, ml/1.73m^2 (±SD)	96.2±34.4	96.6±34.7	90.9±34.3	0.006
Left ventricular ejection fraction <30%	2.0% (8)	2.4% (8)	1.6% (6)	0.69
Multi-vessel disease	32.4% (226)	57.0% (385)	78.8% (519)	<0.0001
SYNTAX score (±SD)	5.7±2.4	13.3±2.3	25.5±6.7	N/A
Indication for Treatment				
Revascularization for angina or MI	86.8% (606)	88.9% (601)	89.4% (589)	0.14
Stable angina	37.5% (262)	31.8% (215)	30.2% (199)	0.004
Unstable angina	21.6% (151)	19.7% (133)	14.9% (98)	0.002
Acute MI	27.7% (193)	37.4% (253)	44.3% (292)	<0.0001

SXscore, SYNTAX score; SD, standard deviation; MI, myocardial infarction; CAD, coronary artery disease; PCI, percutaneous coronary intervention; N/A, not applicable

Baseline Clinical Characteristics

Baseline clinical parameters stratified according to SXscore tertiles are presented in **Table** 1. Advanced patient age, male gender, the presence of diabetes mellitus and multivessel disease, and presentation with an acute MI were all significantly more common in the $SXscore_{HIGH}$ tertile. Conversely hypercholesterolaemia and presentation with stable angina were significantly more frequent in the $SXscore_{LOW}$ tertile.

Table 2. Baseline lesion and procedural characteristics

Variable %, (n)	SXscore ≤9 (N=698)	9<SXscore≤17 (N=676)	SXscore>17 (N=659)	P Value
Extent of Disease				
Number of disease lesions (±SD)	1.5±0.7	2.5±1.1	4.0±1.6	<0.0001
One vessel disease	67.6% (472)	26.9% (182)	7.4% (49)	0.005
Two vessel disease	29.1% (203)	54.3% (367)	36.1% (238)	<0.0001
Three vessel disease	2.1% (15)	18.8% (127)	56.4% (372)	<0.0001
Lesion Location				
Left main stem	0.0% (0)	0.6% (4)	5.8% (38)	<0.0001
Right coronary artery	46.8% (327)	60.7% (410)	75.9% (500)	<0.0001
Circumflex artery	34.1% (238)	53.3% (360)	74.5% (491)	<0.0001
LAD artery	51.3% (358)	77.4% (523)	95.1% (627)	<0.0001
Proximal LAD involvement	8.7% (61)	21.0% (142)	44.9% (296)	<0.0001
All *de novo* lesions	89.3% (620)	92.5% (620)	90.6% (591)	0.39
Lesion Characteristics				
≥1 Bifurcation lesion	25.9% (181)	56.2% (380)	75.6% (498)	<0.0001
≥1 Trifurcation lesion	0.6% (4)	3.6% (24)	6.4% (42)	<0.0001
≥1 Ostial lesion	1.6% (11)	3.0% (20)	4.9% (32)	0.0005
≥1 Occlusion	3.6% (25)	25.3% (171)	49.3% (325)	<0.0001
≥1 Tortuous lesion	24.8% (171)	45.0% (304)	62.7% (413)	<0.0001
≥1 Lesion ≥ 20mm	8.0% (55)	29.6% (200)	53.0% (349)	<0.0001
≥ 1 Calcified lesion	3.0% (21)	10.4% (70)	21.5% (142)	<0.0001
≥ 1 Lesion with thrombus	5.8% (40)	6.5% (44)	10.9% (72)	0.0004
≥ 1 In-stent restenosis lesion	9.1% (63)	5.5% (37)	7.7% (50)	0.30
Off-label indication*	49.9% (348)	67.2% (454)	80.9% (533)	<0.0001
Procedural Characteristics				
Number of treated lesions (±SD)	1.2±0.4	1.5±0.6	1.9±1.0	<0.0001
Number of stents implanted (±SD)	1.5±0.8	1.9±1.1	2.6±1.6	<0.0001
Total stent length, mm (±SD)	25.7±16.3	35.3±22.9	48.1±30.3	<0.0001
Mean duration of DAPT, days (±SD)	315±97	319±90	308±102	0.20

SXscore, SYNTAX score; LAD, left anterior descending artery; DAPT, dual anti-platelet therapy
*Off-label use included patients with at least one of the following clinical and lesion characteristics; renal insufficiency (≥ 140 µmol/L), ejection fraction < 30%, acute myocardial infarction (≤72 h), > 1 lesion per vessel, ≥ 2 vessels stented; lesions > 27 mm, bifurcations, bypass grafts, in-stent restenosis, unprotected left main, lesions with thrombus, or total occlusion.

Baseline Angiographic Characteristics

Baseline lesion and procedural characteristics are shown in **Table 2**. In line with its method of derivation, the frequency of triple vessel disease and all markers of increased lesion complexity such as the presence of bifurcation lesions and total occlusions were all significantly higher in the $SXscore_{HIGH}$ tertile. Correspondingly the number of treated lesions, stents implanted and mean stent length were also higher in the $SXscore_{HIGH}$ tertile.

Clinical Outcomes

Clinical outcomes at 1 year are shown in **Table 3**, whilst cumulative survival curves are displayed in **Figure 1**. Overall the POCE, the safety endpoint of death/MI, and the rates of MI and repeat revascularization were all significantly higher in the $SXscore_{HIGH}$ tertile. No trends were noted between rates of death, and definite, definite/probable or any ST and the patient's SXscore tertile.

Table 3: Clinical Outcomes at 12-Months on an intention-to-treat basis

Variable %, (n)	SXscore ≤9 (N=698)	9<SXscore≤17 (N=676)	SXscore>17 (N=659)	P Value
Death	1.9% (13)	1.0% (7)	2.7% (18)	0.25
Cardiac death	1.0% (7)	0.4% (3)	2.1% (14)	0.06
Any MI*	8.0% (56)	12.1% (82)	18.2% (120)	<0.0001
Any MI†	3.2% (22)	3.8% (26)	5.3% (39)	0.01
Target vessel MI†	2.7% (19)	3.6% (24)	5.6% (37)	0.006
Any repeat revascularization	5.0% (35)	7.7% (52)	13.7% (90)	<0.0001
Clinically indicated TLR	2.0% (14)	2.7% (18)	5.3% (35)	0.0007
Death or MI	4.7% (33)	4.7% (32)	8.2% (54)	0.01
Target lesion failure‡	5.2% (36)	5.9% (40)	11.7% (77)	<0.0001
Patient Orientated Composite Endpoint§	8.5% (59)	11.2% (76)	20.0% (132)	<0.0001
ARC definite stent thrombosis	0.4% (3)	0.6% (4)	1.1% (7)	0.16
ARC definite/probable stent thrombosis	0.9% (6)	0.7% (5)	1.7% (11)	0.15
ARC any stent thrombosis	1.4% (10)	0.9% (6)	2.6% (17)	0.10

SXscore, SYNTAX score; TLR, target lesion revascularization; ARC, Academic Research Consortium; MI, myocardial infarction

* Defined according to the ARC(18)

† Extended historical definition(19)

‡ Target Lesion Failure: cardiac death, MI† (not clearly attributable to a non-target vessel) and clinically indicated TLR

§ Patient Orientated Composite Endpoint: a composite of all-cause mortality, MI (Q- and non-Q wave) or any revascularization

Multivariate analysis

The results of the Cox multivariable analysis are shown in **Table 4**. Following adjustment of confounding factors the SXscore remained an independent predictor of clinical outcomes such as MI, repeat revascularisation, TLF, and POCE.

Table 4. Cox Multi-variate Analysis

Clinical Outcome	Hazard Ratio for SYNTAX score* [95% Confidence Interval]	P Value
Death	1.19 [0.80-1.76]	0.40
MI†	1.52 [1.17-1.99]	0.002
Any repeat revascularisation	1.75 [1.44-2.13]	<0.001
Target lesion failure‡	1.68 [1.36-2.06]	<0.001
Patient Orientated Composite Endpoint§	1.68 [1.43-1.96]	<0.001
Any stent thrombosis	1.39 [0.89-2.15]	0.15

*After adjustment of confounding factors: age greater than 65, gender, presentation with an acute MI, presence of diabetes, and stent type.
†, ‡, § defined as in Table 3
MI, myocardial infarction

SXscore vs. ACEF score vs. CSS

Table 5 reports the respective C-statistics for the SXscore, ACEF score and CSS for a range of clinical outcomes at 12-months follow-up. The SXscore's discriminatory ability was best for repeat revascularization, poorest for the assessment of mortality, and comparable to the CSS for the composite endpoints of TLF and POCE.

Table 5: Comparison of Discriminatory Ability of SYNTAX score, ACEF score and Clinical SYNTAX score.

Variable %, (n)	C-statistic SXscore (2033 patients)	C-statistic ACEF score (1218 patients)	C-statistic CSS (1098 patients)
Death	0.57	0.78	0.67
Cardiac death	0.61	0.84	0.71
Any myocardial infarction†	0.60	0.58	0.65
Any repeat revascularization	0.63	0.50	0.59
Target lesion failure‡	0.62	0.59	0.63
Patient Orientated Composite Endpoint§	0.62	0.56	0.63
ARC any stent thrombosis	0.60	0.72	0.68

SXscore, SYNTAX score; CSS, Clinical SYNTAX score; TLR, target lesion revascularization
†, ‡, § defined as in Table 3.

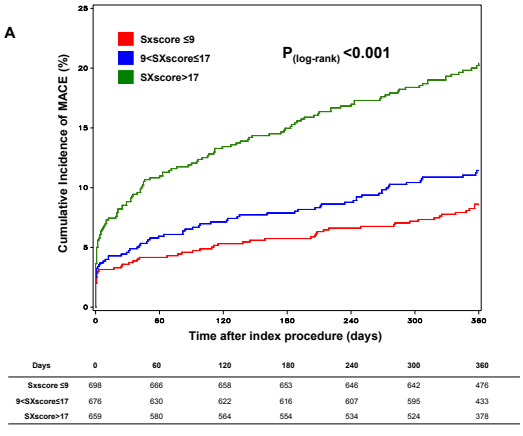
Zotarolimus vs. Everolimus

For illustrative purposes a comparison of outcomes amongst patients in each SXscore tertile stratified according to stent type was performed. Overall rates of TLF, the device oriented primary endpoint of the Resolute All Comers study, and the POCE were comparable between R-ZES and EES in all three SXscore groups (p>0.05). Notably, in 659 patients with the most complex CAD, mortality was significantly higher in patients treated with EES (R-ZES 1.3% vs. EES 4.1%, p=0.03), whilst rates of clinically-indicated TLR (7.2% vs. 3.5%, p=0.04) and definite ST (2.2% vs. 0.0%, p=0.006) were significantly higher in those treated with R-ZES.

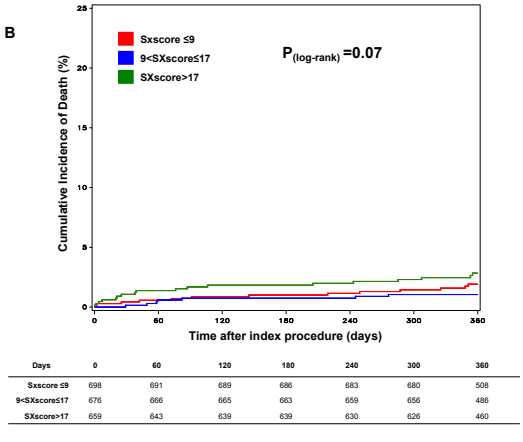
DISCUSSION

This study, which represents the largest assessment of the SXscore in patients treated with PCI and is the first to assess its ability to stratify risk in patients treated entirely with second generation DES, demonstrates a consistent ability of the SXscore to identify patients at highest risk of adverse events following PCI.

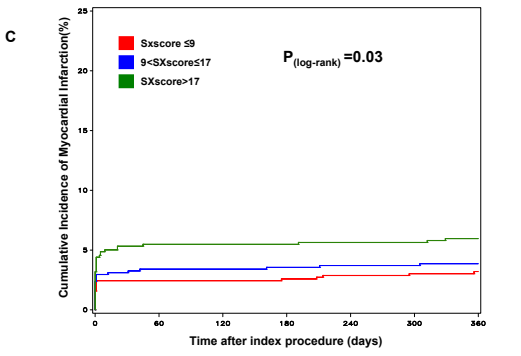
A key to optimizing outcomes in patients undergoing PCI is the ability to reliably identify those patients at highest risk of undesired events. With respect to this, the SXscore has been consistently shown to be an important tool for risk stratification, however prior assessments of the score in PCI populations have been limited by being retrospective (5-9,20) and largely including only those patients with the most complex CAD (4,7-8,20). In addition, other than the LEADERS study,(3) all other studies have enrolled patients treated with first generation DES.(4-9) The current prospective study had an all-comers design, such that any patient with symptomatic CAD suitable for PCI, who consented to enrolment, could be included, thereby ensuring the patient cohort provided a good



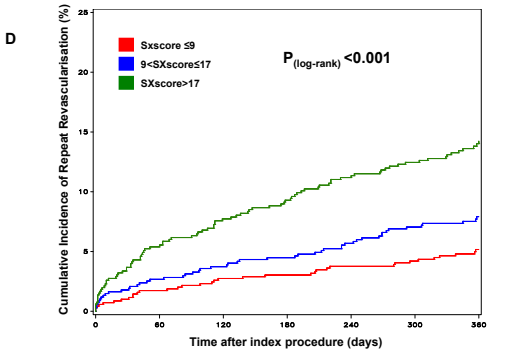
Days	0	60	120	180	240	300	360
Sxscore ≤9	698	666	658	653	646	642	476
9<SXscore≤17	676	630	622	616	607	595	433
SXscore>17	659	580	564	554	534	524	378



Days	0	60	120	180	240	300	360
Sxscore ≤9	698	691	689	686	683	680	508
9<SXscore≤17	676	666	665	663	659	656	486
SXscore>17	659	643	639	639	630	626	460



Days	0	60	120	180	240	300	360
Sxscore ≤9	698	674	673	669	664	661	496
9<SXscore≤17	676	644	643	640	635	632	465
SXscore>17	659	609	605	605	595	591	433



Days	0	60	120	180	240	300	360
Sxscore ≤9	698	680	671	666	659	654	485
9<SXscore≤17	676	649	641	635	624	612	449
SXscore>17	659	607	590	580	559	549	396

Figure 1. Kaplan Meier curves
Kaplan Meier survival curves for (A) the patient oriented composite endpoint (a composite of all-cause death, any myocardial infarction and any repeat revascularization; (B) Any death; (C) Any myocardial infarction; (D) Any repeat revascularization out to 12-months follow-up.

reflection of those patients routinely seen in 'real-world' contemporary practice. Furthermore all patients received second generation DES, which have been shown to have superior safety and efficacy, compared to earlier devices (10-12). The confirmation of this ability of the SXscore to independently predict adverse clinical outcomes in any patient presenting for PCI treated with second generation DES is therefore important evidence to support the routine use of the SXscore in everyday practice. This ability to identify those patients at greatest risk of adverse events facilitates appropriate informed consent and counseling, whilst also prompting increased surveillance, and aggressive secondary preventative therapy and life style modifications in those at highest risk.

Analysis of the SXscore distribution in the current study clearly indicates the patients with very complex CAD are being treated with PCI; a consequence of the increasing age and co-morbidities of

patients presenting for revascularization (21), and the advancements in PCI technology. Objective evidence of this increase is reflected in the mean SXscores of the SIRTAX and LEADERS studies, which were 11.7±7.3 and 13.5±8.7 (3,6), respectively, compared to 14.6±9.2 in the current study. Moreover the percentage of patients with SXscores>32, a group with the most complex CAD and previously identified in the SYNTAX trial as the threshold above which surgical revascularization provided the optimal outcome, is also increasing with respective rates of 1.0% and 2.9% in the SIRTAX and LEADERS studies, compared to 4.4% in the present analysis. The current study lacked a surgical control arm, and it is therefore not possible to state whether PCI was appropriate for those patients in the highest SXscore tertile. Moreover, at present no data are available comparing outcomes in patients randomized to treatment with PCI using second generation DES or CABG, however the utility of using EES compared to CABG in patients with complex CAD (SXscore<33) is currently being assessed in the ongoing EXCEL study.

Despite the more complex patient population in the current study it is reassuring that no significant differences in mortality were noted across SXscore tertiles, a finding at variance with the LEADERS study, which did identify the SXscore as an independent predictor of mortality (3). Furthermore, whilst both studies indicated significantly higher rates of their respective primary study endpoints and repeat revascularization in patients in the highest SXscore tertile, the same was not true for MI in the LEADERS study or ST in the current study. This variation in the ability of the SXscore to predict 'hard' clinical endpoints is not clearly explained. Without doubt it could be the consequence of underpowered sub-group analyses (22-23); however it may also reflect the limitations of using a risk model assessing only one type of variable. Consistent with previous studies (15-16), there were variations in the discriminatory ability of the SXscore, ACEF score and CSS, which respectively represent an anatomical, clinical and combination clinical/anatomical risk model, depending on the outcome measure being assessed. The C-statistic for mortality was highest for the ACEF score, reflecting the heavy influence of pre-morbid characteristics on this outcome. Similarly, the C-statistic for repeat revascularization was highest for the SXscore. One of the previous valid concerns with using the SXscore is the absence of clinical variables in its calculation, a deficiency which can be corrected through its combination with a clinical based score as reported previously (16,24), and highlighted in the present study through the improved C-statistics for all outcomes, apart from repeat revascularization, when using the CSS compared to the SXscore.

The rates of definite ST in the current study were lower than those seen in corresponding tertiles of the SXscore in LEADERS, differences which may partly explain the lack of association between ST and SXscore tertile in the present study. It must be acknowledged that the current study is underpowered to assess for this outcome, however the numerically different rates of ST according to SXscore teriles despite comparable duration of DAPT, suggest that there may be an additional role for the SXscore in helping tailor anti-platelet therapy on an individual level. Confirmation of this hypothesis however requires adequately powered randomized trials.

The 12-months outcomes from the RESOLUTE All Comers study demonstrated that R-ZES was non-inferior to EES with respect to the primary clinical endpoint of TLF. Reassuringly the present study

indicates that comparable outcomes with respect to TLF were also maintained between both stents irrespective of the severity of underlying CAD. Of note, whilst the between-stent differences in mortality and definite ST amongst patients in the highest SXscore tertile followed the trends seen in the full patient cohort, the same was not true for the differences seen in clinically indicated TLR. Similarly, in the LEADERS study a significant between-stent difference in cardiac death was observed amongst patients in the highest SXscore tertile which was not seen in the full patient cohort (25). Whilst these observations may suggest potential differences in stent performance with different severities of CAD, they should be regarded in the first instance as being underpowered, hypothesis generating analyses, and should ultimately be used as a stimulus for further more directed and adequately powered studies. Nevertheless, these observations do serve to highlight a new potential application of the SXscore as a means to further assess and compare the performance of new coronary devices.

LIMITATIONS

The SXscore has several limitations including intra- and inter-observer variability (2,26), which is inherent to its subjective derivation using coronary angiography; and the absence of specific algorithms for patients with prior percutaneous or surgical revascularization. Specifically, the current analysis may have limitations, such as underpowered results and chance findings, which are inherent to the use of sub-group analysis (22-23). Missing quantitative values for the ejection fraction and serum creatinine also lead to the ACEF score and CSS being available in only approximately half of the study population.

CONCLUSION

The SYNTAX score is able to stratify risk amongst an all-comers population treated with PCI using second generation DES; however improvements can be made with the inclusion of clinical variables.

REFERENCES

1. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219-27.
2. Serruys PW, Onuma Y, Garg S, et al. Assessment of the SYNTAX score in the Syntax study. EuroIntervention 2009;5:50-6.
3. Wykrzykowska J, Garg S, Girasis C, et al. Value of the Syntax Score (SX) for Risk Assessment in the "All-comers" Population of the Randomized Multicenter Leaders Trial. J Am Coll Cardiol 2010;56:272-277.
4. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961-72.
5. Capodanno D, Di Salvo ME, Cincotta G, Miano M, Tamburino C, Tamburino C. Usefulness of the SYNTAX Score for Predicting Clinical Outcome After Percutaneous Coronary Intervention of Unprotected Left Main Coronary Artery Disease. Circ Cardiovasc Intervent 2009;2:302-308.
6. Girasis C, Garg S, Raber L, et al. Prediction of 5-year clinical outcomes using the SYNTAX score in patients undergoing PCI from the Sirolimus eluting stent compared with paclitaxel eluting stent for coronary revascularisation (SIRTAX) trial. Abstract at American College of Cardiology meeting, March 14-16th 2010, Atlanta GA.
7. Serruys PW, Onuma Y, Garg S, et al. 5-Year Clinical Outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the Sirolimus-Eluting Stent in the Treatment of Patients With Multivessel De Novo Coronary Artery Lesions. J Am Coll Cardiol 2010;55:1093-1101.
8. Onuma Y, Girasis C, Piazza N, et al. Long-Term Clinical Results Following Stenting of the Left Main Stem: Insights From RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) and T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) Registries. J Am Coll Cardiol Intv 2010;3:584-594.
9. Garg S, Sarno G, Serruys PW, et al. Prediction of 1-year clinical outcomes using the SYNTAX score in patients with acute ST-elevation myocardial infarction undergoing primary PCI: A sub-study of the STRATEGY and MULTI-STRATEGY trials. J Am Coll Cardiol Intv 2011;4:66-75.
10. Garg S, Serruys PW. Coronary stents - Current Status. J Am Coll Cardiol 2010;56:S1-S42.
11. Stone GW, Rizvi A, Newman W, et al. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med 2010;362:1663-74.
12. Kedhi E, Joesoef KS, McFadden E, et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet 2010;375:201-9.
13. Serruys PW, Silber S, Garg S, et al. Comparison of Zotarolimus-Eluting and Everolimus-Eluting Coronary Stents. N Engl J Med 2010;363:123-135.
14. Ranucci M, Castelvecchio S, Menicanti L, Frigiola A, Pelissero G. Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony. Circulation 2009;119:3053-61.
15. Wykrzykowska J, Garg S, Onuma Y, et al. Value of Age, Creatinine and Ejection Fraction (ACEF score) in assessing risk in patients undergoing percutaneous coronary interventions in an "all-comers" LEADERS trial. In press. Circ Cardiovasc Interv 2011.
16. Garg S, Sarno G, Garcia-Garcia HM, et al. A New Tool for the Risk Stratification of Patients With Complex Coronary Artery Disease: The Clinical SYNTAX Score. Circ Cardiovasc Interv 2010;3:317-326.
17. SYNTAX working-group. SYNTAX score calculator: www.syntaxscore.com. Launched 19th May 2009.

18. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-51.

19. Vranckx P, Cutlip DE, Mehran R, et al. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. EuroIntervention 2010;5:871-4.

20. Kim Y-H, Park D-W, Kim W-J, et al. Validation of SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) Score for Prediction of Outcomes After Unprotected Left Main Coronary Revascularization. J Am Coll Cardiol Intv 2010;3:612-623.

21. Hilliard AA, From AM, Lennon RJ, et al. Percutaneous revascularization for stable coronary artery disease temporal trends and impact of drug-eluting stents. JACC Cardiovasc Interv 2010;3:172-9.

22. Lagakos SW. The challenge of subgroup analyses--reporting without distorting. N Engl J Med 2006;354:1667-9.

23. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine--reporting of subgroup analyses in clinical trials. N Engl J Med 2007;357:2189-94.

24. Capodanno D, Miano M, Cincotta G, et al. EuroSCORE refines the predictive ability of SYNTAX score in patients undergoing left main percutaneous coronary intervention. Am Heart J 2010;159:103-109.

25. Wykrzykowska J. All-comers LEADERS Trial: Biolimus-eluting stents reduce mortality in patients with high SYNTAX scores in the 'all-comers' LEADERS trial. Presentation at EuroPCR, May 25th 2010, Paris, France. 2010.

26. Garg S, Girasis C, Sarno G, et al. The SYNTAX score revisited: A reassessment of the SYNTAX score reproducibility. Catheter Cardiovasc Interv 2010;75:946-952.

Chapter 6.3

Prediction of 1-year clinical outcomes using the SYNTAX score in patients with acute ST-elevation myocardial infarction undergoing primary PCI: A sub-study of the STRATEGY and MULTI-STRATEGY trials

J Am Coll Cardiol Intv 2011; 4(1):66-75

Scot Garg, Giovanna Sarno, Patrick W. Serruys, Alfredo Rodriguez, Leonardo Bolognese, Maurizio Anselmi, Nicoletta De Cesare, Salvatore Colangelo, Raul Moreno, Stefania Gambetti, Monia Monti, Laura Bristot, Marco Bressers, Hector M. Garcia-Garcia, Giovanni Parrinello, Gianluca Campo, Marco Valgimigli on behalf of the STRATEGY and MULTI-STRATEGY investigators

Prediction of 1-Year Clinical Outcomes Using the SYNTAX Score in Patients With Acute ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

A Substudy of the STRATEGY (Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent Versus Abciximab and Bare-Metal Stent in Acute Myocardial Infarction) and MULTISTRATEGY (Multicenter Evaluation of Single High-Dose Bolus Tirofiban Versus Abciximab With Sirolimus-Eluting Stent or Bare-Metal Stent in Acute Myocardial Infarction Study) Trials

Scot Garg, MB, ChB,* Giovanna Sarno, MD, PhD,* Patrick W. Serruys, MD, PhD,* Alfredo E. Rodriguez, MD, PhD,‡ Leonardo Bolognese, MD,§ Maurizio Anselmi, MD,‖ Nicoletta De Cesare, MD,¶ Salvatore Colangelo, MD,# Raul Moreno, MD,‡‡ Stefania Gambetti, BSc,** Monia Monti, BSc,** Laura Bristot, BSc,** Marco Bressers, MSc,† Hector M. Garcia-Garcia, MD, PhD,† Giovanni Parrinello, PhD,†† Gianluca Campo, MD,** Marco Valgimigli, MD, PhD,** on behalf of the STRATEGY and MULTISTRATEGY Investigators

Rotterdam, the Netherlands; Buenos Aires, Argentina; Arezzo, Verona, Pavia, Turin, Ferrara, Brescia, Italy; and Madrid, Spain

Objectives This study sought to evaluate the impact of SYNTAX score (SXscore), and compare its performance in isolation and combination with the PAMI (The Primary Angioplasty in Myocardial Infarction Study) score, for the prediction of 1-year clinical outcomes in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention.

Background Patients with STEMI were excluded from the original SYNTAX score (SXscore) algorithm. Therefore, the utility of using the SXscore in this patient group remains undefined.

Methods SXscore was calculated retrospectively in 807 patients with STEMI enrolled in the randomized STRATEGY (Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent Versus Abciximab and Bare-Metal Stent in Acute Myocardial Infarction) and MULTISTRATEGY (Multicenter Evaluation of Single High-Dose Bolus Tirofiban Versus Abciximab With Sirolimus-Eluting Stent or Bare-Metal Stent in Acute Myocardial Infarction Study) clinical trials. Clinical outcomes of all-cause death, reinfarction, and clinically driven target vessel revascularization were subsequently stratified according to SXscore tertiles: $SX_{LOW} \leq 9$ (n = 311), $9 < SX_{MID} \leq 16$ (n = 234), $SX_{HIGH} > 16$ (n = 262).

Results At 1-year follow-up, all clinical outcomes including mortality, mortality/reinfarction, major adverse cardiac events (MACE) (a composite of all-cause death, reinfarction and target vessel revascularization), and definite, definite/probable, and any stent thrombosis were all significantly higher in patients in the highest SXscore tertile. SXscore was identified as an independent predictor of mortality, MACE, and stent thrombosis out to 1-year follow-up. The combination SYNTAX-PAMI score led to a net reclassification improvement of 15.7% and 4.6% for mortality and MACE, respectively. The C-statistics for the SXscore, PAMI score, and the combined SYNTAX-PAMI score were 0.65, 0.81, and 0.73 for 1-year mortality, and 0.68, 0.64, and 0.69 for 1-year MACE, respectively.

Conclusions SXscore does have a role in the risk stratification of patients with STEMI having primary percutaneous coronary intervention; however, this ability can be improved through a combination with clinical variables. (Multicentre 2×2 Factorial Randomised Study Comparing Tirofiban Versus Abciximab and SES Versus BMS in AMI; NCT00229515) (J Am Coll Cardiol Intv 2011;4:66–75)

Currently, several validated patient-based risk scores are in use in patients presenting with ST-segment elevation myocardial infarction (STEMI) (1–5). Most of these scores, apart from the Zwolle and CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) scores, rely entirely on patient-based variables such as Killip class, serum creatinine levels, and degree of ST-segment change. This is not surprising given these models were developed before the widespread use of primary percutaneous coronary intervention (PCI) for the treatment of STEMI. Overall, the individual ability of these scores to predict mortality is somewhat variable (6), and a notable limitation is the absence of any assessment of lesion characteristics.

The SYNTAX score (SXscore) is an angiographic scoring system that has been shown to be able to aid revascularization decisions, and predict mortality and morbidity in patients irrespective of disease severity, at both short- and long-term follow-up (7–15). These previous assessments of the SXscore have been largely limited to elective patients. At present, therefore, the SXscore has not been validated in patients with STEMI, and as such, the utility of risk stratifying these patients using the SXscore remains unknown.

The objective of this study was to assess the impact of the SXscore and compare its performance in isolation, and in combination, with an entirely clinical-based score, the PAMI (Primary Angioplasty in Myocardial Infarction) study score, for the prediction of 1-year clinical outcomes in patients with STEMI treated with primary PCI, who were enrolled in the prospective randomized STRATEGY (Single High Dose Bolus Tirofiban and Sirolimus Eluting Stent Versus Abciximab and Bare-Metal Stent in Myocardial Infarction) (16) and MULTISTRATEGY (Multicenter Evaluation of Single High-Dose Bolus Tirofiban Versus Abciximab With Sirolimus-Eluting Stent or Bare-Metal Stent in Acute Myocardial Infarction) (17) studies.

From the *Department of Interventional Cardiology, Erasmus Medical Center, Rotterdam, the Netherlands; †Cardialysis, Rotterdam, the Netherlands; ‡Department of Cardiology, Otamendi Hospital, Buenos Aires, Argentina; §Cardiovascular Departments, San Donato Hospital, Arezzo, Italy; ‖Department of Biomedical and Surgical Sciences, Cardiology Section, University of Verona, Verona, Italy; ¶Istituto di Ricovero e Cura a Carattere Scientifico, Policlinico San Matteo, Pavia, Italy; #Cardiovascular Intervention Laboratory, San Giovanni Bosco Hospital, Turin, Italy; **Department of Cardiology, Cardiovascular Institute, University of Ferrara, Ferrara, Italy; ††Medical Statistics Unit, University of Brescia, Brescia, Italy; and the ‡‡Department of Cardiology, La Paz University Hospital, Madrid, Spain. Dr. Bolognese has received honoraria for lectures from Merck and Eli Lilly. Dr. Valgimigli has received honoraria for lectures/advisory board and research grants from Eli Lilly, Medtronic, Merck, and Iroko; and honoraria for advisory board from Cordis, Abbott, Eisai, AstraZeneca, The Medicines Company, Eli Lilly Co., Daiichi Sankyo, Inc., and Medtronic. All other authors report that they have no relationships to disclose.

Manuscript received August 2, 2010; accepted September 3, 2010.

Methods

Study population. The STRATEGY and MULTISTRATEGY studies have been published previously (16,17). In brief, the single-center prospective STRATEGY study randomized 175 patients to treatment with either tirofiban and sirolimus-eluting stents (SES) or abciximab and bare-metal stents (BMS), whereas the multicenter MULTISTRATEGY study randomized 745 patients between an infusion of either tirofiban or abciximab and stenting with either a SES or BMS.

Patient selection. Inclusion and exclusion criteria were similar for both studies. Patients presenting with STEMI who had: 1) chest pain for >30 min with ST-segment elevation of ≥1 mm in ≥2 contiguous electrocardiographic leads or with presumably new left bundle-branch block; and 2) admission either <12 h of symptom onset or between 12 and 24 h with evidence of continuing ischemia were eligible for enrollment. Exclusion criteria included administration of fibrinolytic agents in the previous 30 days, history of bleeding diathesis or allergy to the study drugs, major surgery within 15 days, and active bleeding or previous stroke in the last 6 months. The institutional review board at each participating center approved the protocol, and all patients gave written informed consent.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
IRA = infarct-related artery
MACE = major adverse cardiac event(s)
PCI = percutaneous coronary intervention
ROC = receiver-operator characteristic
SES = sirolimus-eluting stent(s)
ST = stent thrombosis
STEMI = ST-segment elevation myocardial infarction
SXscore = SYNTAX score
TIMI = Thrombolysis In Myocardial Infarction
TVR = target vessel revascularization

Randomization and procedure. Detail information regarding the randomization procedure for both studies is provided elsewhere (16,17). In brief, before angiography open-label 1:1 and 1:1:1:1 randomization was performed in the STRATEGY and MULTISTRATEGY studies, respectively. In STRATEGY, patients were randomized to an infusion of tirofiban and then PCI with SES or an infusion of abciximab followed by PCI with BMS. In MULTISTRATEGY, patients were randomized to an infusion of tirofiban or abciximab followed by PCI with either SES or BMS. Tirofiban and abciximab were administered before sheath insertion. Crossover to a BMS was only allowed when SES implantation failed or when it was impossible to match SES diameter with coronary reference diameter.

Details of angiographic and electrocardiographic analysis together with dosage regimes of the parenteral periprocedural anticoagulants heparin, tirofiban, and abciximab are provided elsewhere (16,17). All patients received aspirin

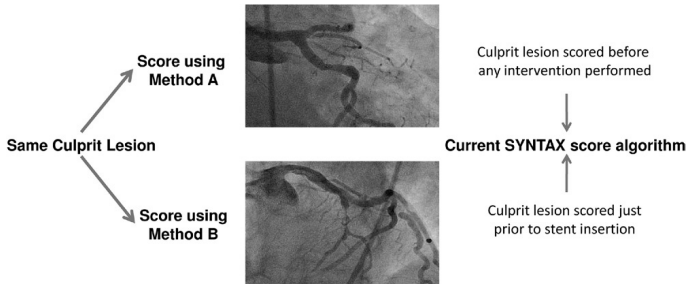


Figure 1. Schematic Diagram Indicating the Different Scoring Methods Used to Calculate the SYNTAX Score of the Culprit Lesion

Each culprit lesion was scored using Method A, where the lesion SYNTAX score was calculated before any instrumentation of the vessel, and then using Method B, where the lesion SYNTAX score was calculated using the angiographic film just before stent implantation. In this example, both images are of the same lesion in the left anterior descending artery; on the initial angiographic films **(top)** the left anterior descending artery was occluded, following wiring, and before dilation **(bottom)**, an open vessel was seen with an underlying bifurcation lesion. Therefore, the lesion was scored as an acute occlusion using Method A, and a bifurcation lesion using Method B. The results of the scores calculated using Method B are available in the Online Appendix.

Table 1. Baseline Characteristics of the Patients Stratified Into SYNTAX Score Tertiles

Variable	SYNTAX Score ≤9 (n = 311)	SYNTAX Score >9–16 (n = 234)	SYNTAX Score >16 (n = 262)	p Value
Baseline characteristics				
Age, yrs	61.8 ± 11.9	63.3 ± 11.1	66.1 ± 11.7	<0.001
Male	234 (75.2)	183 (78.2)	191 (72.9)	0.39
Risk factors				
Diabetes	32 (10.3)	29 (12.4)	49 (18.7)	0.01
Hypertension	170 (54.8)	128 (55.2)	156 (59.8)	0.69
Hyperlipidemia	130 (41.8)	88 (37.8)	103 (39.5)	0.91
Current cigarette use	131 (42.1)	92 (39.5)	84 (32.4)	0.07
Creatinine clearance, ml/min				0.003
Median	80.7	81.1	73.1	
IQR	63.5–102.6	61.7–102.4	55.3–94.3	
Prior myocardial infarction	17 (5.5)	20 (8.6)	27 (10.3)	0.33
Prior percutaneous coronary intervention	13 (4.2)	10 (4.3)	13 (5.0)	0.88
Prior stroke or transient ischemic attack	7 (2.3)	13 (5.6)	14 (5.3)	0.13
Left ventricular ejection fraction*				
Median	50	45	42	<0.001
IQR	45–55	40–52	35–50	
Killip class ≥II	30 (9.7)	32 (13.9)	55 (21.2)	<0.001
Heart rate, beats/min				
Median	72	75	75	0.06
IQR	60–85	62–89	66–89	
Time from onset of symptoms to hospital presentation, min				
Median	110	120	107	0.23
IQR	61–180	65–207	65–196	
Time from hospital presentation to angioplasty, min†				
Median	87	80	90	0.31
IQR	60–122	57–120	60–126	

Values are n (%) or mean ± SD, unless otherwise stated. *Assessed at standard transthoracic echocardiogram at discharge; †calculated as the time difference between first hospital contact and first balloon inflation.

IQR = interquartile range.

(160 to 325 mg orally or 250 mg intravenously, followed by 80 to 125 mg/day orally indefinitely) and clopidogrel (300 mg orally and then 75 mg/day for at least 3 months).

SYNTAX score. SXscore for each patient was calculated retrospectively by scoring all coronary lesions with a diameter stenosis ≥50%, in vessels ≥1.5 mm, using the SXscore algorithm, which is described in full elsewhere (7,11) and is available on the SXscore website (18). All angiographic variables pertinent to SXscore calculation were computed by 2 investigators blinded to clinical outcomes (S.G., G.S.). In the event of disagreement, the opinion of a third investigator was sought, and the final decision was made by consensus.

There is currently no validated method of calculating the SXscore in patients with STEMI as this patient group was excluded from the initial SXscore algorithm (7). To overcome this, 2 different methods of scoring the infarct-related artery (IRA) were investigated in this study. The first

Table 2. Procedural Results and Use of Medications Stratified Into Tertiles of the SYNTAX Score

Variable	SYNTAX Score ≤9 (n = 311)	SYNTAX Score >9–16 (n = 234)	SYNTAX Score >16 (n = 262)	p Value
Extent of disease				<0.001
Single-vessel disease	195 (62.7)	111 (47.4)	84 (32.1)	
Double-vessel disease	97 (31.2)	84 (35.9)	90 (34.4)	
Triple-vessel disease	19 (6.11)	39 (16.7)	88 (33.6)	
Infarct-related vessel				<0.001
Left anterior descending coronary artery	87 (28.1)	104 (44.8)	169 (65.0)	
Left circumflex artery	71 (22.9)	37 (16.0)	25 (9.6)	
Right coronary artery	151 (48.7)	90 (38.8)	63 (24.2)	
Left main coronary artery	1 (0.3)	1 (0.4)	3 (1.2)	
Lesion characteristics				
Number of diseased lesions				
Median	1	2	3	<0.001
IQR	1–2	1–3	2–4	
Range	1–4	1–6	1–7	
≥1 bifurcation lesion	67 (21.5)	119 (50.9)	184 (70.2)	<0.001
≥1 occlusion	120 (38.6)	144 (61.5)	210 (80.2)	<0.001
≥1 tortuous lesion	22 (7.1)	23 (9.8)	43 (16.4)	<0.001
≥1 lesion ≥20 mm	70 (22.5)	91 (38.9)	138 (52.7)	<0.001
≥1 calcified lesion	7 (2.3)	22 (9.4)	67 (25.6)	<0.001
≥1 lesion with thrombus	65 (20.9)	64 (27.4)	64 (24.4)	0.21
Procedural characteristics				
Number of stents implanted in the culprit lesion				
Median	1	1	1	0.004
IQR	1–1	1–1	1–1	
Range	0–3	0–4	0–4	
Total length of stent in the culprit lesion, mm				
Median	18	23	22	<0.001
IQR	18–23	18–28	18–28	
Incomplete revascularization	97 (31.2)	159 (67.9)	210 (80.2)	<0.001
Abciximab therapy*	149 (47.9)	119 (49.2)	125 (47.7)	0.56
Tirofiban therapy†	162 (52.1)	115 (50.9)	137 (52.3)	
Use of intra-aortic balloon pump	0 (0)	3 (1.3)	14 (5.4)	<0.001
Medications at discharge‡				
Number evaluated	309	229	254	
Aspirin	299 (96.8)	222 (96.9)	244 (96.1)	0.39
Clopidogrel or ticlopidine	292 (94.5)	224 (97.8)	245 (96.4)	0.71
Beta-blockers	242 (78.3)	182 (79.5)	200 (78.7)	0.90
Statins	270 (87.4)	196 (85.6)	216 (85.0)	0.82
ACE inhibitors	238 (77.0)	179 (78.2)	203 (79.9)	0.89

Values are n (%) or mean ± SD, unless otherwise stated. *Two patients who were randomized to abciximab were mistakenly treated with tirofiban; †1 patient randomized to tirofiban received both tirofiban and abciximab; ‡differences in the numbers of patients who were evaluated are due to the deaths of patients before discharge.

ACE = angiotensin-converting enzyme; other abbreviations as in Table 1.

method (Method A) involved calculating the SXscore using the current algorithm, with the culprit lesion scored using the angiographic views of the IRA before any intervention. Therefore, if the IRA was occluded it was scored as an occluded artery of <3-months' duration. The second method (Method B) still used the current scoring algorithm; however, the angiographic films just before stent implantation were used to score the culprit lesion (Fig. 1). Clinical outcomes according to the SXscore calculated using Method B, and a comparison of the 2 different scoring methods is reported in the Online Appendix; the SXscores calculated using Method A are presented in the rest of this article.

PAMI score. The PAMI score was selected as a comparative risk score as only clinical variables such as patient age, Killip class, heart rate, diabetic status, and location of myocardial infarction are required for its calculation, in contrast to the angiographic variable used in the SXscore. The PAMI score was calculated retrospectively using algorithms that are described in detail elsewhere (1). A combination of the SXscore (calculated using Method A) and the PAMI score, the SX-PAMI score, was also created as described in the Online Appendix.

Study end points. The primary end point of this post hoc study was mortality at 1-year follow-up. Secondary end points included: reinfarction; clinically driven target vessel revascularization (TVR), major adverse cardiac events (MACE) (a composite of death, reinfarction, and TVR), and stent thrombosis (ST) out to 1-year follow-up. An independent blinded clinical events committee evaluated all clinical end points, and a data and safety monitoring board ensured the safe conduct of the trial.

Definitions. Complete definitions are provided elsewhere (16,17). Deaths from all causes are reported. Re-infarction was defined as: 1) ≤24 h of randomization: recurrent ischemic symptoms with new, persistent ST-segment elevation ≥1 mm in ≥2 contiguous leads or new persistent ST-segment depression ≥1 mm in ≥2 contiguous leads not due to changes from evolution of the index STEMI; 2) between 24 h and 7 days of randomization: ischemic symptoms ≥20 min and either a creatinine kinase level ≥twice the upper limit of normal or further elevations ≥50% above the previous lowest level in patients with already elevated enzyme levels; and 3) after 7 days of randomization: either a typical increase and decrease of levels of biochemical markers of myocardial necrosis to greater than the upper limit of normal or, if markers are already elevated, further elevation of a marker ≥50% of the lowest recovery level from the index STEMI with either ischemic symptoms or other ischemic changes on the electrocardiogram. Clinically driven TVR was defined as any coronary artery bypass graft surgery, or a second PCI of the original target vessel, driven by clinical symptoms of myocardial ischemia with either a positive stress test or electrocardiographic evidence of ischemic changes at rest attributable to the target vessel and the presence of luminal stenosis of ≥70% of the reference luminal diameter by visual estimate. A successful PCI was defined as a residual stenosis <30% in the treated vessel with Thrombolysis In Myocardial Infarction (TIMI) coronary flow grade 3. Stent thrombosis was classified according to the Academic Research Consortium classification (19).

Statistical analysis. All analyses were conducted according to the intention-to-treat principle. All variables were stratified according to SXscore tertiles. Discrete data were summarized as frequencies (%), whereas parametric continuous data were expressed as mean ± SD, and nonparametric continuous data were expressed as median (interquartile range). The Fisher exact test (categorical variables), 1-way analysis of variance test (parametric, continuous variables), and Kruskal-Wallis test (nonparametric, continuous variables) were used to analyze differences between the 3 study

Table 3. Clinical Outcomes at 12 Months Stratified Into Tertiles of the SYNTAX Score

Outcome	SYNTAX score ≤9 (n = 311)	SYNTAX score >9–16 (n = 234)	SYNTAX Score >16 (n = 262)	p Value
Hierarchical outcomes at 1 yr	(n = 311)	(n = 234)	(n = 262)	
Death	10 (3.2)	10 (4.3)	24 (9.2)	0.006
Reinfarction	4 (1.3)	6 (2.6)	16 (6.1)	
Death or reinfarction	14 (4.5)	16 (6.8)	40 (15.3)	<0.001
MACE*	24 (7.7)	31 (13.2)	65 (24.8)	<0.001
Nonhierarchical outcomes at 1 yr				
Reinfarction	4 (1.3)	7 (3.0)	18 (6.9)	0.001
Target vessel revascularization	11 (3.5)	17 (7.3)	32 (12.2)	0.001
Definite ST	1 (0.3)	2 (0.9)	10 (3.8)	0.002
Definite or probable ST	2 (0.6)	5 (2.1)	14 (5.3)	0.001
Definite or probable or possible ST	4 (1.3)	7 (3.0)	18 (6.9)	0.001

Values are n (%). *A composite of death, reinfarction and target vessel-revascularization.
MACE = major adverse cardiac events; ST = stent thrombosis; other abbreviations as in Table 1.

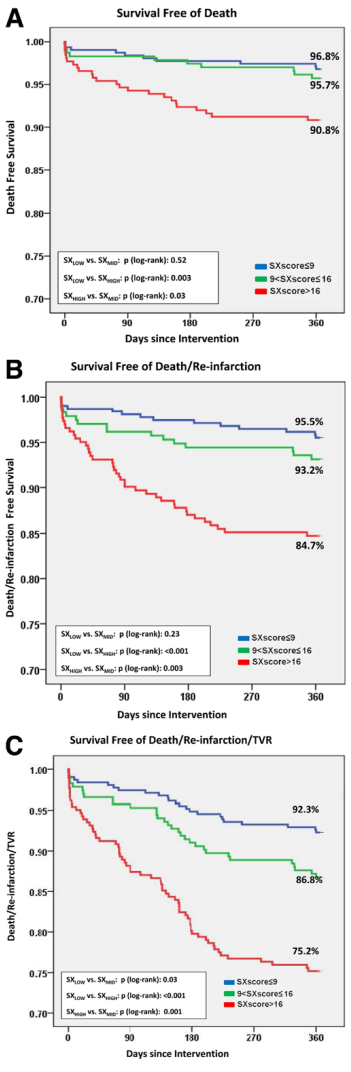


Figure 2. Kaplan-Meier Survival Curves

Kaplan-Meier survival curves for **(A)** death; **(B)** the composite of death and reinfarction, and **(C)** the composite of death, re-infarction and target vessel revascularization. Patients in the highest SYNTAX score tercile have significantly poor outcomes compared to those in the lower 2 terciles.

groups. Event-free survival curves were generated by the Kaplan-Meier method, and survival between groups was compared using the log-rank test. Cox regression analysis was used to find independent predictors of mortality, MACE, and any ST with those variables with a p value of <0.10 in the univariate analysis being included in the backward stepwise multivariate model. A reclassification analysis was used to compare the SXscore calculated by Methods A and B, and the SXscore with the SX-PAMI score, as described in the Online Appendix. Receiver-operator characteristic (ROC) curves were used to compare the discrimination of the SXscore, PAMI score, and SX-PAMI score. A 2-sided p value <0.05 was considered significant for all tests. All analyses were performed using SPSS software (version 17.0, SPSS, IBM, Somers, New York).

Results

In total, the STRATEGY and MULTISTRATEGY studies enrolled 945 patients. The SXscore was subsequently calculated in 807 (85.4%) patients (1,584 lesions); the primary reasons for the incomplete dataset were missing angiogram compact discs and the presence of coronary artery bypass grafts.

SYNTAX score. SXscore ranged from 0 to 66, with a mean ± SD of 13.9 ± 8.6 and a median (interquartile range) of 12.3 (11.4). SXscore was not normally distributed (Kolmogorov-Smirnov $p < 0.05$). In this post hoc analysis, patients were stratified according to approximate SXscore tertiles defined as: $SX_{LOW} \leq 9$ (n = 311), $9 < SX_{MID} \leq 16$ (n = 234), $SX_{HIGH} > 16$ (n = 262).

Baseline clinical angiographic and procedural characteristics. Baseline clinical, angiographic, and procedural characteristics stratified according to SXscore tertile are summarized in Tables 1 and 2. Patient age and the incidence of diabetes were both significantly higher, whereas left ventricular function and creatinine clearance were both significantly lower in the SX_{HIGH} tertile. In line with its method of derivation, markers of increased lesion complexity such as the presence of bifurcation lesions and total occlusions were all significantly higher in the SX_{HIGH} tertile.

Clinical outcomes. Clinical outcomes through to 12-months follow-up are shown in Table 3, whereas Kaplan-Meier cumulative curves are shown in Figure 2. Overall, all clinical outcomes including the primary end point of all-cause death; the composite of death/reinfarction; MACE; and rates of definite, definite/probable, and any ST were all significantly higher in the highest SXscore tertile.

Multivariate analysis. The results of the Cox multivariate analysis for death, the composite of MACE and any ST are shown in Table 4. Following multivariate adjustment, the SXscore remained an independent predictor of death, MACE, and any ST at 1-year follow-up.

Table 4. Univariate and Multivariate Predictors of Death, MACE, and Any ST

	Univariate Predictors		Multivariate Predictors	
Variable	HR (95% CI)	p Value	HR (95% CI)	p Value
Death				
Creatinine clearance	0.97 (0.96–0.98)	<0.001		
Left ventricular function	0.92 (0.89–0.94)	<0.001	0.95 (0.92–0.98)	0.003
Male sex	0.51 (0.28–0.94)	0.03		
PAMI score	1.34 (1.24–1.47)	<0.001	1.15 (1.00–1.09)	0.03
SYNTAX score	1.05 (1.03–1.08)	<0.001	1.05 (1.00–1.09)	0.02
Major adverse cardiovascular events				
Creatinine clearance	0.99 (0.98–1.00)	0.01		
Door-to-balloon time	1.01 (1.00–1.02)	0.02		
Left ventricular function	0.94 (0.92–0.96)	<0.001	0.97 (0.95–0.99)	0.001
PAMI score	1.17 (1.10–1.23)	<0.001	1.09 (1.00–1.18)	0.045
Sirolimus-eluting stent use	0.55 (0.38–0.80)	0.002	0.64 (0.43–0.98)	0.04
SYNTAX score	1.06 (1.04–1.08)	<0.001	1.07 (1.04–1.10)	<0.001
Any stent thrombosis				
Left ventricular function	0.91 (0.87–0.96)	<0.001	0.95 (0.91–0.99)	0.02
PAMI score	1.25 (1.12–1.39)	<0.001	1.13 (0.97–1.30)	0.11
SYNTAX score	1.07 (1.04–1.10)	<0.001	1.06 (1.02–1.11)	0.008

CI = confidence interval; HR = hazard ratio; PAMI = Primary Angioplasty in Myocardial Infarction; other abbreviations as in Tables 1 and 3.

SXscore calculated using Method B. Clinical outcomes and the results of a Cox multivariate analysis using the SXscore calculated using Method B are reported in the Online Appendix, Online Tables 1 and 2, and Online Figure 1. To compare both methods of SXscoring, a reclassification analysis was also performed and this demonstrated that compared with Method A, the SXscore calculated using Method B inappropriately reclassified over 12% of patients for the end point of mortality, and just under 1% of patients for the end point of MACE. The results of this reclassification analysis are provided in full in the Online Appendix and Online Tables 3 and 4.

SXscore versus PAMI score. The PAMI score was available in 791 patients and ranged from 0 to 14, with a mean ± SD of 3.9 ± 3.3 and a median (interquartile range) of 3 (5). On Cox multivariate analysis, the PAMI score was an independent predictor of mortality and MACE out to 1-year follow-up; however, unlike the SXscore, it was only a univariate predictor of any ST. The ROC curves and the respective C-statistics for the SXscore calculated using Methods A and B, the PAMI score, and SX-PAMI score for 1-year mortality, mortality/reinfarction, TVR, and MACE are shown in Figure 3.

SX-PAMI score. A reclassification analysis was performed to compare the SXscore with the combination SX-PAMI score for the end points of mortality and MACE. Results are presented in full in the Online Appendix and Online Tables 5 and 6. In brief, use of the SX-PAMI lead to an overall net reclassification improvement of 15.7% and 4.6% for mortality and MACE, respectively.

Discussion

This study represents the first dedicated analysis of the SXscore in patients with STEMI and demonstrates that the SXscore does have a utility in the assessment of patients having primary PCI, being an independent predictor of mortality, MACE, and any ST out to 1-year follow-up.

Mechanical revascularization, which is now the preferred treatment option for patients presenting with STEMI (20) is virtually always performed using PCI. It follows, therefore, that the goal of risk stratification in patients having primary PCI is not to determine appropriate treatment strategy, but more to determine the risk of adverse cardiac events after procedure that may guide discharge planning and follow-up schedule (5,21), while also serving as a means for individual operators, institutions, and regulatory bodies to access and compare performance.

The current study has demonstrated that patients with higher SXscores, irrespective of whether they are calculated using Method A or B, are at increased risk of mortality and MACE when presenting with STEMI. This is consistent with data from the assessment of patients having elective PCI (7–15), and also in line with previous studies of primary PCI that identify variables associated with higher SXscores such as TIMI flow grade <3 (21,22), and the presence of multivessel disease as significant independent predictors of MACE (23).

In this current analysis, 2 different methods of applying the SXscore were investigated as the initial SXscore algorithm did not include any specific reference to patients with

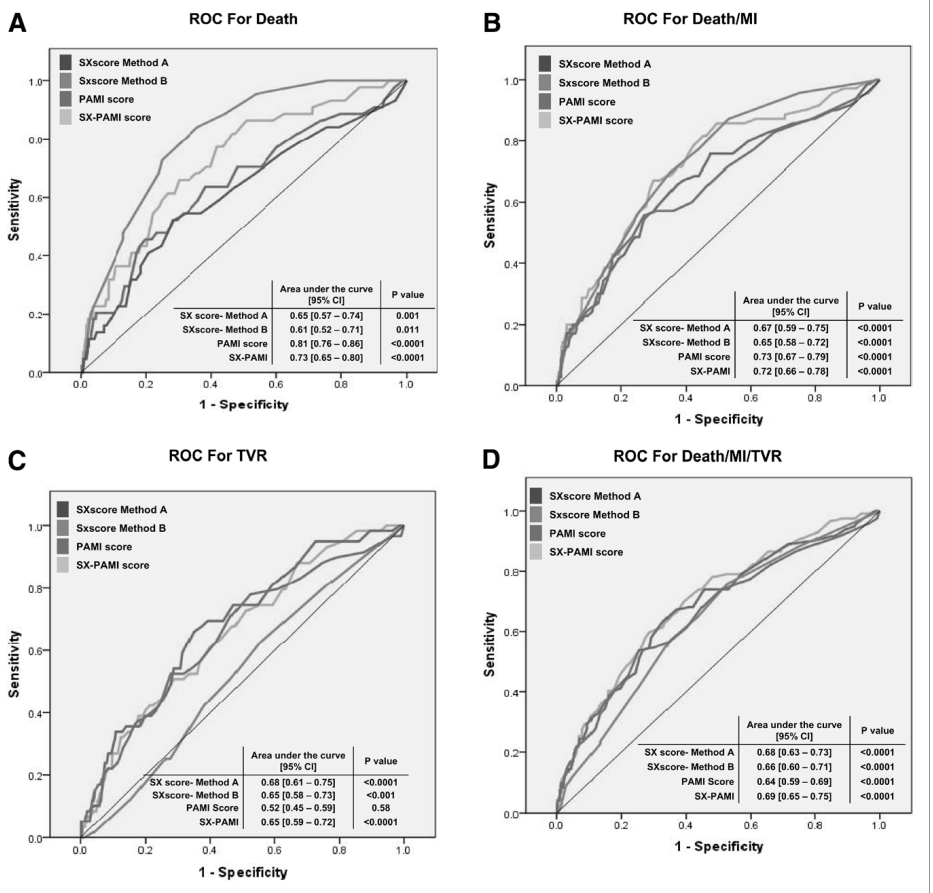


Figure 3. Receiver-Operator Characteristic Curves and Corresponding C-Statistics for the SYNTAX Score

Receiver-operator characteristic curves and corresponding C-statistics for the SYNTAX score calculated using Method A, the SYNTAX score calculated using Method B, the PAMI score and the SX-PAMI for **(A)** death, **(B)** composite of death and re-infarction, **(C)** target vessel revascularization and **(D)** the composite of death, re-infarction, and target vessel revascularization. The discriminatory ability of the SYNTAX score calculated using Method A is consistently superior to that calculated using Method B. Similarly, whilst the discriminatory ability of the SYNTAX score appears inferior to the PAMI and SX-PAMI for the assessment of death and death/re-infarction, it is superior for assessment of target vessel revascularization. The combination score, however, is superior for the assessment of the composite of death, reinfarction, and target vessel revascularization.

STEMI (7). Although both methods of scoring identified those patients at highest risk of events, and were independent predictors of clinical outcomes, there were some important differences between both scores. Of note, the SXscore calculated using Method B had an inferior discriminatory ability compared with Method A, as well as inappropriately reclassified patients with respect to the end points of death and MACE. Although both scores had the same range, the mean SXscores calculated using Method A were significantly higher than those calculated using

Method B (Method A mean: 13.9 vs. Method B mean: 10.3, $p < 0.05$). This partly reflects the weighting factor in the SXscore algorithm, which gives an occlusion-multiplying factor of 5, compared with a multiplier of 2 if the vessel has a diameter stenosis between 50% and 99%. In the setting of primary PCI, this important difference in calculation provides a possible explanation for the inappropriate reclassification observed using Method B. Patients with pre-PCI TIMI flow grade 0/1 in the IRA have been shown to have a significantly higher risk of 6-month mortality compared with those with TIMI flow grade 3 (22). It follows that this higher risk is only translated into higher SXscores calculated using Method A, when the IRA is scored as an occlusion, and not Method B. It would seem evident that the calculation of the SXscore in patients undergoing primary PCI should be performed using Method A.

One of the limitations of using the SXscore for risk stratification is the absence of clinical variables in its calculation, a deficiency that can be successfully addressed through its combination with clinical-based risk models (24,25). The present study provides additional evidence to support this: first, by demonstrating improvements in the discriminatory ability of the SXscore when combined with the PAMI score, and second, through the observed appropriate reclassification of patients following use of the combination score. Despite these modifications, the purely clinical-based PAMI score still had the greatest discriminatory ability for hard clinical end points such as mortality, indicating that these outcomes are influenced more by pre-morbid clinical characteristics than by lesion complexity. Consistent with this, Peterson et al. (26) reported only a marginal change in the C-statistic of in-hospital mortality when angiographic variables such as lesion class, vessel location, and TIMI flow grade were removed from the NCDR (National Cardiovascular Data Registry) risk score. With respect to soft end points such as TVR, the superior discriminatory ability of the SXscore may be explained by the significantly greater risk of TVR in those with incomplete revascularization (76.2% vs. 23.8%, $p = 0.007$), which in turn was significantly related to the initial SXscore.

In view of its high associated morbidity and mortality, and unpredictability, ST remains an ongoing concern following PCI, particularly following implantation of drug-eluting stent in patients with STEMI (27). The presence of thrombus can increase the risk of incomplete stent apposition, which together with delayed healing and a poorer compliance to dual antiplatelet therapy are factors implicated in increasing the risk of ST in STEMI patients (28,29). The current analysis demonstrates an important relationship between SXscore and the risk of ST, which has previously been reported in the "all-comers" LEADERS (Limus Eluted From a Durable Versus Erodable Stent Coating) population (14). Importantly, this relationship may help identify those patients who would benefit from additional measures to reduce the risk of ST such as the assessment of platelet reactivity, higher loading doses of clopidogrel, and more intensive counseling regarding compliance to dual antiplatelet therapy (30).

Study limitations. This study is limited by its post-hoc nature. The ROC method of analysis, although well suited for diagnostic purposes (31), may not be appropriate for prognostic models, because these models need to incorporate the dimension of time, which adds a stochastic element (32). Therefore, it has been suggested that ROC analysis methods are not well validated for the assessment of time-censored data; however, in the current study, the same methods have been used to assess both scoring systems, and these methods are consistent with previous published studies evaluating risk models (33). The relatively small sample size of the current study reiterates the need to validate the findings in a larger patient cohort. Unfortunately, the absence of relevant data prevented the calculation of a previously validated combined angiographic and clinical–based score such as the CADILLAC score (2). Finally, the role of calculating the SXscore after revascularization is as yet unexplored, but this may well provide important data to help determine which patients require further revascularization.

Conclusions

SXscore does have a role in the risk stratification of patients with STEMI having primary PCI; however, this ability can be improved through a combination that includes clinical variables.

Reprint requests and correspondence: Dr. Marco Valgimigli, Cardiovascular Institute, Azienda Opedaliera Universitaria di Ferrara, and Corso Giovecca 203, 44100, Ferrara, Italy. E-mail: vlgmrc@unife.it.

REFERENCES

1. Addala S, Grines CL, Dixon SR, et al. Predicting mortality in patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention (PAMI risk score). Am J Cardiol 2004; 93:629–32.
2. Halkin A, Singh M, Nikolsky E, et al. Prediction of mortality after primary percutaneous coronary intervention for acute myocardial infarction: the CADILLAC risk score. J Am Coll Cardiol 2005;45: 1397–405.
3. Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation: an intravenous nPA for treatment of infarcting myocardium early II trial substudy. Circulation 2000;102:2031–7.
4. Eagle KA, Lim MJ, Dabbous OH, et al., for the GRACE Investigators. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. JAMA 2004;291:2727–33.

5. De Luca G, Suryapranata H, van't Hof AW, et al. Prognostic assessment of patients with acute myocardial infarction treated with primary angioplasty: implications for early discharge. Circulation 2004; 109:2737–43.
6. Lev EI, Kornowski R, Vaknin-Assa H, et al. Comparison of the predictive value of four different risk scores for outcomes of patients with ST-elevation acute myocardial infarction undergoing primary percutaneous coronary intervention. Am J Cardiol 2008;102:6–11.
7. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219–27.
8. Serruys PW, Onuma Y, Garg S, et al., for the ARTS-II Investigators. 5-year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. J Am Coll Cardiol 2010;55:1093–101.
9. Valgimigli M, Serruys PW, Tsuchida K, et al., for the ARTS-II Investigators. Cyphering the complexity of coronary artery disease using the syntax score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. Am J Cardiol 2007;99:1072–81.
10. Serruys PW, Morice MC, Kappetein AP, et al., for the SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.
11. Serruys PW, Onuma Y, Garg S, et al. Assessment of the SYNTAX score in the SYNTAX study. EuroIntervention 2009;5:50–6.
12. Capodanno D, Capranzano P, Di Salvo ME, et al. Usefulness of SYNTAX score to select patients with left main coronary artery disease to be treated with coronary artery bypass graft. J Am Coll Cardiol Intv 2009;2:731–8.
13. Capodanno D, Di Salvo ME, Cincotta G, Miano M, Tamburino C, Tamburino C. Usefulness of the SYNTAX score for predicting clinical outcome after percutaneous coronary intervention of unprotected left main coronary artery disease. Circ Cardiovasc Interv 2009;2:302–8.
14. Wykrzykowska J, Garg S, Girasis C, et al. Value of the SYNTAX score (SX) for risk assessment in the "all-comers" population of the randomized multicenter LEADERS Trial. J Am Coll Cardiol 2010;56:272–7.
15. Girasis C, Garg S, Raber L, et al. Prediction of 5-year clinical outcomes using the SYNTAX score in patients undergoing PCI from the sirolimus eluting stent compared with paclitaxel eluting stent for coronary revascularisation (SIRTAX) trial. Abstract presented at: American College of Cardiology meeting; March 14–16, 2010; Atlanta, GA.
16. Valgimigli M, Percoco G, Malagutti P, et al., for the STRATEGY Investigators. Tirofiban and sirolimus-eluting stent vs abciximab and bare-metal stent for acute myocardial infarction: a randomized trial. JAMA 2005;293:2109–17.
17. Valgimigli M, Campo G, Percoco G, et al., for the MULTISTRATEGY Investigators. Comparison of angioplasty with infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarction: the MULTISTRATEGY Randomized Trial. JAMA 2008;299:1788–99.
18. SYNTAX Score Working Group. SYNTAX Score Calculator [online algorithm]. Available at: http://www.syntaxscore.com. Accessed June 1, 2009.
19. Cutlip DE, Windecker S, Mehran R, et al., for the Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
20. Wijns W, Kolh P, Danchin N, et al., for the European Association for Percutaneous Cardiovascular Interventions, ESC Committee for Practice Guidelines, EACTS Clinical Guidelines Committee. Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2010;31:2501–55.
21. Heggunje PS, Harjai KJ, Stone GW, et al. Procedural success versus clinical risk status in determining discharge of patients after primary angioplasty for acute myocardial infarction. J Am Coll Cardiol 2004; 44:1400–7.
22. Stone GW, Cox D, Garcia E, et al. Normal flow (TIMI-3) before mechanical reperfusion therapy is an independent determinant of survival in acute myocardial infarction: analysis from the primary angioplasty in myocardial infarction trials. Circulation 2001;104:636–41.
23. Mehta RH, O'Neill WW, Harjai KJ, et al., for the PAMI and CADILLAC Investigators. Prediction of one-year mortality among 30-day survivors after primary percutaneous coronary interventions. Am J Cardiol 2006;97:817–22.
24. Garg S, Sarno G, Garcia-Garcia HM, et al., for the ARTS-II Investigators. A new tool for the risk stratification of patients with complex coronary artery disease: the clinical SYNTAX score. Circ Cardiovasc Interv 2010;3:317–26.
25. Capodanno D, Miano M, Cincotta G, et al. EuroSCORE refines the predictive ability of SYNTAX score in patients undergoing left main percutaneous coronary intervention. Am Heart J 2010;159:103–9.
26. Peterson ED, Dai D, DeLong ER, et al. Contemporary mortality risk prediction for percutaneous coronary intervention: results from 588,398 procedures in the National Cardiovascular Data Registry. J Am Coll Cardiol 2010;55:1923–32.
27. Garg S, Serruys PW. Benefits of and safety concerns associated with drug-eluting coronary stents. Expert Rev Cardiovasc Ther 2010;8:449–70.
28. Finn AV, Nakazawa G, Kolodgie F, Virmani R. Drug eluting or bare metal stent for acute myocardial infarction: an issue of safety? Eur Heart J 2009;30:1828–30.
29. Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. Circulation 2006;113:2803–9.
30. Holmes DR Jr., Kereiakes DJ, Garg S, et al. Stent thrombosis. J Am Coll Cardiol 2010;56:1357–65.
31. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143:29–36.
32. Soreide K. Receiver-operating characteristic curve analysis in diagnostic, prognostic and predictive biomarker research. J Clin Pathol 2009;62:1–5.
33. Pencina MJ, D'Agostino RB. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. Stat Med 2004;23:2109–23.

Key Words: infarct-related artery ■ major adverse cardiac events ■ percutaneous coronary intervention ■ stenting ■ stent thrombosis ■ ST-segment elevation myocardial infarction ■ SYNTAX score ■ target vessel revascularization ■ Thrombolysis In Myocardial Infarction.

APPENDIX

For supplementary methods and results, please see the online version of this article.

SUPPLEMENTARY METHODS

SX-PAMI score

A combination of the SXscore (calculated using Method A) and the PAMI score was developed through a simple addition of both scores.

Additional Statistical Methods

Further to the statistical methods described in the main manuscript, a comparison of the SXscore calculated using both scoring Methods, and of the SXscore compared with the SX-PAMI score was performed using previously described methodology.(1) In both comparisons the SXscore calculated using Method A was designated as the control. Firstly, discrimination of the models was assessed using the C-statistic from the receiver operator curves (ROC). Secondly, the net reclassification improvement was calculated for mortality using Method B. Amongst patients experiencing an event, movement from a low to a high risk group was considered favourable, whilst movement from a high risk group to a lower risk group detrimental. Conversely amongst patients not experiencing an event, movement from a low to high group was detrimental, whilst movement form a high to low risk group beneficial. The Net reclassification improvement was subsequently calculated by considering the difference between the proportion of patients who experienced an event and were reclassified, and the proportion of patients who did not experience an event and were reclassified.(1)

SUPPLEMENTARY RESULTS

The SXscore calculated using method B ranged from 0-66, with a mean of 10.3±8.1. The median (inter-quartile range) was 8(9), which was significantly lower than the median score calculated using Method A ($p<0.05$). Further analysis was performed after stratifying clinical outcomes according to SXscore terciles defined as: SX_{LOW} <6 (n=250), 6≤SX_{MID}≤11 (n=288); SX_{HIGH}>11 (n=269).

Clinical Outcomes

Clinical outcomes through to 1-year follow-up are shown in **Supplementary Table 1**, whilst corresponding Kaplan Meier survival curves are shown in **Supplementary Figure 1**. As with clinical outcomes stratified using Method A, patients in the highest SXscore tercile calculated using Method B had a significantly higher risk of mortality; the composite of death or re-infarction, overall major adverse cardiovascular events, and rates of definite, definite/probable and any stent thrombosis compared to those in the lower two terciles.

Multi-variate Analysis

The results of the Cox multivariate analysis for death, overall MACE and any stent thrombosis are shown in **Supplementary Table 2**. After multi-variate adjustment the SXscore calculated using Method B remained an independent predictor of death, MACE and any stent thrombosis.

Method A vs. Method B

The ROC curves and corresponding C-statistics for mortality, TVR and the composite of MACE are shown in **Figure 3**. As demonstrated the SXscore calculated using Method A had a superior discriminatory ability when compared to Method B for all outcome measures. Reclassifications following the application of Method B for mortality and MACE are shown in **Supplementary Tables 3 and 4**. In total 44 patients died, of whom 7 were reclassified into a higher SXscore tercile (upward movement), and 8 were reclassified into a lower SXscore tercile (lower movement) with the use of Method B. The net gain in reclassification was therefore -1/44= -2.3%. Among the 763 patients who did not die, use of Method B lead to 107 patients being downgraded and 183 patients upgraded. The net gain in reclassification was therefore 76/763=10.0%, and the overall net reclassification improvement for Method B was -12.3%. Therefore when using mortality as an endpoint over 12% of patients in this study were inappropriately reclassified by the use of Method B. Similarly for MACE, the use of Method B resulted in an overall net reclassification improvement of -0.9%.

SX-PAMI Score

The ROC curves and corresponding C-statistics for mortality, TVR and the composite of MACE are shown in **Figure 3**. Whilst the discriminatory ability of the SX-PAMI score lay between the SXscore and PAMI scores for the endpoints of death, death/re-infarction and TVR, it was superior to both for overall MACE. Reclassifications following the use of the SX-PAMI score are shown in **Supplementary**

Supplementary Table 1. Clinical Outcomes at 1-year stratified according to SYNTAX score tercile.

Outcome, n (%)	SYNTAX Score <6 (N=250)	SYNTAX Score ≥6-11 (N=288)	SYNTAX Score >11 (N=269)	P Value
Hierarchical Outcomes at 1-year				
Death	9 (3.6)	11 (3.8)	24 (8.9)	0.009
Re-infarction	3 (1.6)	7 (2.4)	16 (5.9)	
Death or Re-infarction	12 (4.8)	18 (6.3)	40 (14.9)	<0.001
MACE	22 (8.8)	33 (11.5)	65 (24.2)	<0.001
Non-Hierarchical Outcomes at 1-year				
Re-infarction	3 (1.5)	7 (2.4)	19 (7.1)	0.001
Target vessel revascularisation	11 (4.4)	18 (6.3)	31 (11.5)	0.007
Definite ST	0 (0.0)	4 (1.4)	9 (3.3)	0.01
Definite/Probable ST	1 (0.4)	5 (1.7)	15 (5.6)	0.001
Definite or Probable or Possible ST	4 (1.6)	6 (2.1)	19 (7.1)	0.001

ST, stent thrombosis; MACE, major adverse cardiovascular events, a composite of death, re-infarction and target vessel revascularisation

Tables 5 and **6**. In total 44 patients died, of whom 10 and 0 were respectively reclassified into a higher and lower terciles with the use of the SX-PAMI score, giving a net gain in reclassification of 22.7%. Among the 747 patients who did not die, use of the SX-PAMI lead to 52 patients and 104 patients being downgraded and upgraded, respectively, giving a net gain in reclassification of 7.0%, and a subsequent overall net reclassification improvement for the SX-PAMI of 15.7%. Therefore when using mortality as an endpoint over 15% of patients in this study were appropriately reclassified by the use of the SX-PAMI. Similarly for MACE, the overall net reclassification improvement for the SX-PAMI was 4.6%.

Supplementary Table 2: Multivariate Predictors of Death, MACE and Stent Thrombosis

Variable	Univariate Predictors		Multivariate predictors	
	95% [CI]	P value	95% [CI]	P value
Death				
Creatinine clearance	0.97 [0.96-0.98]	<0.001		
Left ventricular function	0.92 [0.89-0.94]	<0.001	0.94 [0.91-0.98]	0.002
Male	0.51 [0.28-0.94]	0.03		
PAMI Score	1.34 [1.24-1.47]	<0.001	1.14 [1.00-1.29]	0.04
SYNTAX score Method B	1.04 [1.01-1.07]	0.002	1.04 [1.00-1.08]	0.047
Major Adverse Cardiovascular Events				
Creatinine clearance	0.99 [0.98-1.00]	0.01		
Door to balloon time	1.01 [1.00-1.02]	0.02		
Left ventricular function	0.94 [0.92-0.96]	<0.001	0.96 [0.94-0.99]	0.001
PAMI Score	1.17 [1.10-1.23]	<0.001	1.09 [1.00-1.18]	0.03
Sirolimus-eluting stent use	0.55 [0.38-0.80]	0.002	0.63 [0.41-0.94]	0.03
SYNTAX score Method B	1.05 [1.04-1.07]	<0.001	1.06 [1.04-1.09]	<0.0001
Stent Thrombosis				
Left ventricular function	0.91 [0.87-0.96]	<0.001	0.95 [0.90-0.99]	0.02
PAMI Score	1.25 [1.12-1.39]	<0.001	1.13 [0.98-1.30]	0.11
SYNTAX score Method B	1.05 [1.02-1.09]	0.001	1.05 [1.01-1.10]	0.01

CI, confidence interval

Supplementary Table 3: 1-year all-cause mortality classified according to terciles of the SYNTAX score calculated using Method A and Method B.

DEATH (number of patients)		SYNTAX Score Method A		
		Tercile 1 (≤9)	Tercile 2 (>9-16)	Tercile 3 (>16)
SYNTAX Score Method B	Tercile 1 (<6)	7	2	2
	Tercile 2 (≥6-11)	1	4	4
	Tercile 3 (>11)	0	6	18

No DEATH (number of patients)		SYNTAX Score Method A		
		Tercile 1 (≤9)	Tercile 2 (>9-16)	Tercile 3 (>16)
SYNTAX Score Method B	Tercile 1 (<6)	188	43	10
	Tercile 2 (≥6-11)	110	111	54
	Tercile 3 (>11)	3	70	174

Supplementary Table 4: 1-Year Major Adverse Cardiovascular events (MACE) classified according to terciles of the SYNTAX score calculated using Method A and Method B.

MACE (number of patients)		**SYNTAX Score Method A**		
		Tercile 1 (≤9)	Tercile 2 (>9-16)	Tercile 3 (>16)
SYNTAX Score Method B	Tercile 1 (<6)	15	4	3
	Tercile 2 (≥6-11)	8	16	9
	Tercile 3 (>11)	1	11	53

No MACE (number of patients)		**SYNTAX Score Method A**		
		Tercile 1 (≤9)	Tercile 2 (>9-16)	Tercile 3 (>16)
SYNTAX Score Method B	Tercile 1 (<6)	180	39	9
	Tercile 2 (≥6-11)	105	99	49
	Tercile 3 (>11)	2	65	139

Supplementary Table 5: 1-year all-cause mortality classified according to terciles of the SYNTAX score calculated using Method A and terciles of the SX-PAMI score.

DEATH (number of patients)		**SYNTAX Score Method A**		
		Tercile 1 (≤9)	Tercile 2 (>9-16)	Tercile 3 (>16)
SX-PAMI Score	Tercile 1 (<12)	5	0	0
	Tercile 2 (≥12-21)	5	5	0
	Tercile 3 (>21)	0	5	24

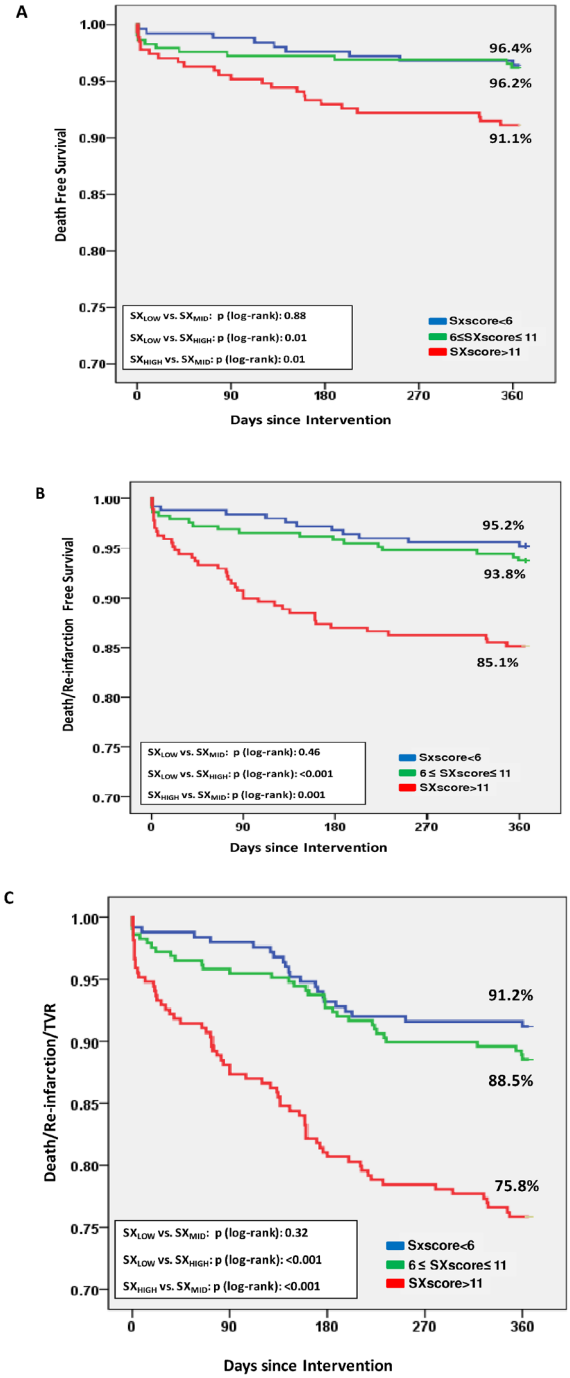
No DEATH (number of patients)		**SYNTAX Score Method A**		
		Tercile 1 (≤9)	Tercile 2 (>9-16)	Tercile 3 (>16)
SX-PAMI Score	Tercile 1 (<12)	222	22	0
	Tercile 2 (≥12-21)	73	165	30
	Tercile 3 (>21)	0	31	204

Supplementary Table 6: 1-Year Major Adverse Cardiovascular events (MACE) classified according to terciles of the SYNTAX score calculated using Method A and terciles of the SX-PAMI score.

MACE (number of patients)		**SYNTAX Score Method A**		
		Tercile 1 (≤9)	Tercile 2 (>9-16)	Tercile 3 (>16)
SX-PAMI Score	Tercile 1 (<12)	15	1	0
	Tercile 2 (≥12-21)	9	20	3
	Tercile 3 (>21)	0	9	62

No MACE (number of patients)		**SYNTAX Score Method A**		
		Tercile 1 (≤9)	Tercile 2 (>9-16)	Tercile 3 (>16)
SX-PAMI Score	Tercile 1 (<12)	212	21	0
	Tercile 2 (≥12-21)	69	150	27
	Tercile 3 (>21)	0	27	166

Supplementary Figure 1: Kaplan Meier survival curves for (A) death; (B) the composite of death and re-infarction, and (C) the composite of death, re-infarction and target vessel revascularisation (TVR).



SUPPLEMENTARY REFERENCES

1. Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157-72; discussion 207-12.

Chapter 6.4

A patient level pooled analysis assessing the impact of the SYNTAX score on 1-year clinical outcomes in 6,508 patients enrolled in contemporary coronary stent trials

J Am Coll Cardiol Intv. In press

Scot Garg, Giovanna Sarno, Chrysafios Girasis, Pascal Vranckx, Ton de Vries, Marco Bressers, Michael Swart, Hector Garcia-Garcia; Gerrit-Anne van Es, Lorenz Räber, Gianluca Campo, Marco Valgimigli, Keith D. Dawkins, Stephan Windecker, Patrick W. Serruys

ABSTRACT

Background: The SYNTAX score (SXscore) has been demonstrated to have an ability to predict clinical outcomes in patients undergoing percutaneous revascularization. Current studies are limited by the relatively small number of patients in each SXscore group.

Aims: To assess the impact of the SXscore on clinical outcomes in patients undergoing PCI.

Methods: Patient level data from seven contemporary coronary stent trials were pooled by an independent Academic Research Organisation (Cardialysis, The Netherlands). Analysis was performed on a cohort of 6508 patients who were treated with drug-eluting stents, and had a calculated SXscore. Clinical outcomes in terms of death, myocardial infarction (MI), repeat revascularisation and major adverse cardiovascular events (MACE, a composite of death, MI and repeat revascularisation) were subsequently stratified according to SXscore quartiles: $SXscore_{Q1} \leq 8$ (n=1702); $8 < SXscore_{Q2} < 15$ (n=1528); $15 \leq SXscore_{Q3} < 23$ (n=1620); and $SXscore_{Q4} \geq 23$ (n=1658).

Results: One-year outcomes were available in 6496 patients (99.8%). At 1-year follow-up, all clinical outcomes including mortality, MI, repeat revascularisation, MACE, definite and any stent thrombosis were all significantly higher in patients in the highest SXscore quartile. Similar trends were observed in a sub-group of 2093 patients (32.2%) who presented with an ST- or non-ST elevation MI. The rate of MACE amongst patients with a SXscore>32 and ≤32 was 24.9% and 14.0%, respectively ($p<0.001$). The SXscore was identified as an independent predictor of all clinical outcomes including mortality, MACE and ST ($p<0.001$ for all).

Conclusions: This study confirms the consistent ability of the SXscore to identify patients who are at highest risk of adverse events.

Keywords: SYNTAX score, drug-eluting stent

INTRODUCTION

The SYNTAX score (SXscore) is an angiographic scoring system which was developed to quantify the complexity of coronary artery disease (CAD) in patients undergoing coronary revascularisation.(1-2) The score was initially developed for use in the SYNTAX trial as a means of bringing together the cardiologist and cardiac surgeon to study in great detail the coronary angiogram of patients selected for enrolment.(3) Subsequent analyses however have indicated that the SXscore can be used to assist in deciding the optimal revascularisation strategy in patients with complex CAD,(3-4) whilst also identifying those patients treated by percutaneous coronary intervention (PCI) who are at highest risk of adverse cardiac events.(3-13) This ability to risk stratify patients has been evaluated in numerous studies which include those with an all-comers design,(8-9) and those more specifically enrolling patients with multi-vessel disease,(5-6) complex CAD (triple vessel and/or left main disease)(3,11-13) or those presenting with ST-elevation myocardial infarction (STEMI).(10) Importantly, the SXscore has consistently been identified as an independent predictor of major adverse cardiac events and/or mortality at follow-up ranging from between one and five years.(5-12)

These assessments of the SXscore are limited however by the relatively small number of patients in each SXscore tercile, which have ranged from approximately 200 to 470 patients.(5,8) In an effort to overcome these limitations, the present study pooled patient-level data from seven contemporary coronary stent trials(3,14-19) where the SXscore was available, thereby enabling a more precise evaluation of the benefit of calculating the SXscore in patients treated by PCI.

METHODS

Study Design and Patient Population

We identified seven contemporary coronary stent trials (SIRTAX, LEADERS, RESOLUTE, ARTS-II, SYNTAX, STRATEGY and MULTI-STRATEGY) in which the SXscore was available.(3,14-19) Detailed individual study design and trial results are available elsewhere;(3,14-19) in brief all studies included patients with obstructive CAD which was amendable to coronary stent implantation; with drug-eluting stents (DES) used exclusively in all but two studies. Study inclusion criteria were deliberately heterogeneous ranging from an all-comers design,(14-16) to studies only recruiting patients with complex CAD,(3,17) or only those with ST-elevation myocardial infarction (STEMI).(18-19) A summary

Table 1. Baseline clinical characteristics

Variable, % (n) unless stated	SXscore≤8 (n=1702)	8<SXscore<15 (n=1528)	15≤SXscore<23 (n=1620)	SXscore≥23 (n=1658)	P Value
Baseline Characteristics					
Male gender	73.7(1254)	74.3(1136)	76.1(1233)	77.0 (1276)	0.01
Age (years±SD)	62.2±10.7	62.8±10.8	63.7±10.7	66.5±10.3	<0.001
Body Mass Index ±SD	27.6±4.3	27.9±4.4	27.5±4.3	27.7±4.6	0.78
Risk factors					
Previous MI	28.9(423/1464)	29.3(397/1354)	30.4(447/1471)	33.3(536/1611)	0.007
Diabetes	18.7(316/1689)	20.4(310/1519)	24.5(395/1611)	29.2(483/1653)	<0.001
Hypertension	68.7(1159/1686)	68.1(1032/1516)	69.8(1120/1605)	71.4(1177/1648)	0.06
Hypercholesterolemia	65.4(1110/1681)	63.1(954/1511)	65.8(1054/1602)	68.1(1119/1642)	0.04
Family history ischaemic heart disease	40.6(396/976)	35.8(312/871)	35.7(353/988)	28.5(338/1188)	<0.001
Current smoker	36.0(510/1417)	33.6(441/1311)	32.3(448/1385)	22.9(341/1489)	<0.001
Peripheral vascular disease	5.9(57/964)	7.2(62/865)	7.0(69/991)	9.1(111/1221)	0.007
Previous PCI	31.8(468/1470)	24.8(339/1369)	19.1(285/1492)	12.8(208/1623)	<0.001
Previous stroke	3.9(34/879)	2.9(24/830)	4.4(43/974)	7.0(87/1240)	<0.001
Creatinine Clearance (ml/1.73m^2±SD)	95.0±42.4	94.0±35.1	89.7±32.9	84.9±31.7	<0.001
Creatinine >200μmol/l	0.6(8/1392)	1.0(14/1367)	0.7(11/1487)	1.8(28/1576)	0.004
Ejection Fraction	58.2±11.0	56.2±11.7	56.0±12.6	55.5±13.4	<0.001
SYNTAX score	5.0±2.2	11.4±1.7	18.3±2.3	31.8±8.3	<0.001
Indication for Treatment					
Stable angina	38.5(656)	36.5(558)	35.6(576)	42.1(698)	0.07
Unstable angina	19.4(330)	17.1(262)	19.8(321)	24.5(406)	<0.001
ST-elevation MI	18.4(314)	23.3(356)	22.3(362)	14.6(242)	0.005
Non-ST-elevation MI	15.3(261)	15.1(231)	12.1(196)	7.9(131)	<0.001
Silent ischemia	9.9(62/625)	9.7(61/630)	9.8(79/809)	8.6(100/1157)	0.37

SD for standard deviation;
MI, myocardial infarction
PCI, percutaneous coronary intervention

of all studies, including pertinent inclusion and exclusion criteria, study stents, study procedures, and dual anti-platelet therapy regimes are shown in **Supplementary Table 1**. All studies complied with the Declaration of Helsinki, and were approved by the ethical review board in each institution. All patients provided written, informed consent for participation in the individual studies.

After identification of appropriate studies, the principal investigators of each study were subsequently contacted, and individual patient data were requested on a broad range of core baseline clinical variables, procedural results, and clinical outcomes at 1-year follow-up. Clinical outcomes included data on death, myocardial infarction (MI), any repeat revascularization (either PCI or coronary artery

Table 2. Baseline lesion and procedural characteristics

Variable, % (n) unless stated	SXscore≤8 (n=1702)	8<SXscore<15 (n=1528)	15≤SXscore<23 (n=1620)	SXscore≥23 (n=1658)	P Value
Extent of Disease					
Number of disease lesions	1.4±0.7	2.3±1.0	3.0±1.2	4.1±1.6	<0.001
One vessel disease	69.6(1185)	30.6(467)	15.4 (250)	6.1(101)	<0.001
Two vessel disease	25.7(437)	49.6(758)	42.4 (687)	24.9(413)	0.11
Three vessel disease	2.7(46)	17.2 (263)	40.4 (655)	66.7 (1106)	<0.001
Lesion Location					
Left Main Stem	0.4(7)	3.8(58)	6.2(100)	21.1(350)	<0.001
Right Coronary artery	47.9(816)	58.5(894)	67.4(1092)	80.5(1335)	<0.001
Circumflex artery	33.9(577)	49.3(754)	63.4(1027)	81.7(1354)	<0.001
LAD artery	47.2(803)	72.6(1110)	88.7 (1437)	93.8(1555)	<0.001
Proximal LAD involvement	8.0(136)	19.9(304)	34.8 (563)	60.3(1000)	<0.001
All *de novo* lesions	92.7(1304/1407)	93.9(1303/1388)	95.3(1432/1503)	96.5(1547/1603)	<0.001
Lesion Characteristics					
≥1 Bifurcation lesion	18.9(322)	48.7(744)	60.9(986)	71.6(1187)	<0.001
≥1 Trifurcation lesion	0.5(9)	2.0(31)	3.2(52)	8.0(132)	<0.001
≥1 Ostial lesion	1.8(30)	3.9(60)	4.2(68)	8.1(134)	<0.001
≥1 Occlusion	7.9(135)	21.1(323)	33.1(537)	42.9(712)	<0.001
≥1 Tortuous lesion	15.0(256)	29.1(444)	41.6(674)	62.7(1039)	<0.001
≥1 Lesion ≥ 20mm	12.3(209)	28.1(430)	46.0(745)	66.9(1109)	<0.001
≥ 1 Calcified lesion	3.1(52)	11.8(180)	21.1(342)	43.6(723)	<0.001
≥ 1 Lesion with thrombus	5.2 (88)	6.3(97)	6.7(108)	6.2(103)	0.18
Procedural Characteristics					
Number of stents implanted ±SD	1.7±1.1	2.2±1.5	2.9±2.0	4.0±2.3	<0.001
Total stent length(mm±SD)	24.6±15.3	36.3±24.0	51.7±35.0	75.7±46.3	<0.001
≥100mm of stent implanted	0.4(4/1086)	2.1(20/966)	9.7(104/1075)	24.9(312/1253)	<0.001
Post procedural Hospital stay (days±SD)	2.1±2.8	2.5±2.7	2.8±3.3	3.8±6.3	<0.001

LAD, left anterior descending artery

bypass surgery [CABG]) and stent thrombosis (ST). Death and MI were available from all studies, whilst any repeat revascularisation was only available from four studies: ARTS-II, SYNTAX, RESOLUTE, and LEADERS. Of the remaining three studies, two (STRATEGY and MULTI-STRATEGY) reported only clinically-indicated target vessel revascularisation (TVR),(18-19) whilst one (SIRTAX) reported clinically and non-clinically driven target lesion revascularisation (TLR) and TVR.(15) ST was available from all studies. A summary of individual trial endpoints is shown in **Supplementary Table 2.**

Patient-level based data were subsequently transferred to an independent Academic Research Organisation (Cardialysis), where they were merged with a database containing the calculated SXscore and its components. Data from each trial were re-coded by researchers SG, MS and TdV and finally two researchers (SG, PWS) analyzed and interpreted the data.

SYNTAX Score

The SXscore for each patient was calculated by scoring all coronary lesions with a diameter stenosis≥50%, in vessels ≥1.5 mm, using the SXscore algorithm which is described in full elsewhere (1-2) and available on the SXscore website.(20) In the SYNTAX, LEADERS and RESOLUTE studies all angiographic variables required to calculate the SXscore were recorded prospectively by a team of two core lab analysts (Cardialysis, Rotterdam, The Netherlands).(3,14,16) In contrast the SXscore in the SIRTAX, ARTS-II, STRATEGY and MULTI-STRATEGY studies was calculated retrospectively by individual teams made up of two researchers (SG, GS, CG, MV).(15,17-19) Of note, all investigators were blinded at the time of the calculation to clinical data, clinical presentation and outcomes. In the event of disagreement, the opinion of a third analyst was sought, and the final decision was established by consensus. Core lab analysts and researchers have been shown on two occasions to have a similar degree of intra-observer variability.(2,21)

The initial description of the SXscore calculation did not include patients presenting with STEMI or those with restenotic lesions. Patients with occluded infarct related arteries were subsequently scored as occlusions of unknown duration in a similar manner as any chronically occluded artery. Similarly, patients with lesions due to restenosis or in-stent restenosis were scored in the same manner as if the lesion were a *de novo* lesion. Although this methodology was not described in the original description of the SXscore, it has previously been applied to other all-comers, and STEMI populations.(8-10)

Clinical End Points and Definitions

The primary end point of this pooled analysis was all-cause mortality at 1-year follow-up. The secondary end points included major adverse cardiac events (MACE), a composite of death, MI and any repeat revascularisation; a combined safety endpoint of death and MI; and the individual end points of MI, repeat revascularization (PCI or CABG), and stent thrombosis. In patients presenting with an MI, clinically-indicated TVR is also reported.

Complete definitions are available in the individual study publications.(3,14-19) Deaths from all causes are reported. As indicated in **Supplementary Table 3** there was a wide variation in the definition of MI between studies which reflects the heterogeneous study inclusion criteria, the variations

Table 3: Clinical outcomes at 1-year follow-up amongst all patients, and those presenting with a myocardial infarction.

Variable, % (n) unless stated	SXscore≤8 (n=1702)	8<SXscore<15 (n=1526)	15≤SXscore<23 (n=1617)	SXscore≥23 (n=1651)	P Value
All Patients					
Death	1.6 (28)	1.2 (19)	3.2(52)	4.6(76)	<0.001
Cardiac death*	0.8(12/1567)	0.8(11/1412)	2.3(35/1515)	3.6(57/1599)	<0.001
Myocardial Infarction	2.9(50)	3.2(49)	3.8(61)	6.1(101)	<0.001
Any Repeat revascularization†	7.7(94/1215)	8.7(102/1167)	11.4(151/1324)	15.4(236/1529)	<0.001
Death or MI	4.3(73)	4.1(62)	6.5(105)	9.4(156)	<0.001
Death/MI or repeat revascularization†	10.8(131/1215)	11.4(133/1167)	15.7(209/1324)	21.1(323/1529)	<0.001
ARC any stent thrombosis‡	1.3(22/1692)	1.9(28/1448)	3.1(43/1373)	4.9(45/920)	<0.001
ARC definite stent thrombosis‡	0.6(10/1692)	1.2(17/1448)	1.5(21/1373)	2.9(27/920)	<0.001
Patients presenting with Myocardial Infarction ¶					
	N=575	**N=587**	**N=558**	**N=373**	
Death	2.4(14)	1.7(10)	5.6(31)	4.3(16)	0.006
Cardiac death*	0.9(4/440)	1.1(5/473)	3.9(18/456)	2.8(9/321)	0.005
Myocardial Infarction	1.7(10)	2.9(17)	3.4(19)	6.4(24)	<0.001
Any Repeat revascularization†	7.3(21/287)	9.4(33/351)	12.3(43/349)	17.6(50/284)	<0.001
Clinically-indicated Target Vessel Revascularization	2.8(16)	4.4(26)	6.5(36)	9.7(36)	<0.001
Death or MI	4.0(23)	4.3(25)	8.2(46)	9.9(37)	<0.001
Death/MI or repeat revascularization†	9.8(28/287)	12.3(43/351)	18.1(63/349)	22.5(64/284)	<0.001
ARC any stent thrombosis	1.4(8)	2.2(13)	5.0(28)	5.9(22)	<0.001
ARC definite stent thrombosis	0.7(4)	1.4(8)	2.7(15)	4.3(16)	<0.001

ARC, Academic Research Consortium; MI, myocardial infarction

*Cardiac death not available in the STRATEGY and MULTI-STRATEGY studies

†Any repeat revascularisation was not available in the SIRTAX, STRATEGY or MULTI-STRATEGY studies.

‡Any stent thrombosis or definite stent thrombosis defined according to ARC was not available in the SYNTAX study.

¶Includes ST-elevation MI and non-ST elevation MI. Patients with acute MI were excluded from the SYNTAX and ARTS-II study.

in study design and the different time periods during which studies were performed. As all clinical events from each individual trial were adjudicated by independent clinical event committees, no attempt was made to readjudicate MI events in the different trials to compensate for the differences in individual definition of MI. Therefore all MIs reported in the current study are as per individual protocol definitions. All repeat revascularisation procedures were reported. The definitions of TLR and TVR, and the criteria for a clinically driven revascularisation used in the five studies reporting these outcomes(14-16,18-19) are provided in **Supplementary Table 2**. All studies apart from the SYNTAX study reported ST defined according to the Academic Research Consortium definitions.(22)

Statistical Analysis

All patients with a calculated SXscore were included in the analysis. All variables were stratified according to SXscore quartiles. Discrete data were summarized as percent (frequencies), whereas continuous data were expressed as mean±standard deviation (SD). Testing for (linear) trends was done by using generalized linear models with SYNTAX class as a co-variable for continuous variables, and the Cochran-Armitage test for trend in categorical data. The distribution of the SXscore was assessed for normality using the Kolmogorov-Smirnov test. Clinical outcomes are presented separately for all patients, those presenting with an MI (STEMI or non-STEMI), and those patients with a SXscore>32, which was the highest SXscore tertile in the SYNTAX study.(3) Survival curves were constructed for time-to-event variables using Kaplan-Meier estimates, and compared by the log-rank test. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. A Cox multi-variate model was performed using the co-variates gender, age greater than 65, diabetic status, urgency of procedure, SXscore and use of a 1st generation DES. A p value of <0.05 was considered significant, and all tests were two-tailed. Data were analyzed with SAS version 9.2 (SAS, Carey, NC).

RESULTS

The SXscore was available in 6508 of the 7639 patients (85.2%) enrolled in the seven individual studies. The main reasons for absent SXscores were missing baseline angiograms, the presence of prior surgical revascularisation or treatment with bare metal stents. In total the SXscore ranged from 0 to 83, with a mean±standard deviation of 16.7±11.1, and a median of 15 (inter-quartile range of 15; 8 to 23). The distribution of the SXscore is shown in **Figure 1**; the score was not normally distributed

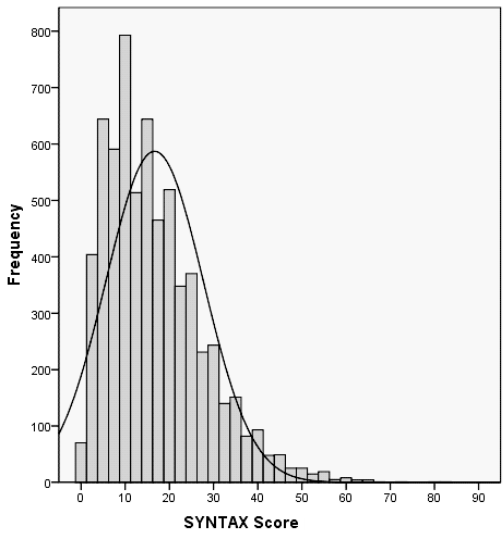


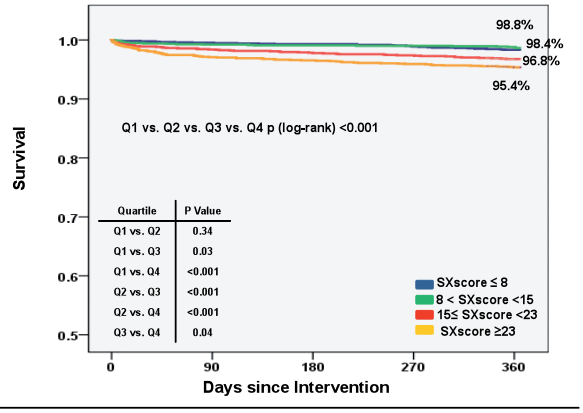
Figure 1: Distribution of the SYNTAX scores amongst the 6508 patients enrolled in the study.

(Kolmogorov-Smirnov test p<0.05). In this analysis the 6508 patients were divided according to their SXscore into quartiles defined as: $SXscore_{Q1} \leq 8$ (n=1702), $8 < SXscore_{Q2} < 15$ (n=1528); $15 \leq SXscore_{Q3} < 23$ (n=1620); $SXscore_{Q4} \geq 23$ (n=1658).

Baseline angiographic and procedural characteristics

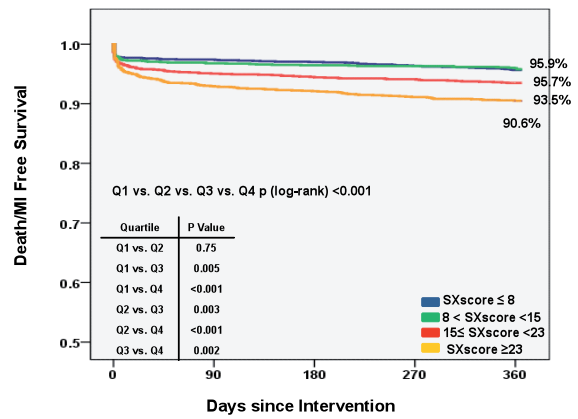
Baseline clinical, angiographic and procedural characteristics of the study population, stratified according to SXscore quartiles, are shown in **Tables 1** and **2**. **Table 2** demonstrates that indicators of lesion complexity, such as an ostial lesion, a total occlusion and the presence of a bifurcation, were all significantly more common in the highest SXscore quartile, reflecting the higher calculated SXscore for these lesions.

A



Days	0	90	180	270	360
Patients at risk	6496	6375	6343	6286	5493

B



Days	0	90	180	270	360
Patients at risk	6496	6178	6137	6071	5299

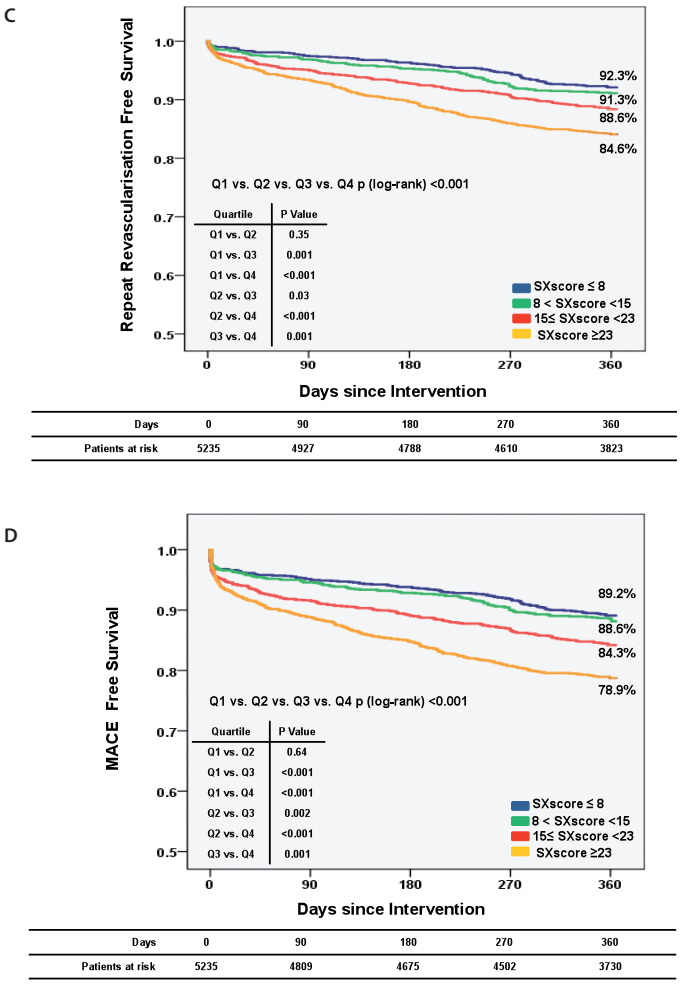


Figure 2: Kaplan Meier cumulative curves for (A) death; (B) the composite of death and myocardial infarction; (C) repeat revascularisation; and (D) major adverse cardiovascular events (MACE, a composite of death, myocardial infarction and repeat revascularisation) at 1-year follow-up stratified according to SYNTAX score quartiles.

Outcomes at 12-months

Clinical outcomes at 12-months, which were available in 6496 patients (99.8%) and a sub-set of 2093 patients (32.2%) presenting with an STEMI or non-STEMI, are shown in **Table 3**, whilst cumulative survival curves for all patients and those presenting with an MI are shown in **Figure 2** and **Supplementary Figure 1**, respectively. Overall the primary endpoint of death was significantly higher in the highest SXscore quartile (1.6% vs. 1.2% vs. 3.2% vs. 4.6%, p<0.001). A similar trend was noted for all other clinical endpoints, including the safety composite of death/MI and overall MACE, a composite of death/MI and repeat revascularisation. All clinical outcomes in patients presenting with an MI,

apart from death and cardiac death, were also significantly worse in those patients in the highest SXscore quartile.

The rate of ST followed the same trend as other clinical outcomes, with the highest rate noted in $SXscore_{Q4}$. Of note, rates of ST were higher in all quartiles for patients presenting with an MI compared to the full patient cohort.

Clinical outcomes in patients with a SYNTAX score above and below 32

In the current analysis 9.3% of patients had a SXscore>32. The clinical outcomes of patients with a SXscore above and below 32 are shown in **Table 4**, whilst cumulative survival curves are shown in **Supplementary Figure 2**. All events were at least 1.5 times more common in patients with a SXscore>32 (p<0.001 for all), and overall approximately one quarter of patients in this high risk group experienced an event (death, myocardial infarction, or repeat revascularisation) within 12-months.

Table 4: Clinical outcomes at 1-year follow-up amongst patients with SYNTAX score above and below 32.

Variable, % (n) unless stated	SXscore≤32 (n=5895)	SXscore>32 (n=601)	RR [95% CI]	P Value
All Patients				
Death	2.3(135)	6.7(40)	2.58 [1.94-3.42]	<0.001
Cardiac death*	1.5(85/5508)	5.1(30/585)	2.81 [2.05-3.86]	<0.001
Myocardial Infarction	3.8(222)	6.5(39)	1.66 [1.23-2.24]	0.001
Any Repeat revascularization†	10.3(479/4660)	18.1(104/575)	1.76 [1.45-2.14]	<0.001
Death or MI	5.6(330)	11.0 (66)	1.90 [1.50-2.40]	<0.001
Death/MI or repeat revascularization†	14.0(652/4660)	24.9(143/575)	1.85 [1.55-2.20]	<0.001
ARC any stent thrombosis‡	2.3(122/5199)	6.8(16/234)	2.82 [1.75-4.55]	<0.001
ARC definite stent thrombosis‡	1.3(65/5199)	4.3(10/234)	3.19 [1.77-5.76]	<0.001

ARC, Academic Research Consortium; MI, myocardial infarction

*Cardiac death not available in the STRATEGY and MULTI-STRATEGY studies

†All repeat revascularisation was not available in the SIRTAX, STRATEGY or MULTI-STRATEGY studies.

‡Any stent thrombosis or definite stent thrombosis defined according to ARC was not available in the SYNTAX study.

Multivariable analysis

The results of the Cox multivariable analysis are shown in **Table 5**. Following adjusting of the confounding factors: age >65years, gender, urgency of procedure, diabetic status, and use of a first generation DES, the SXscore remained an independent predictor of clinical outcomes such as mortality, MACE, and ST (any and definite).

Table 5: Cox Multi-Variable Analysis

Clinical Outcome	Hazard Ratio for SYNTAX score* [95% Confidence Interval]	P Value
Death	1.40 [1.21-1.62]	<0.001
MI	1.33 [1.19-1.49]	<0.001
Any repeat revascularisation	1.29 [1.19-1.39]	<0.001
Death or MI	1.33 [1.21-1.46]	<0.001
Death, MI or repeat revascularisation	1.30 [1.21-1.40]	<0.001
Definite Stent Thrombosis	1.64 [1.31-2.05]	<0.001
Any Stent Thrombosis	1.51 [1.28-1.78]	<0.001

*After adjustment of confounding factors: age greater than 65, gender, urgency of procedure, diabetic status, and use of a first generation drug-eluting stent.
MI, myocardial infarction

DISCUSSION

This study is the largest assessment of the SXscore in patients treated with PCI, and confirms the ability of the SXscore to identify patients who are at highest risk of adverse events, which is irrespective of clinical presentation.

Several risk models have been developed for patients undergoing PCI, however few, if any, have become embedded into regular clinical practice. Most of these risk models including the Mayo Clinic Risk Score, the euroSCORE and the National Cardiovascular Database Registry CathPCI Risk score utilise a selection of clinical variables that have been identified as independent predictors of adverse outcome in those treated by PCI.(23-29)

In contrast the SXscore assesses the angiographic complexity of CAD, and does not include any clinical variables in its calculation. The score was initially developed for the SYNTAX trial(3) to ensure the angiograms of patients selected for enrolment were appropriately scrutinized by members of the Heart Team; thereby ensuring patients entered the appropriate arm of the trial. At the time of its development it was hypothesised that the SXscore may help in identifying patients at highest risk of adverse events.(1) Subsequent evaluations of the SXscore have confirmed this,(3-13) however studies have been hampered by relatively modest sized patient cohorts, which for the purpose of analysis have been further sub-divided into tertiles. Of note, the largest published assessment of the SXscore to date in patients treated with PCI, reported outcomes in 1397 patients, with only 472 patients in the largest tertile.(8) Importantly the current pooled analysis has demonstrated findings consistent with previous evaluations of the SXscore, and to its strength over 1500 patients were present in each subgroup, alleviating some of the earlier concerns, and ensuring robustness of the results. Furthermore, the identification of the SXscore as an independent predictor of clinical outcomes, including mortality MACE and ST, also provides further evidence to support the more routine use of the SXscore in the assessment of patients undergoing PCI.

This ability to identify patients at higher risk of adverse events has important clinical and research implications. From a clinical point of view it enables physicians to more adequately inform/counsel their patients regarding the potential risk of adverse events and in the choice of revascularization procedure (CABG versus PCI). Consequently this should act as a trigger for more aggressive secondary preventative therapy, and life style modification in those at highest risk as well as close clinical monitoring of recurrent signs or symptoms of ischemia. Importantly the present data also indicate that the SXscore is an independent predictor of ST, which speculatively may help in identifying those patients who would benefit most from assessment of platelet function together with more intensive, tailored and/or prolonged anti-platelet therapy. In clinical research the ability to identify a population of patients with a particular anticipated event rate may help in determining inclusion criteria for the design of more appropriately powered studies.

Previous studies which have assessed the SXscore and included a surgical treatment arm have concluded that SXscores greater than 32/34 are the threshold above which patients fare better with CABG.(3-4) In the present study a tenth of the cohort had a SXscore over 32, and it is noteworthy that a quarter of these patients experienced an event (death, MI or repeat revascularization) within 12-months, confirming the poor outcomes associated with very high SXscores. In comparison, patients in the SYNTAX study with a SXscore>32, treated with CABG had a one-year rate of major adverse cardiovascular and cerebrovascular events of 10.7%.(3) This disparity reiterates the importance of discussing the most appropriate method of revascularization, which in this complex subgroup of patients should ideally be CABG.

The absence of clinical variables has been raised as a limitation of assessing risk using just the SXscore. Consequently several modifications to the SXscore have been proposed by combining it with risk models using patient variables such as the ACEF score and euroSCORE.(30-31) Evaluations of these combined scores have shown promising early results, however data are limited to initial evaluations in small patient populations, and examination in large robust populations is currently lacking. An extension to this concept has recently been reported by Chen *et al* who included not only clinical and angiographic variables, but also procedural variables such as the stenting technique employed.(32) Although these additional variables were shown to improve the accuracy of risk prediction, these operator dependent variables cannot be reliably predicted prior to undertaking revascularisation, and therefore unacceptably their inclusion moves the ability to accurately calculate risk to a time point after the procedure has been completed.

LIMITATIONS

This study is limited by the absence of a CABG comparator arm, and also by the limited duration of follow-up. Unfortunately, comparisons of the SXscore with clinical models such as the euroSCORE and ACEF score, and combined scores such as the Clinical SYNTAX score were hindered by the respective absence of recorded euroSCOREs, and the large number of missing quantitative values for the

left ventricular ejection fraction and/or creatinine clearance, both of which are needed to calculate the ACEF and Clinical SYNTAX score.

CONCLUSIONS

This study confirms the consistent ability of the SXscore to identify patients who are at highest risk of adverse events, which is irrespective of clinical presentation. These results provide important evidence to support the more routine use of the SXscore in any patient undergoing percutaneous coronary revascularization.

REFERENCES

1. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219-27.
2. Serruys PW, Onuma Y, Garg S, et al. Assessment of the SYNTAX score in the Syntax study. EuroIntervention 2009;5:50-6.
3. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961-72.
4. Capodanno D, Capranzano P, Di Salvo ME, et al. Usefulness of SYNTAX score to select patients with left main coronary artery disease to be treated with coronary artery bypass graft. JACC Cardiovasc Interv 2009;2:731-8.
5. Valgimigli M, Serruys PW, Tsuchida K, et al. Cyphering the complexity of coronary artery disease using the syntax score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. Am J Cardiol 2007;99:1072-81.
6. Serruys PW, Onuma Y, Garg S, et al. 5-Year Clinical Outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the Sirolimus-Eluting Stent in the Treatment of Patients With Multivessel De Novo Coronary Artery Lesions. J Am Coll Cardiol 2010;55:1093-1101.
7. Capodanno D, Di Salvo ME, Cincotta G, Miano M, Tamburino C, Tamburino C. Usefulness of the SYNTAX Score for Predicting Clinical Outcome After Percutaneous Coronary Intervention of Unprotected Left Main Coronary Artery Disease. Circ Cardiovasc Intervent 2009;2:302-308.
8. Wykrzykowska J, Garg S, Girasis C, et al. Value of the Syntax Score (SX) for Risk Assessment in the "All-comers" Population of the Randomized Multicenter Leaders Trial. J Am Coll Cardiol 2010;56:272-277.
9. Girasis C, Garg S, Raber L, et al. Prediction of 5-year clinical outcomes using the SYNTAX score in patients undergoing PCI from the Sirolimus eluting stent compared with paclitaxel eluting stent for coronary revascularisation (SIRTAX) trial. Abstract at American College of Cardiology meeting, March 14-16th 2010, Atlanta GA.
10. Garg S, Sarno G, Serruys PW, et al. Prediction of 1-year clinical outcomes using the SYNTAX score in patients with acute ST-elevation myocardial infarction undergoing primary PCI: A sub-study of the STRATEGY and MULTI-STRATEGY trials. J Am Coll Cardiol Intv 2011;4:66-75.
11. Morice MC, Serruys PW, Kappetein AP, et al. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. Circulation 2010;121:2645-53.
12. Onuma Y, Girasis C, Piazza N, et al. Long-Term Clinical Results Following Stenting of the Left Main Stem: Insights From RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) and T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) Registries. J Am Coll Cardiol Intv 2010;3:584-594.
13. Kim Y-H, Park D-W, Kim W-J, et al. Validation of SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) Score for Prediction of Outcomes After Unprotected Left Main Coronary Revascularization. J Am Coll Cardiol Intv 2010;3:612-623.
14. Serruys PW, Silber S, Garg S, et al. Comparison of Zotarolimus-Eluting and Everolimus-Eluting Coronary Stents. N Engl J Med 2010;363:123-135.
15. Windecker S, Remondino A, Eberli FR, et al. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. N Engl J Med 2005;353:653-62.

16. Windecker S, Serruys PW, Wandel S, et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet 2008;372:1163-73.
17. Serruys PW, Ong ATL, Morice M-C, et al. Arterial Revascularisation Therapies Study Part II - Sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. EuroIntervention 2005;1:147-156.
18. Valgimigli M, Percoco G, Malagutti P, et al. Tirofiban and sirolimus-eluting stent vs abciximab and bare-metal stent for acute myocardial infarction: a randomized trial. JAMA 2005;293:2109-17.
19. Valgimigli M, Campo G, Percoco G, et al. Comparison of Angioplasty With Infusion of Tirofiban or Abciximab and With Implantation of Sirolimus-Eluting or Uncoated Stents for Acute Myocardial Infarction: The MULTI-STRATEGY Randomized Trial. JAMA 2008;299:1788-99.
20. SYNTAX working-group. SYNTAX score calculator: www.syntaxscore.com. Launched 19th May 2009.
21. Garg S, Girasis C, Sarno G, et al. The SYNTAX score revisited: A reassessment of the SYNTAX score reproducibility. Catheter Cardiovasc Interv 2010;75:946-952.
22. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-51.
23. Block PC, Peterson EC, Krone R, et al. Identification of variables needed to risk adjust outcomes of coronary interventions: evidence-based guidelines for efficient data collection. J Am Coll Cardiol 1998;32:275-282.
24. Qureshi MA, Safian RD, Grines CL, et al. Simplified scoring system for predicting mortality after percutaneous coronary intervention. J Am Coll Cardiol 2003;42:1890-1895.
25. Wu C, Hannan EL, Walford G, et al. A Risk Score to Predict In-Hospital Mortality for Percutaneous Coronary Interventions. J Am Coll Cardiol 2006;47:654-660.
26. Singh M, Lennon RJ, Holmes DR, Jr., Bell MR, Rihal CS. Correlates of procedural complicationsand a simple integer risk scorefor percutaneous coronary intervention. J Am Coll Cardiol 2002;40:387-393.
27. Shaw RE, Anderson HV, Brindis RG, et al. Development of a risk adjustment mortality model using the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR) experience: 1998-2000. J Am Coll Cardiol 2002;39:1104-1112.
28. Peterson ED, Dai D, DeLong ER, et al. Contemporary Mortality Risk Prediction for Percutaneous Coronary Intervention: Results From 588,398 Procedures in the National Cardiovascular Data Registry. J Am Coll Cardiol 2010;55:1923-1932.
29. Romagnoli E, Burzotta F, Trani C, et al. EuroSCORE as predictor of in-hospital mortality after percutaneous coronary intervention. Heart 2009;95:43-8.
30. Garg S, Sarno G, Garcia-Garcia HM, et al. A New Tool for the Risk Stratification of Patients With Complex Coronary Artery Disease: The Clinical SYNTAX Score. Circ Cardiovasc Interv 2010;3:317-326.
31. Capodanno D, Miano M, Cincotta G, et al. EuroSCORE refines the predictive ability of SYNTAX score in patients undergoing left main percutaneous coronary intervention. Am Heart J 2010;159:103-109.
32. Chen S, Chen JP, Mintz GS, et al. Comparison between the NEw Risk Stratification (NERS) score and the SYNTAX score in outcome prediction for unprotected left main stenting. J Am Coll Cardiol Intv 2010;3:632-641.

SUPPLEMENTARY APPENDIX

This appendix has been provided by the authors to give readers additional information about their work.

SUPPLEMENTARY METHODS

Supplementary Tables 1, 2 and **3** provide additional background information on the individual trials which were used in this pooled analysis.

- **Supplementary Table 1** summarizes the inclusion and exclusion criteria, study procedures, and recommended use of dual anti-platelet therapy in each of the individual studies.
- **Supplementary Table 2** summarizes the clinical endpoints reported in each individual study.
- **Supplementary Table 3** summarizes the criteria used in each individual study to adjudicate an event as a myocardial infarction.

Supplementary Table 1: Summary of Individual Trials

	SIRTAX(1)	LEADERS(2)	RESOLUTE(3)	ARTS-II(4)	SYNTAX(5)	STRATEGY(6)	MULTI-STRATEGY(7)
Enrolment Period	04/2003-05/2004	11/2006-05/2007	04/2008-10/2008	02/2003-11/2003	03/2005-04/2007	03/2003 - 04/2004	10/2004 - 04/2007
Study Design	RCT	RCT	RCT	Registry	RCT	RCT	RCT
Number of Patients	1012	1707	2292	607	1101	175	745
Number of Patients with SYNTAX score Total (acute†)	858 (345)	1397 (535)	2068 (736)	607 (0)	1101 (0)	100 (100)	377 (377)
Stents Used	SES , PES	SES , BES	EES, ZES	SES	PES	SES, BMS	SES, BMS

	SIRTAX(1)	LEADERS(2)	RESOLUTE(3)	ARTS-II(4)	SYNTAX(5)	STRATEGY(6)	MULTI-STRATEGY(7)
Inclusion criteria	Patients aged ≥18 years old **AND** Presentation: Stable angina, ACS, STEMI **AND** ≥1 lesion ≥50% DS in vessel with RVD 2.25-4.00mm* No restriction on total number of treated lesions, treated vessels, lesion length or number of stents implanted.			Presentation: stable angina, unstable angina or silent ischaemia, **AND** ≥2 coronary lesions, located in different major epicardial vessels and/ or their side-branches suitable for stenting >50% DS in the LAD, and ≥1 other major epicardial coronary artery. No restriction on the total implanted stent length.	Presentation: stable angina, unstable angina or silent ischaemia, **AND** >50% DS in three major epicardial coronary arteries and/or LMS No restriction on the total implanted stent length.	STEMI **AND** Chest pain >30 mins with ST elevation of ≥1mm in ≥2 contiguous ECG leads **OR** presumably new LBBB **AND** Admission <12 hours of symptom onset **OR** between 12-24 hours with evidence of continuing ischemia	

		SIRTAX(1)	LEADERS(2)	RESOLUTE(3)	ARTS-II(4)	SYNTAX(5)	STRATEGY(6)	MULTI-STRATEGY(7)
Exclusion criteria		Inability to take dual anti-platelet therapy Allergy to study medicines Terminal illness <6 months life expectancy Pregnancy Participation in another trial			Previous PCI or CABG LMS disease Congestive heart failure LVEF <30 percent History of a CVA, MI in the preceding week Allergy to study medicines Terminal illness Need for concomitant major surgery	Previous PCI or CABG Acute MI Need for concomitant cardiac surgery	Administration of fibrinolytics < 1 month History of bleeding diathesis Allergy to study drugs Major surgery <15 days Active bleeding or previous stroke <6mths	
Study Procedure		Stenting procedure at operator's discretion; Direct stenting was allowed Aim for complete revascularisation					Stenting procedure at operator's discretion Direct stenting was allowed	
DAPT	**Aspirin**‖	100mg	≥75mg	≥75mg	100mg	≥70mg	80-125mg	
	Clopidogrel (duration)	75mg (12 months)	75 mg (12 months)	75 mg (≥ 6 months)	75 mg (2 months)	75 mg (≥ 6 months)	75mg (≥ 3 months)	

*2.25-3.50mm in LEADERS

†Acute- ST-elevation and Non-ST elevation myocardial infarction

‖Recommend indefinitely in all studies

ACS, acute coronary syndrome; BES, biolimus-eluting stent; BMS, bare metal stent; CABG, coronary artery bypass grafting; CVA, cerebrovascular accident; DAPT, dual anti-platelet therapy; DS, diameter stenosis; EES, everolimus-eluting stent; LAD, left anterior descending artery; LMS, left main stem; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; RCT, randomized controlled trial; RVD, reference vessel diameter; SES, sirolimus-eluting stent; STEMI, ST-elevation myocardial infarction; ZES, zotarolimus-eluting stent.

Supplementary Table 2: Clinical outcomes reported per study, and supplementary definitions.

Outcome	SIRTAX(1)	LEADERS(2)	RESOLUTE(3)	ARTS-II(4)	SYNTAX(5)	STRATEGY(6)	MULTI-STRATEGY(7)
All-cause Death	•	•	•	•	•	•	•
Cardiac-death	•	•	•	•	•		
Myocardial Infarction*	•	•	•	•	•	•	•
All revascularisation		•	•	•	•		
TLR †	•	•	•	•			
TVR ‡	•	•	•				
Clinically-indicated TLR†	•#	•#	•#				
Clinically-indicated TVR‡	•#	•#	•#			•¶	•¶
Non-TLR Revascularisation†		•	•	•			
ARC defined stent thrombosis	•	•	•	•		•	•

*Individual protocol definition of myocardial infarction provided in **Supplementary Table 3**.

†TLR, target lesion revascularisation: defined as a repeat revascularisation due to a stenosis within the stent, or within a 5mm border proximal or distal to the stent.

‡TVR, target vessel revascularisation: defined as any repeat percutaneous coronary intervention or surgical bypass of any segment within the entire major coronary vessel proximal and distal to a target lesion, including upstream and downstream branches and the target lesion itself.

Clinically indicated if on quantitative coronary angiography (QCA) the lumen diameter stenosis of the treated lesion was ≥50% in the presence of ischaemic signs or symptoms, or ≥70% in the absence of ischaemia

¶ Clinically indicated if driven by clinical symptoms of myocardial ischemia with either a positive stress test or electrocardiographic evidence of ischemic changes at rest attributable to the target vessel, and the presence of a luminal diameter stenosis of ≥70%.

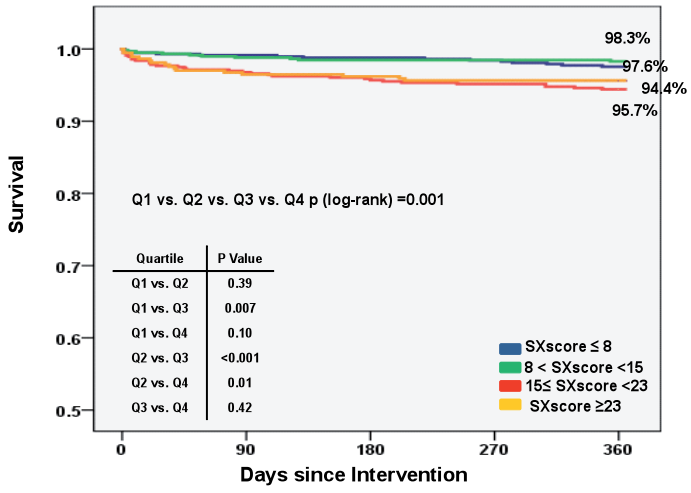
ARC, Academic Research Consortium

Supplementary Table 3: Individual Protocol Definitions of Myocardial Infarction

SIRTAX(1)	LEADERS(2)*	RESOLUTE(3)*	ARTS-II(4)	SYNTAX(5)		STRATEGY(6)	MULTI-STRATEGY(7)
				<7 days of Rx	**After randomisation & before Rx**	**≤24 hours of randomization**	
New Q waves in ≥2 contiguous leads **AND** any elevated CK-MB	New Q waves in ≥2 contiguous leads	New Q waves in ≥2 contiguous leads **AND** chest pain **OR** any elevation of cardiac enzymes		New Q waves in ≥2 contiguous leads **AND** CK-MB:CK ratio ≥ 0.1 **OR** CK-MB >5x ULN	Either: New Q waves in ≥2 contiguous leads and elevated CK-MB **OR** CK> 2x ULN + elevated CK-MB **OR** CK> 2x ULN	Recurrent ischemic symptoms and either: persistent ST elevation ≥1 mm in ≥ 2 contiguous leads **OR** new persistent ST depression ≥1 mm in ≥2 contiguous leads not due to changes from evolution of the index STEMI	
					<7 days of Rx	**24 hours - 7 days after randomization**	
In the absence of Q waves CK > 2x ULN **AND** any elevated CK-MB **OR** TNI	In the absence of Q waves CK > 2x ULN **AND** any elevated CK-MB **OR** TNI	In the absence of Q waves CK > 2x ULN **AND** any elevated CK-MB			Either: New Q waves & CK-MB:CK ratio ≥ 0.1 **OR** CK-MB >5x ULN **OR** CK >5x ULN	Ischemic symptoms ≥20 minutes and either: a CK ≥ 2x ULN **OR** further elevations ≥50% above the previous lowest level in patients with already elevated enzyme levels	
	<48 PCI or <7 days of CABG			**≥7 days of Rx**	**≥7 days of Rx**	**>7 days of randomization**	
	Either: CK >2x ULN & elevated CK-MB or TNI **OR** CK-MB >3x ULN **OR** TNI >5x 99th percentile			Any two of: chest pain >20mins new Q waves raised cardiac enzymes	Either: New Q waves **OR** CK-MB:CK ratio ≥ 0.1 **OR** CK-MB> 5x ULN **OR** CK >5x ULN	Either: a typical increase and decrease of levels of biochemical markers of myocardial necrosis to >ULN **OR** if markers are already elevated, further elevation of a marker ≥50% of the lowest recovery level from the index STEMI with either ischemic symptoms or other ischemic changes on the ECG.	

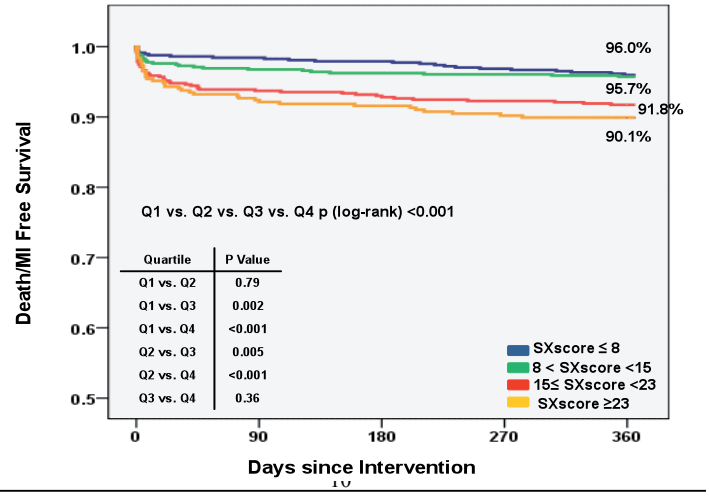
CK-MB, creatine kinase myoglobin band; ULN, upper limit of normal; TNI, troponin; CK, creatine kinase; Rx, treatment; STEMI, ST-elevation myocardial infarction.
*These two studies employed detailed algorithms to determine whether patients presenting with STEMI had re-infarcted, as detailed elsewhere.(8)

SUPPLEMENTARY FIGURES



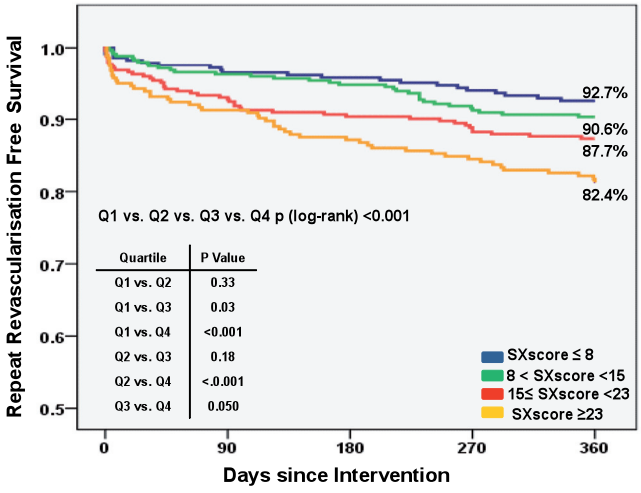
Days	0	90	180	270	360
Patients at risk	2093	2032	2020	1999	1787

Supplementary Figure 1A: Kaplan Meier cumulative curve for death at 1-year follow-up amongst patients presenting with an ST- or non-ST elevation myocardial infarction.



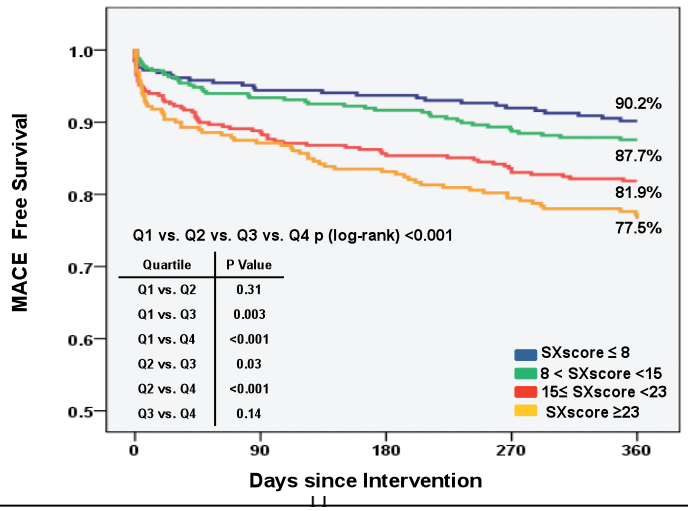
Days	0	90	180	270	360
Patients at risk	2093	1984	1968	1938	1734

Supplementary Figure 1B: Kaplan Meier cumulative curve for death or re-infarction at 1-year follow-up amongst patients presenting with an ST- or non-ST elevation myocardial infarction.



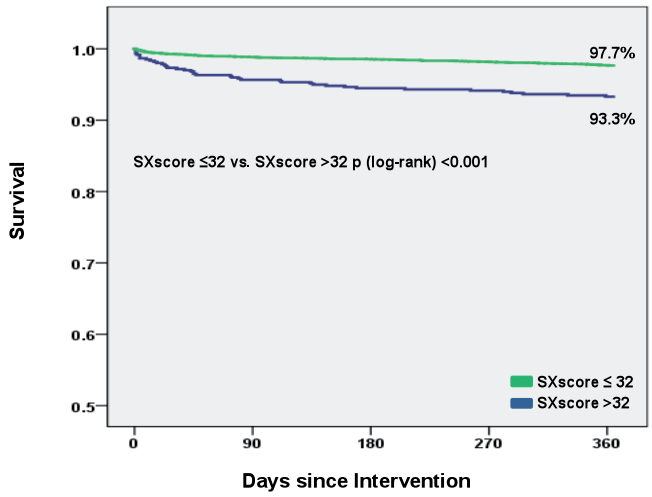
Days	0	90	180	270	360
Patients at risk	1271	1161	1129	1086	892

Supplementary Figure 1C: Kaplan Meier cumulative curve for repeat revascularisation at 1-year follow-up amongst patients presenting with an ST- or non-ST elevation myocardial infarction.



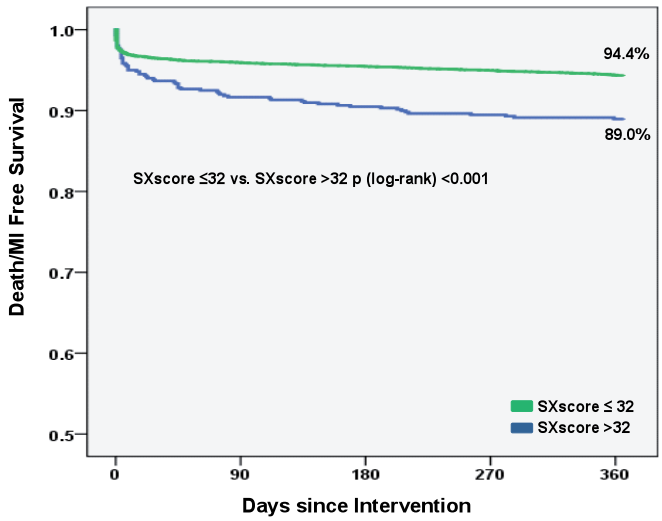
Days	0	90	180	270	360
Patients at risk	1271	1143	1112	1070	881

Supplementary Figure 1D: Kaplan Meier cumulative curve for major adverse cardiovascular events (MACE) at 1-year follow-up amongst patients presenting with an ST- or non-ST elevation myocardial infarction.



Days	0	90	180	270	360
Patients at riskSxscore ≤32	5895	5803	5779	5726	4978
Patients at riskSxscore >32	601	570	563	560	515

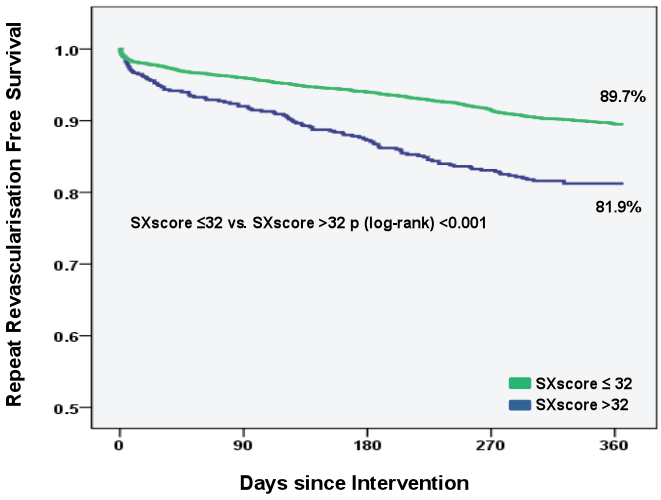
Supplementary Figure 2A: Kaplan Meier cumulative curve for death at 1-year follow-up amongst patients with a SYNTAX score >32 and ≤32.



Days	0	90	180	270	360
Patients at riskSxscore ≤32	5895	5632	5598	5539	4809
Patients at riskSxscore >32	601	546	539	532	490

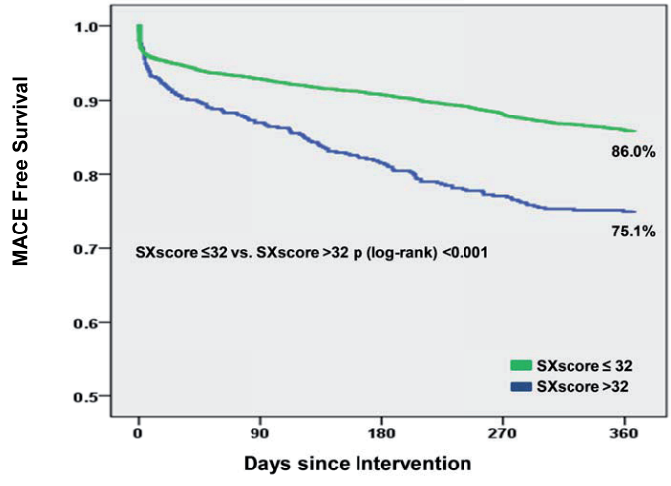
12

Supplementary Figure 2B: Kaplan Meier cumulative curve for death or myocardial infarction at 1-year follow-up amongst patients with a SYNTAX score >32 and ≤32.



Days	0	90	180	270	360
Patients at riskSxscore ≤32	4660	4416	4308	4157	3418
Patients at riskSxscore >32	585	510	479	452	404

Supplementary Figure 2C: Kaplan Meier cumulative curve for repeat revascularization at 1-year follow-up amongst patients with a SYNTAX score >32 and ≤32.



Days	0	90	180	270	360
Patients at risk Sxscore ≤32	4660	4312	4209	4062	3336
Patients at risk Sxscore >32	575	497	466	440	394

Supplementary Figure 2D: Kaplan Meier cumulative curve for major adverse cardiovascular events (MACE) at 1-year follow-up amongst patients with a SYNTAX score >32 and ≤32.

Supplementary References

1. Windecker S, Remondino A, Eberli FR, et al. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. N Engl J Med 2005;353:653-62.
2. Windecker S, Serruys PW, Wandel S, et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet 2008;372:1163-73.
3. Serruys PW, Silber S, Garg S, et al. Comparison of Zotarolimus-Eluting and Everolimus-Eluting Coronary Stents. N Engl J Med 2010;363:123-135.
4. Serruys PW, Ong AT, Morice MC, et al. Arterial Revascularisation Therapies Study Part II - Sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. EuroIntervention 2005;1:147-56.
5. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961-72.
6. Valgimigli M, Percoco G, Malagutti P, et al. Tirofiban and sirolimus-eluting stent vs abciximab and bare-metal stent for acute myocardial infarction: a randomized trial. JAMA 2005;293:2109-17.
7. Valgimigli M, Campo G, Percoco G, et al. Comparison of Angioplasty With Infusion of Tirofiban or Abciximab and With Implantation of Sirolimus-Eluting or Uncoated Stents for Acute Myocardial Infarction: The MULTI-STRATEGY Randomized Trial. JAMA 2008;299:1788-99.
8. Vranckx P, Cutlip D, Mehran R, et al. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. Eurointervention 2010;5:871-874.

Chapter 6.5

Implantation of the biodegradable polymer biolimus eluting stent in patients with high SYNTAX score is associated with decreased cardiac mortality compared to a permanent polymer sirolimus eluting stent. Two year follow-up results from the all-comers LEADERS trial.

EuroIntervention. In press

Joanna J. Wykrzykowska, Scot Garg, Yoshinobu Onuma, Ton de Vries, Marie-Angele Morel, Gerrit-Anne van Es, Pawel Buszman, Axel Linke, Thomas Ischinger, Volker Klauss, Roberto Corti, Franz Eberli, William Wijns, Marie-Claude Morice, Carlo di Mario, Robert Jan van Geuns, Peter Juni, Stephan Windecker, Patrick W. Serruys

ABSTRACT:

Background: The SYNTAX score (SXscore) has been shown to be an effective predictor of clinical outcomes in patients undergoing percutaneous coronary intervention (PCI).

Methods: The SXscore was prospectively collected in 1,397 of the 1,707 patients enrolled in the "all-comers" LEADERS trial (patients post-surgical revascularization were excluded). Post-hoc analysis was performed by stratifying clinical outcomes at 2 year follow-up, according to one of three SXscore tertiles: $SX_{LOW} \leq 8$ (n=464), $8 < SX_{MID} \leq 16$ (n=472) and $SX_{HIGH} > 16$ (n=461).

Results: At 2 year follow-up the rate of major adverse cardiovascular events was 18.4%, 12.0% and 9.4% in the SX_{HIGH}, SX_{MID}, and SX_{LOW} tertile, respectively (HR 1.45; CI 1.21-1.74; p<0.01). There was a significantly higher rate of cardiac death in patients in the highest SXscore tertile (7% SX_{HIGH} vs. 2.4% SX_{MID} vs. 1.8% SX_{LOW}; HR 2.22 (CI 1.5-3.27); p<0.001). Within the SX_{HIGH} tertile the rate of cardiac death was significantly lower in patients treated with the biolimus-eluting stent compared with the sirolimus-eluting stent (4.7% vs. 9.6%, HR 0.48; CI 0.23-0.99; p=0.046).

Conclusions: The SXscore allows prospective risk stratification of 'all-comers' patients undergoing PCI. In addition, the SXscore appears to be able to separate the performance of devices in high risk patient groups.

INTRODUCTION:

The SYNTAX score (SXscore) is a comprehensive angiographic scoring system derived from the coronary anatomy and lesion characteristics[1-3] which was initially designed to quantify coronary lesion complexity. Additional analyses have subsequently demonstrated its ability to predict major adverse cardiac events (MACE) following percutaneous coronary intervention (PCI) in patients with multivessel coronary artery disease at follow-up ranging from one- to five-years.[4-6] At one year follow-up in the ARTS-II study, patients with a SXscore in the highest tertile had a significantly higher rate of MACE compared with patients in the lower tertiles (HR 3.5; CI 1.7-7.4; p=0.0001); while a multivariate analysis demonstrated that the SXscore independently predicted a fourfold increase in the risk of MACE. Furthermore, the SX score also showed a better discrimination ability than the AHA/ACC modified lesion classification (c-statistic 0.67 vs. 0.58, p<0.001).

The SXscore has not only been assessed in patients with complex coronary artery disease[4-6] and left main disease,[7-8] but it has also been demonstrated to be a predictor of peri-procedural myocardial infarction (MI) amongst patients undergoing elective PCI for long lesions and bifurcation lesions.[7] Most recently our group has evaluated its value for risk assessment in the setting of a randomised trial with an 'all-comers' population. In the sub-study of the LEADERS trial (Limus Eluted from A Durable versus ERodable Stent coating), where the SXscore was collected prospectively in 1,397 "all-comer" patients, we reported its prognostic value for MACE events at 1 year follow-up.[8] In the current substudy we assess the value of the SXscore at 2 year follow-up and also assess its ability to discriminate between the performance of two stainless steel drug-eluting stents, one eluting biolimus from a biodegradable polymer and one sirolimus from a durable polymer, in the highest risk patient group.

METHODS:

Study population:

LEADERS was a multicenter European non-inferiority trial comparing the safety and efficacy of the BioMatrix™ Flex biolimus-eluting stent (BES) (Biosensors, Morges, Switzerland) to the Cypher® sirolimus-eluting stent (SES) (Cordis, Warren, NJ, USA) in 1,707 'all-comers' patients. Patients over the age of 18 with chronic stable coronary artery disease or acute coronary syndromes including ST-elevation MI were eligible if they had at least one lesion with ≥50% diameter stenosis and reference vessel diameter 2.25 to 3.5 mm. The aim was for the patient population to reflect real world clinical practice and thus no limits were set on the number or complexity of the lesions stented. The only exclusion criteria were: known allergy to acetylsalicylic acid, clopidogrel, heparin, stainless steel, sirolimus, biolimus or contrast material that cannot be pre-medicated; planned surgery within 6 months of PCI unless the dual anti-platelet therapy could be maintained throughout the peri-surgical period; pregnancy; participation in another trial before reaching the primary end-point and lastly inability to give informed consent. The study complied with the Declaration of Helsinki and was approved by all institutional ethics committees. All patients provided written, informed consent for participation in the trial.

SXscore and angiographic analysis:

From the baseline diagnostic angiogram, each coronary lesion producing ≥50% diameter stenosis in vessels ≥1.5 mm was scored separately and added together to provide the overall SXscore, which was calculated prospectively using the SXscore algorithm that is described in full elsewhere.[1-3] All angiographic variables pertinent to SXscore calculation were computed by independent core laboratory analysts (Cardialysis B.V., Rotterdam, The Netherlands).

The initial description of the SXscore did not report a methodology for calculating the SXscore in patients presenting with an ST-elevation MI or those with in-stent restenosis lesions. Nevertheless, in the present study core lab analysts were blinded to all clinical data and therefore patients presenting with a ST-elevation MI had their occluded infarct related artery scored as an occlusion of unknown duration in the same manner as any chronically occluded artery; a methodology which has subsequently been confirmed as the most appropriate method of SXscoring these patients.[9] No validation of calculating the SXscore has been performed in patients with in-stent restenotic lesions, and they were therefore scored in the same manner as if the lesion was a *de novo* lesion.

Limitations: The methods employed for scoring in-stent restenosed arteries has not been validated, and does not take into account some of the potentially different lesion characteristics of an acutely occluded artery or a restenosed lesion compared to a *de novo* lesion. However these methods do allow the weighted score of the anatomical segment to be recorded, and do allow some of the lesion characteristics to be scored (eg lesion length, tortuosity, calcification etc).

Randomization and Procedures:

Randomization was done centrally after diagnostic cardiac catheterization and before percutaneous coronary intervention (PCI) by use of a telephone allocation service (Limburgia telefonische Antwoord Service BV, 3068 NP Rotterdam, Netherlands). The allocation sequence was computer generated, stratified according to center, and blocked with block sizes of 8 and 16, which varied randomly. Patients were randomly allocated on a 1:1 basis to treatment with BES or SES, and to active angiographic follow-up at 9 months or clinical follow-up only on a 1:3 basis with a factorial design.

BES were available in diameters of 2.25, 2.5, 3.0 and 3.5 mm and in lengths of 8, 11, 14, 18, 24 and 28 mm. SES were available in diameters of 2.25, 2.5, 2.75, 3.0 and 3.5 mm and in lengths of 8, 13, 18, 23, 28 and 33 mm. Balloon angioplasty and stent implantation were performed according to standard technique and direct stenting was allowed. No mixture of drug eluting stents was permitted within a given patient, unless the operator was unable to insert the study stent, in which case crossover to another device of the operator's choice was possible. Before or at the time of the procedure, patients were given ≥75 mg of acetylsalicylic acid, 300-600 mg loading dose of clopidogrel, and unfractionated heparin at a dose ≥5,000 I or 70-100 IU/kg. After the procedure, all patients were advised to take aspirin indefinitely and clopidogrel for at least 12 months. In case of inter-current revascularization procedures requiring stent implantation, treating cardiologists were encouraged to use the study stent. For other details please refer to the primary endpoint manuscript.[10]

Follow-up:

Adverse events were assessed in the hospital and at 1, 6, 9, and 12 and 24 months. One in four patients was asked to return for angiographic follow-up at 9 months.

Study endpoints:

Definitions of all endpoints are provided elsewhere.[10] The primary endpoint of this sub-study was MACE, defined as the composite of cardiac death, MI, and clinically-indicated target vessel revascularization (TVR) within 24-months. Secondary endpoints were any target lesion revascularization (TLR) (both clinically and non-clinically indicated), which was defined as repeat revascularization due to a stenosis within the stent or within a 5 mm border proximal or distal to the stent; any TVR, cardiac death, death from any cause, MI, stent thrombosis (defined according to the Academic Research Council[11]), device success (defined as achievement of a final residual diameter stenosis <50% during the initial procedure), and lesion success (achievement of < 50% stenosis with any approach for PCI).

The pre-specified principal outcome of the angiographic sub-study was in-stent percent diameter stenosis. Secondary angiographic outcomes were in-segment percent diameter stenosis, minimal lumen diameter, late lumen loss, and binary restenosis. Angiographic measurements were obtained within the stented segment (in-stent) and over the entire segment consisting of the stent and 5 mm proximal and distal margins (in segment). Percent diameter stenosis was defined as ([reference vessel diameter-minimal luminal diameter]/reference vessel diameter) X 100%; late lumen loss was defined as the difference between minimal lumen diameter after the procedure and minimal lumen diameter at follow-up; and binary restenosis was defined as a percentage diameter stenosis of ≥50% in the target lesion.

A blinded independent clinical events committee adjudicated all endpoints, and independent study monitors (D-Target, Montagny-pres-Yverdon, Switzerland) verified all case reports from data on-site. Data were store in a database (KIKA Medical, Paris, France), which was maintained by a contract research organization (Cardialysis, Rotterdam, Netherlands) in collaboration with an academic clinical trials unit (CTU Bern, Bern University Hospital, Switzerland). The operators were by necessity aware of the assigned study stent during PCI and angiographic follow-up, but patients and staff involved in follow-up assessment were blinded to the allocated stent type. Angiographic films were centrally assessed at one angiographic core laboratory (Cardialysis, Rotterdam, Netherlands) with assessors unaware of the allocated stent.

Statistical analysis:

A stratified post-hoc analysis of clinical and angiographic outcomes, which was specified after completion of patient recruitment, was performed according to the tertiles of SYNTAX score. The methodology used was similar to that used previously by Valgimigli *et al* in the ARTS-II study, and by Serruys *et al*. in the SYNTAX trial[4-5] as well as by Wykrzykowska *et al.*[8] Dedicated software and visual coronary angiography served to determine the SXscore as previously described.[1-2] All randomized patients without prior surgical revascularisation, in whom the SXscore was collected prospectively (1397/1707), were included in the analysis of primary and secondary clinical endpoints according to

tertiles of SXscore. Analyses of the angiographic sub-study were restricted to lesions from patients who attended follow-up angiography. Angiographic outcomes were analyzed using SAS v8 Proc Mixed for continuous and Proc Genmod for binominal outcomes, taking into account the within-patient correlation structure of these data. We used a Cox proportional hazards model to compare clinical outcomes between the groups. All analyses were performed using SAS 8.02 by a dedicated statistician. All p-values and CIs were two-sided.

RESULTS:

SXscore and baseline characteristics:

The SXscore was collected prospectively in 1,397 of the 1,707 patients (81.8%) enrolled in the LEADERS trial. The predominant reason for not calculating the score was a history of prior surgical revascularisation. In this post-hoc analysis, the 1,397 patients were divided according to their SXscore into tertiles defined as: $SX_{LOW} \leq 8$ (n=467), $8 < SX_{MID} \leq 16$ (n=472) and $SX_{HIGH} > 16$ (n=461).

The baseline clinical and angiographic data according to the three SXscore tertiles has been reported previously and is summarized in **Tables 1 and 2.**[8] Briefly, the SXscore ranged from 1 to 49, with a mean $\pm$ SD of 13.5 ± 8.7, and a median of 12 (inter-quartile range of 12; 7 to 19). Overall, at 1-year, those patients in the highest SXscore tertile had a significantly higher rate of death, TVR, MACE and a trend for higher rates of MI.

Table 1: Baseline clinical characteristics based on SYNTAX score tertiles

Baseline clinical variables, n (%)	SX score <8 N=464	SX score 8-16 N=472	SX score >16 N=461	p-value on Trend (2-sided)
Age >65	210 (45)	224 (47)	239(52)	0.045
Male	346(75)	344(73)	340(74)	0.78
Diabetes	93(20)	117(25)	111(24)	0.14
Current smoking	134(29)	121(26)	126(27)	0.60
Hypertension	353(76)	353(75)	324(70)	0.045
Hypercholesterolemia	314(68)	314(67)	285(62)	0.06
Family history	201(43)	188(40)	168(36)	0.03
Renal insufficiency	17(4)	21(5)	28(6)	0.09
Previous MI	132(28)	145(31)	137(30)	0.67
Previous PCI	179(39)	165(35)	147(32)	0.03
Clinical presentation:				
Stable	146(31)	154 (33)	108 (23)	0.008
Unstable	127(27)	89(19)	88(19)	0.002
ST-elevation MI	46(10)	90(19)	128(28)	<0.001

MI, myocardial infarction; PCI, percutaneous coronary intervention

Table 2: Baseline angiographic characteristics by SYNTAX score tertiles

Angiographic variable, n (%)	SX score <8	SX score 8-16	SX score >16	p-value
Mean no. of diseased lesions per patient, ±SD	1.5±0.7	2.4±1.0	3.5±1.4	<0.001
Mean no. of treated lesions per patient, ±SD	1.2±0.5	1.5±0.7	1.7±0.9	<0.001
Coronary artery treated	162 (35)	242 (51)	296 (64)	<0.001
Left anterior descending artery	140 (30)	144 (31)	164 (36)	0.08
Circumflex	216 (47)	209 (44)	174 (38)	0.007
Right coronary artery				
2-vessel disease	49 (11)	102 (22)	138 (30)	<0.001
3-vessel disease	3 (1)	13 (3)	23(5)	<0.001
Stent type	229 (49)	235 (50)	239 (52)	NS
Biolimus	235 (51)	237 (50)	222 (48)	NS
Sirolimus				
Mean number of implanted stents, ±SD	1.5±0.7	1.9±1.1	2.3±1.4	<0.001
Mean total stent length/patient (mm), ±SD	25.9±16.5	34.2±21.7	42.9±26.2	<0.001
Chronic total occlusion	6 (1)	10 (2)	19 (4)	0.006
Moderate to severe calcification	23 (5)	96 (20)	184(40)	<0.001
Bifurcation lesion	57 (12)	161(34)	184 (40)	<0.001
Use of Glycoprotein 2b3a inhibitors	80 (17)	113 (24)	154 (33)	<0.001

Table 3: Baseline Clinical and Angiographic Characteristics amongst Patients in the Highest SXscore Tertile

Baseline clinical variables, n(%)	BioMatrix Flex™ 239 patients	Cypher® Select™ 222 patients	P Value
Age >65, mean±SD	65.8±10.6	65.2±11.3	0.59
Male	175 (73)	165 (74)	0.83
Hypertension	166 (70)	158 (72)	0.76
Diabetes mellitus	65 (27)	46 (21)	0.13
-insulin dependent	28 (12)	21 (10)	0.45
Hypercholesterolemia	139 (58)	146 (66)	0.10
Family history	86 (36)	82 (37)	0.85
Smoking	61 (26)	65 (29)	0.40
Previous MI	70 (29)	67 (30)	0.84
Previous PCI	78 (33)	69 (31)	0.76
-with drug eluting stent	24 (10)	22 (10)	1.00
Previous CABG	4 (2)	4 (2)	1.00
Chronic stable angina	52(22)	56 (25)	0.38
Acute coronary syndrome	158 (66)	155 (70)	0.43
Unstable angina	48 (20)	40 (18)	0.64
Non ST-elevation MI	50 (21)	47 (21)	1.00
ST-elevation MI	60 (25)	68 (31)	0.21
Left ventricular function %, mean±SD	54±10	53±12	0.21
Mean number of stented lesions per patient, ±SD	1.9±1.0	2.0±1.1	0.25
Mean number of stents implanted per patient, ±SD	2.3±1.3	2.4±1.5	0.39
Mean stent diameter, ±SD	2.9±0.4	2.9±1.4	0.70

MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; SD, standard deviation

Two-year clinical outcomes for the overall study population:

Kaplan Meier survival curves for clinical outcomes out to 2-year follow-up are shown in **Figure 1**. At 2-years the rate of MACE was 9.4%, 12.0% and 18.4%, in the SX_{LOW}, SX_{MID}, SX_{HIGH} tertiles, respectively (HR 1.45; 95% CI 1.21-1.74; p<0.01, **Figure 1A**). Similarly, there were also significantly higher rates of cardiac death, clinically driven TVR and TLR amongst those patients in the highest SXscore tertile (**Figures 1B-1D**). MI rates were highest in those patients in the SX_{MID} and SX_{HIGH} groups (6.2%) compared to those in the SX_{LOW} group (4.3%) (HR 1.18; CI 0.89-1.56; p=0.24, **Figure 1E**).

Differential performance of the BES and SES in the SX_{HIGH} group:

The analyses of outcomes in patients treated with BES versus SES have been performed in all three tertiles of the SXscore, however, significant between stent-differences were only observed in the SX_{HIGH} group (highest risk) and are reported here (**Figure 2**). Baseline clinical and angiographic characteristics, and angiographic outcomes for the SX_{HIGH} group treated with BES versus SES are reported in **Tables 3 and 4**. There were no significant differences between the BES and SES treated group in terms of baseline characteristics and there was an equal distribution of the two devices between the SXscore tertiles (**Table 2**).

Figure 1A: MACE# Rate

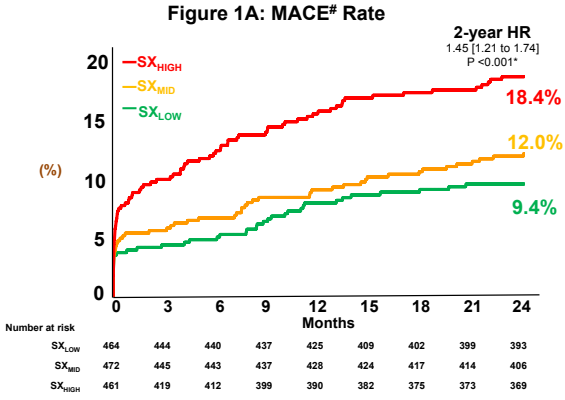


Figure 1B. Cardiac Death

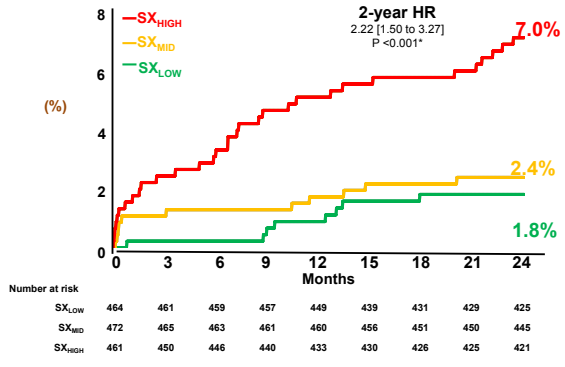


Fig 1C: Clinically Indicated TVR Rate

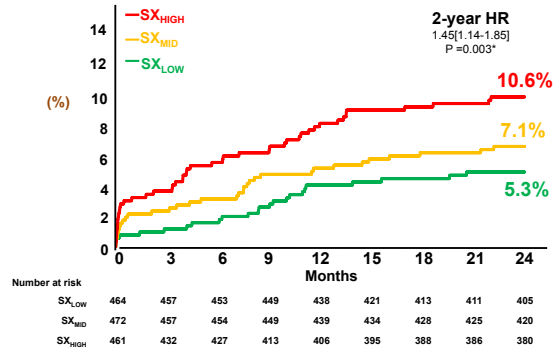


Fig 1D: TLR Rate

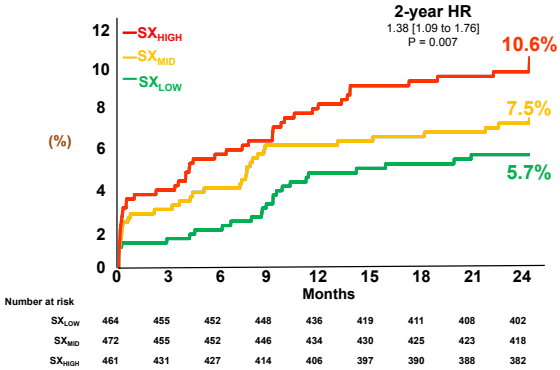


Fig1E: Myocardial Infarction

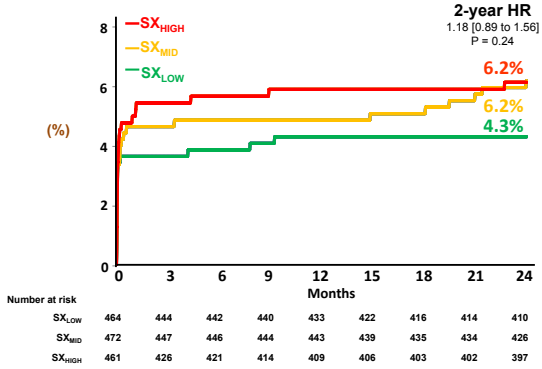


Figure 1: Kaplan Meier survival curves for (A) major adverse cardiovascular events (MACE); (B) cardiac death; (C) clinically indicated target vessel revascularization (TVR); (D) target lesion revascularization (TLR) and (E) myocardial infarction stratified according to SXscore tertiles.
MACE, a composite of cardiac death, MI, or clinically indicated TVR.
*P values for superiority

Table 4: Angiographic Follow-up Results amongst Patients in the Highest SXscore Tertile

	Biolimus Stent (75 lesions)	Sirolimus Stent (73 lesions)	P value
Minimal Lumen Diameter			
in-stent (mm)	2.19 ± 0.61	2.12± 0.68	0.53†
in-segment (mm)	1.97 ± 0.57	1.88 ± 0.63	0.34†
Diameter stenosis			
in-stent (%)	21.7 ± 16.7	22.4 ± 19.2	0.82†
in-segment (%)	27.8 ± 16.1	29.2 ± 17.3	0.60†
Late lumen loss			
in-stent (mm)	0.08 ± 0.36	0.13 ± 0.50	0.51†
in-segment (mm)	0.08 ± 0.35	0.09 ± 0.45	0.84†
Binary restenosis			
in-stent (%)	4 ± 5.3	4 ± 5.5	1.00*
in-segment (%)	5 ± 6.7	4 ± 5.5	1.00*

† Two sided t-test, equal variance

* Fisher exact test used for p-value, 9 5% CI based on t-test

Fig 2A. MACE* Rate

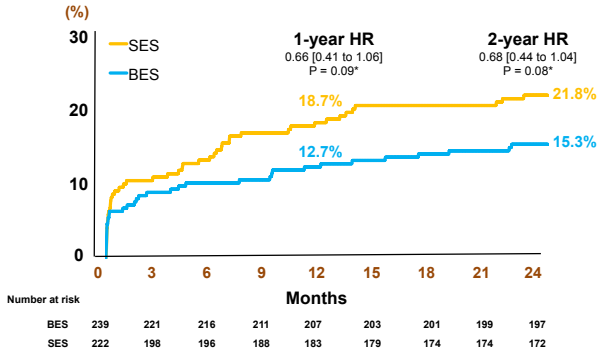
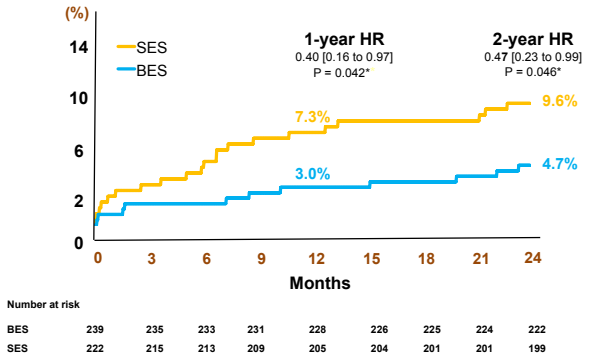
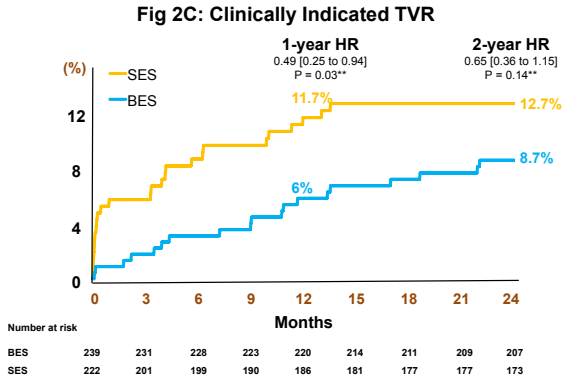
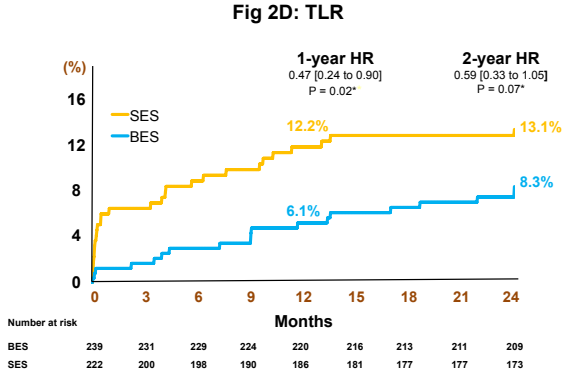


Figure 2B. Cardiac Death







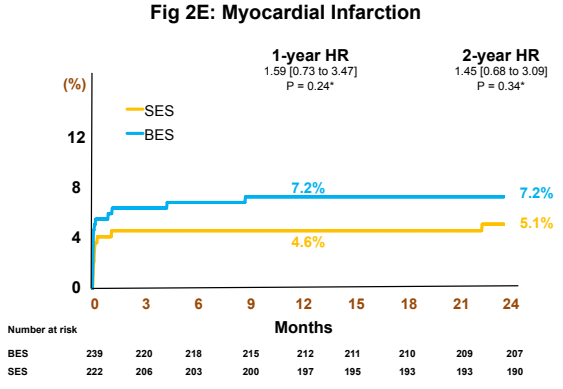


Figure 2 Kaplan Meier survival curves for (A) major adverse cardiovascular events (MACE); (B) cardiac death; (C) clinically indicated target vessel revascularization (TVR); (D) target lesion revascularization (TLR) and (E) myocardial infarction amongst patients in the highest SYNTAX score tertile (>16) stratified according to stent type.

#MACE, a composite of cardiac death, MI, or clinically indicated TVR.

*P values for superiority

Fig 3A: Definite Stent Thrombosis

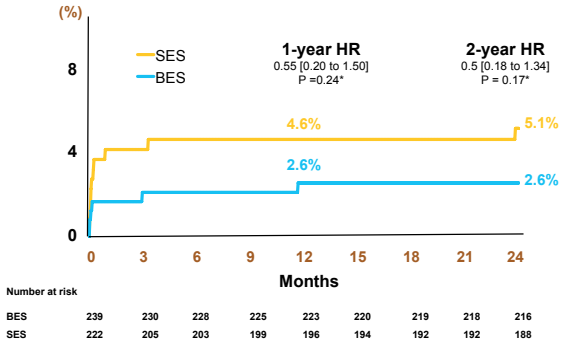


Fig 3B: Definite and Probable Stent Thrombosis

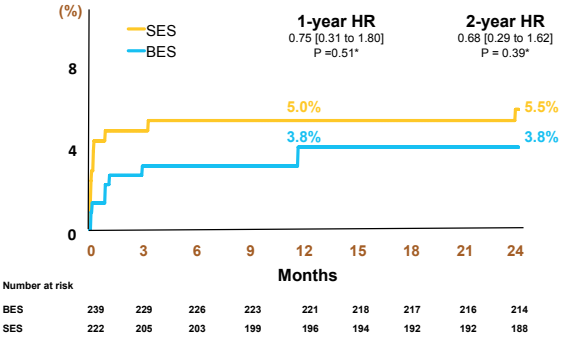
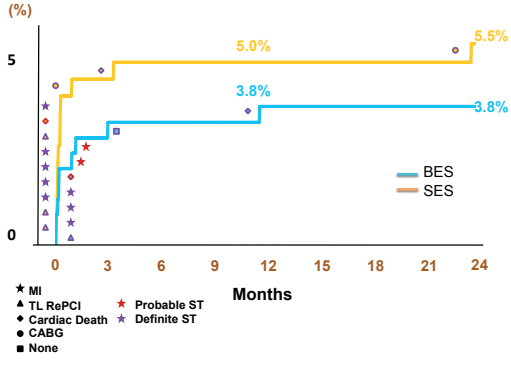


Fig 3C: Definite and Probable Stent Thrombosis and Resulting Worst Clinical Event



Overall MACE rate was 15.3% in SX_{HIGH} group treated with BES versus 21.8% in SX_{HIGH} group treated with SES (HR 0.68; 95% CI: 0.44-1.04; p=0.08, **Figure 2A**). Within the SX_{HIGH} tertile the rate of cardiac death was significantly lower in patients treated with BES 4.7% versus SES 9.6% (HR 0.48; 95% CI: 0.23-0.99; p=0.046, **Figure 2B**). Interaction between SXscore tertile and stent type in a five-covariate model was statistically significant (HR=0.37; p=0.036) and in a three-covariate model showed a trend

Fig 3D: Possible Stent Thrombosis

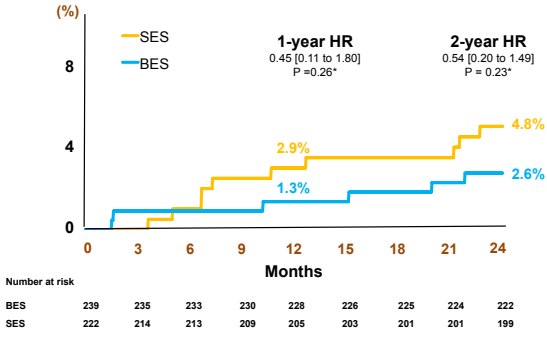


Fig 3E: All Stent Thrombosis

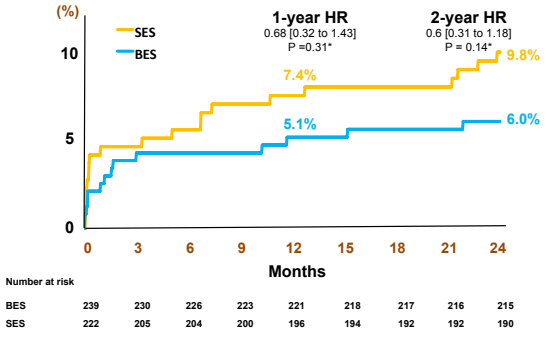


Fig 3F. Stent Thrombosis/ Cardiac Death

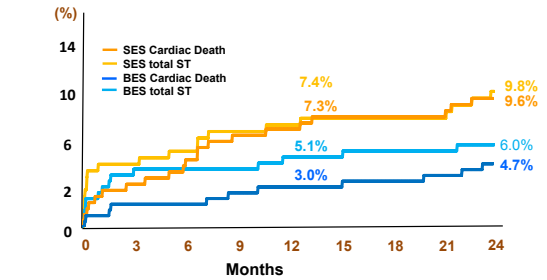


Figure 3: Stent thrombosis rates amongst patients in the highest SYNTAX score tercile (>16). *P values for superiority

towards statistical significance (HR 0.5; p=0.08). Clinically driven TVR (8.7% vs. 12.7%; HR=0.65, 95% CI: 0.36-1.15; p=0.14) and TLR rates (8.3% vs. 13.1% for TLR; HR 0.59; 95% CI 0.33-1.05; p=0.07) also tended to be lower in the BES treated group (**Figures 2C** and **D**). The rate of MI remained numerically higher with BES, which was driven by early events occurring within the first 9-months of stent implantation. Of note, there were no additional MIs with BES between 1- and 2-year follow-up com-

pared with an increase in MI rate from 4.6% to 5.1% between year 1 and 2 in the SES treated group (**Figure 2E**).

Stent thrombosis rates for the SX_{HIGH} group at two year follow-up:
Definite stent thrombosis rates were 2.6% in the BES treated group and 5.1% in the SES treated group within the SX_{HIGH} tertile at two years (HR 0.5; 95% CI 0.18-1.34; p=0.17, **Figure 3A**). Notably, there were no further definite stent thrombosis events in the BES treated group between year 1 and 2. In contrast, the definite stent thrombosis rate increased from 4.6% to 5.1% in the SES treated group. Combined definite and probable stent thrombosis rates were 3.8% (n=9) for BES and 5.5% (n=12) for SES (HR 0.68; 95% CI 0.29-1.62; p=0.39, **Figures 3B** and **Figure 3C**). Most of the events occurred early after stent implantation (**Figure 3C**). Possible stent thrombosis rates were 2.6% in the BES group versus 4.8% in the SES group (HR 0.54; 95% CI 0.2-1.49; p=0.23, **Figure 3D**). The rate of overall stent thrombosis in the SX_{HIGH} group was 6.0% (n=14) in patients treated with BES and 9.8% (n=21) in patients treated with SES (HR 0.6; 95% CI 0.31-1.18; p=0.14, **Figure 3E**). The increase in stent thrombosis in SX_{HIGH} group between year 1 and 2 was 0.9% for patients treated with BES and 2.4% for patients treated with SES. When curves for cardiac death rate and overall stent thrombosis rate were superim-

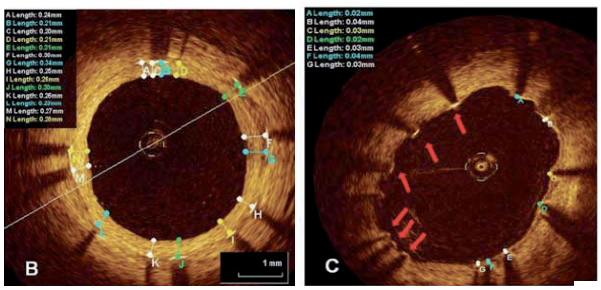


Figure 4: OCT images of strut coverage (from Barlis et al., 2010)

posed, most of the cardiac death events could be accounted for by stent thrombosis events, implying that reduced thrombosis rates may be the mechanism responsible for the reduced cardiac mortality rate in patients treated with BES in the SX_{HIGH} tertile (**Figure 3F**), although this remains speculative.

DISCUSSION:

The SXscore has previously been applied in both the SYNTAX trial and the ARTS-II study, both of which demonstrated the good predictive value of the SXscore in patients with multivessel disease, with those patients in the highest tertile group having significantly more MACE events during short[4-5] and long-term follow-up.[6] More recently we reported the utility of the SXscore as a predictor

of MACE, including cardiac death, in an "all-comers" population of the LEADERS trial at 1 year follow-up.[8] Patients with a high SXscore (SXscore>16) had a 50% higher chance of a MACE event, and a 154% higher chance of cardiac death at one year. A high SX score conferred a 2.5 fold increase in cardiac death, which remained true even after adjustment for other risk factors for cardiac death such as diabetes, presentation with acute coronary syndrome, beta-blocker use and stent type. Here we report that the predictive value of SXscore remains robust at 2 year follow-up in this all-comers patient population.

The major finding of our study is that the SXscore may be an appropriate tool to stratify risk in all patients undergoing PCI out to medium-term follow-up. The second finding in this study is that SXscore appears to be able to discriminate between the performances of different types of stents in high risk lesions. Patients with high SXscores treated with BES had a lower risk of MACE and cardiac death at two year follow-up compared with patients treated with SES. These results suggest that the SXscore may be useful tool in the future clinical trials of new stent devices, particularly those with an "all-comers" design.

The mechanism of this superior performance with BES compared to SES in the high risk lesions and patient populations remains to be established. It remains a possibility that the differences in outcome may be a play of chance considering the small number of patients in the high SXscore tertile. Speculatively, the stent thrombosis data presented here, and the previously reported optical coherence tomography data[12] (**Figure 4**), suggest that the reduction in mortality rate by treatment with BES may be explained by the better stent strut coverage, and less acquired malapposition seen in patients treated with BES compared with SES.

Overall the superior performance of BES compared to SES in these complex patients provides additional data to support the concepts behind the newer generation drug-eluting stents, which were primarily designed to improve overall safety following the concerns raised with first generation devices.[13] In comparison to the permanent polymer present on SES which remains exposed to the coronary artery environment long after its useful function has been served, the polymer on the biolimus-eluting stent completely biodegrades within 6-9months of stent implantation, leaving a bare stainless steel stent. Although the lower stent thrombosis rates, and cardiac mortality observed in this study are encouraging, additional, larger powered studies are required before definitive conclusions can be reached.

LIMITATIONS:

This analysis is subject to inherent limitations of all subgroup analyses such as statistical under-powering. As such it can only be viewed as hypothesis-generating. Patients with prior coronary artery bypass surgery have not been included in the current analysis as the SXscore is algorithm is only currently available for patients with *de novo* disease. Modifications to the SXscore that will allow for risk stratification in patients post-CABG are being developed by our group. While the SXscore

was collected prospectively, the analysis of outcomes was performed post-hoc. In addition, while the SXscore has not been validated in patients post-PCI these patients have been included in this analysis.

CONCLUSION:

This study demonstrates that the prognostic value of the SYNTAX score is valid for all patients with *de novo* coronary artery disease undergoing percutaneous revascularisation out to two-years of follow-up. A potential new application of the SYNTAX score is discriminating the performance of novel versus first-generation stents in high risk lesions in future clinical trials.

REFERENCES:

1. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Van Dyck N, Russell ME, Mohr F, Serruys P. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention.* 2005;1:219-227.
2. Serruys P, Onuma Y, Garg S, Sarno G, Van den Brand M, Kappetein AP, van Dyck N, Mack MJ, Holmes Jr DR, Feldman TE, Morice MC, Colombo A, Bass EJ, Leadley K, Dawkins K, van Es GA, Morel MA, Mohr F. Assessment of the SYNTAX score in the Syntax study *Eurointervention.* 2009;5:50-56.
3. SYNTAX working-group. SYNTAX score calculator: www.syntaxscore.com. Launched 19th May 2009.
4. Valgimigli M, Serruys PW, Tsuchida K, Vaina S, Morel MA, van den Brand MJ, Colombo A, Morice MC, Dawkins K, de Bruyne B, Kornowski R, de Servi S, Guagliumi G, Jukema JW, Mohr FW, Kappetein AP, Wittebols K, Stoll HP, Boersma E, Parrinello G. Cyphering the complexity of coronary artery disease using the syntax score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. *Am J Cardiol.* 2007;99:1072-1081.
5. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med.* 2009;360:961-972.
6. Serruys PW, Onuma Y, Garg S, Vranckx P, De Bruyne B, Morice MC, Colombo A, Macaya C, Richardt G, Fajadet J, Hamm C, Schuijer M, Rademaker T, Wittebols K, Stoll HP. 5-Year Clinical Outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the Sirolimus-Eluting Stent in the Treatment of Patients With Multivessel De Novo Coronary Artery Lesions. *J Am Coll Cardiol.* 2010;55:1093-1101.
7. van Gaal WJ, Ponnuthurai FA, Selvanayagam J, Testa L, Porto I, Neubauer S, Banning AP. The Syntax score predicts peri-procedural myocardial necrosis during percutaneous coronary intervention. *Int J Cardiol.* 2009;135:60-65.
8. Wykrzykowska J, Garg S, Girasis C, de Vries T, Morel MA, van Es GA, Buszman P, Linke A, Ischinger T, Klauss V, Corti R, Eberli F, Wijns W, Morice MC, di Mario C, van Geuns RJ, Juni P, Windecker S, Serruys PW. Value of the Syntax Score (SX) for Risk Assessment in the "All-comers" Population of the Randomized Multicenter Leaders Trial. *J Am Coll Cardiol.* 2010;56:272-277.
9. Garg S, Sarno G, Serruys PW, Rodriguez AE, Bolognese L, Anselmi M, de Cesare N, Colangelo S, Moreno R, Gambetti S, Monti M, Bistrot L, Bressers M, Garcia-Garcia HM, Parrinello G, Campo G, Valgimigli M. Prediction of 1-year clinical outcomes using the SYNTAX score in patients with acute ST-elevation myocardial infarction undergoing primary PCI: A sub-study of the STRATEGY and MULTI-STRATEGY trials. *J Am Coll Cardiol Intv.* 2011;4:66-75.
10. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Juni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet.* 2008;372:1163-1173.
11. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115:2344-2351.
12. Barlis P, Regar E, Serruys PW, Dimopoulos K, van der Giessen WJ, van Geuns RJ, Ferrante G, Wandel S, Wind-

ecker S, van Es GA, Eerdmans P, Juni P, di Mario C. An optical coherence tomography study of a biodegradable vs. durable polymer-coated limus-eluting stent: a LEADERS trial sub-study. *Eur Heart J.* 2010;31:165-176.

13. Garg S, Serruys PW. Benefits of and safety concerns associated with drug-eluting coronary stents. *Expert Rev Cardiovasc Ther.* 2010;8:449-470.

Chapter 6.6

SYNTAX score and Clinical SYNTAX score as predictors of very long term clinical outcomes in patients undergoing percutaneous coronary interventions: A sub-study of SIRolimus-eluting stent compared with pacliTAXel-eluting stent for coronary revascularization (SIRTAX) trial

Submitted

Chrysafios Girasis, Scot Garg, Lorenz Räber, Giovanna Sarno, Marie-Angèle Morel, Hector M. Garcia-Garcia, Patrick W. Serruys, Stephan Windecker

ABSTRACT

Aims: To investigate the ability of SYNTAX score and Clinical SYNTAX score (CSS) to predict very long-term outcomes in an all-comers population receiving drug-eluting stents.

Methods and Results: The SYNTAX score was retrospectively calculated in 848 patients enrolled in the SIRolimus-eluting stent compared with pacliTAXel-Eluting Stent (SIRTAX) trial. The CSS was calculated using age, and baseline left ventricular ejection fraction and creatinine clearance. A stratified post-hoc comparison was performed for mortality, cardiac death, myocardial infarction (MI), ischemia-driven target lesion revascularization (TLR), definite stent thrombosis and major adverse cardiac events (MACE) at 1- and 5-year follow-up.

Tertiles for SYNTAX score and CSS were defined as SSLOW≤7, 7<SSMID≤14, SSHIGH>14 and CSSLOW≤8.0, 8.0<CSSMID≤17 and CSSHIGH>17 respectively. MACE rates were significantly higher in SSHIGH compared to SSLOW at 1-year (14.2% vs. 6.9%, P<0.01) and 5-year follow-up (24.2% vs. 12.5%, P<0.01), which was also seen at 5 years for mortality, cardiac death, MI and TLR. Within SSHIGH, 5-year MACE increased with use of paclitaxel- compared to sirolimus-eluting stents (29.3% vs. 19.3%, P=0.04). Stratifying outcomes across CSS tertiles confirmed and augmented these results. SYNTAX score was an independent predictor of 5-year MACE; categorical CSS was an independent predictor for 5-year MACE and mortality. Areas-under-the-curve for the SYNTAX score and CSS for 5-year MACE were 0.61 and 0.62, and for 5-year mortality were 0.58 and 0.66, respectively.

Conclusion: SYNTAX score and CSS effectively stratified risk for very long-term adverse clinical outcomes in an all-comers population receiving drug-eluting stents. Predictive accuracy for 5-year mortality was improved using CSS.

INTRODUCTION

The SYNTAX score is a lesion based angiographic scoring system originally devised to grade the complexity of coronary artery disease[1] and thereby facilitate consensus in the study of a diagnostic angiogram between surgeons and interventional cardiologists. In the SYNTAX trial[2], it proved effective in predicting clinical outcomes after elective percutaneous coronary intervention (PCI) procedures in patients with three-vessel and/or left main coronary artery disease.[3] A number of reports have subsequently assessed the predictive ability of the SYNTAX score in patient cohorts with a varying extent of coronary artery disease undergoing both elective and emergent PCI procedures.[4-9] These previous studies have been limited however, by the reporting of outcomes at only short to medium term follow-up.

Being solely based on angiographic variables, the SYNTAX score cannot account for the variability related to clinical factors which are widely acknowledged to impact on long-term outcomes, such as the patients' age [10], left ventricular ejection fraction[11] and renal function.[12] A clinical score incorporating the aforementioned variables, the ACEF score, has been retrospectively validated in patients undergoing elective coronary artery bypass grafting (CABG) operations.[13] Integration of this score, modified through the replacement of serum creatinine with creatinine clearance, with the SYNTAX score, in the clinical SYNTAX score (CSS), has recently been shown[14] to improve the predictive ability for adverse clinical outcomes after elective PCI procedures in the ARTS-II study population. Information regarding the predictive accuracy of this score in a larger, all-comers population during short- and long-term is however currently lacking.

The SIRolimus-eluting stent compared with pacliTAXel-Eluting Stent (SIRTAX) trial[15] was a prospective, observer-blind, randomized controlled study comparing the safety and efficacy of sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) in 1,012 patients undergoing PCI for either stable angina or an acute coronary syndrome. This study design offers a convenient setting for describing the distribution of the SYNTAX score and CSS in an all-comers population who presented with less complicated disease compared to the SYNTAX and ARTS II trials. Furthermore, the availability of 5-year clinical outcomes permits a more robust evaluation of both scores in order to confirm their potential to risk stratify clinical outcomes at long- and very long-term follow-up after the implantation of drug-eluting stents.

METHODS

Patient population and coronary intervention

The design of the SIRTAX trial has been previously described.[15] Patients were eligible to participate if they presented at least one lesion with percent diameter stenosis ≥50%, in a vessel with a reference diameter between 2.25 and 4.00 mm that was suitable for stent implantation. There were no limitations on the number of lesions treated, number of vessels diseased or on the length of the lesions. The study complied with the Declaration of Helsinki regarding investigation in humans and

was approved by the institutional ethics committees at the participating centers. Written informed consent was obtained from each patient before enrollment. There was no industry involvement in the design, conduct or analysis of the study.

Patients were randomly assigned on a 1:1 basis to treatment with SES (Cypher®; Cordis, Warren, NJ) or PES (Taxus®, Boston Scientific, Natick, MA). No mixture of drug-eluting stents was allowed within a given patient. All procedures were performed according to interventional standards at the time. Before or at the time of the procedure, patients received at least 100 mg of aspirin, a 300 mg loading dose of clopidogrel, and unfractionated heparin (70–100 U/kg of body weight). After the procedure, all patients were advised to maintain aspirin lifelong, and clopidogrel therapy was prescribed for 12 months irrespective of stent type.

SIRTAX end-points and definitions

Adverse events were assessed at multiple end-points including 1 and 5 years after the intervention. An independent clinical events committee unaware of the patients' treatment assignments adjudicated all endpoints. The pre-specified primary end point was a composite of major adverse cardiac events (MACE) including death from cardiac causes, myocardial infarction (MI), and ischemia-driven target lesion revascularization (TLR). The diagnosis of myocardial infarction was based on the presence of new Q waves of at least 0.4 seconds duration in ≥2 contiguous leads and an elevated creatine kinase MB fraction. In the absence of pathologic Q waves, the diagnosis of MI was based on an increase in the creatine kinase level to more than twice the upper limit of the normal range with an elevated level of creatine kinase MB or troponin I. TLR was defined as an intervention (either surgical or percutaneous) to treat a stenosis within the stent or within the 5-mm borders adjacent to the stent. Revascularization was considered to be driven by ischemia, if percent diameter stenosis was ≥50% on the basis of quantitative coronary angiography in the presence of ischemic signs or symptoms, or ≥70% even in the absence of ischemic signs or symptoms.

Stent thrombosis was diagnosed as an acute coronary syndrome with angiographic documentation of either target vessel occlusion or thrombus within or adjacent to the previously stented segment; applying Academic Research Consortium recommendations,[16] definite stent thrombosis was documented.

SYNTAX score and angiographic analysis

The SYNTAX score algorithm, which is described in full elsewhere and is available on the SYNTAX score website (www.syntaxscore.com), was employed to retrospectively score all coronary lesions deemed to have a percent diameter stenosis ≥50%, in vessels ≥1.5 mm. All angiographic variables pertinent to SYNTAX score calculation were computed by 2 experienced interventional cardiologists (CG, SG) on diagnostic angiograms obtained before the procedure. In case of disagreement, the opinion of a third analyst (GS) was obtained and the final decision was made by consensus. Analysts were blinded to procedural data and clinical outcome. The final score was calculated on a patient basis from the individual lesion scores, which were saved in a dedicated database, and was not made available to the analysts until after the completion of the study. Patients with acute myocardial infarctions

were not included in the SYNTAX trial. In the context of our study the culprit lesions were scored using the angiographic views of the infarct-related arteries before any intervention; in the absence of flow these were scored as total occlusions of <3-months' duration.[9] Patients with prior CABG operation were excluded from the analysis; a dedicated amendment for calculating the score in the presence of grafts has not been made available yet. Finally, in-stent restenosis lesions were scored as de novo ones.

CSS

The modified ACEF score was retrospectively calculated,[14] based on the patients' left ventricular ejection fraction, age and creatinine clearance derived using the Cockcroft-Gault equation.[17] Respective methodology has been amply described elsewhere. Values for variables included in the modified ACEF score were recorded before the index PCI. CSS was calculated multiplying the value of SYNTAX score by the modified ACEF score.

Statistics

Statistical analysis was performed using SPSS 16.0 for Windows (SPSS Inc, Chicago, IL, USA). The scores' distributions were preemptively checked for normality with the one-sample Kolmogorov-Smirnov test; tertile values were reported. Continuous variables are presented as mean ± 1 standard deviation (SD) or median values (25th to 75th percentile=inter-quartile range [IQR]); categorical variables are displayed as counts and/or percentages. Baseline characteristics and procedural data were compared across SYNTAX score tertiles without taking into account the random allocation to SES or PES. Comparisons were performed with one-way analysis of variance (ANOVA) for continuous variables and with the chi-square test for categorical variables. Cumulative event rates at 1- and 5-years follow-up were estimated by means of the Kaplan–Meier method. All-cause mortality, MACE, cardiac death, TLR, MI and definite stent thrombosis rates were compared across SYNTAX score and CSS tertiles according to the Cox proportional-hazards model; the assumption of proportional hazards was verified by visual inspection of the log-minus-log curves. Crude hazard ratios (HRs) and corresponding 95% confidence intervals are reported. Independent predictors of 5-year MACE and all-cause mortality were sought; any variable among baseline or procedural characteristics, including SYNTAX score and CSS, significant beyond the level of P=0.10 in univariate analysis was entered into a multivariate backward stepwise model. Crude and adjusted hazard ratios and corresponding 95% confidence intervals are reported for qualifying variables.

A stratified comparison of clinical outcome between SES and PES was also performed across SYNTAX score and CSS tertiles using Cox regression analysis. To determine whether there was an interaction between treatment arm and scores' tertiles, likelihood ratio tests were used.

Predictive accuracy of SYNTAX score and CSS was assessed for 5-year MACE and all-cause mortality. Receiver-operating characteristic (ROC) curves were constructed and the respective area-under-the-curve was assessed. An area of 1.0 would indicate perfect discrimination, whereas an area of 0.5 indicates total absence of discriminating power. All statistical tests were two-sided and a P value <0.05 was considered statistically significant.

RESULTS

Post-hoc stratified analysis was performed for 848 patients (1792 lesions). Scores were not evaluable in 91 cases due to prior CABG; 30 angiograms were not available for analysis and in 27 cases, either the angiographic study was incomplete or lesions were not fully evaluable in the acquired views. Finally in 16 cases, data on creatinine clearance could not be retrieved, consequently CSS could not be calculated; hence these cases were left out of the analysis, in order to have homogeneous databases for both scores.

The SYNTAX score ranged from 1 to 42, with a mean±SD of 11.7±7.3, and a median of 10 (IQR=8). The CSS ranged from 0.7 to 272.2, with a mean+SD of 17.4±20.5, and a median of 11.6 (IQR=14.8). Both scores were non-parametric and their distribution was skewed to the right (**Figure 1**). Tertiles for SYNTAX score and CSS were defined as $SS_{LOW} \leq 7$, $7 < SS_{MID} \leq 14$, $SS_{HIGH} > 14$ and $CSS_{LOW} \leq 8.0$, $8.0 < CSS_{MID} \leq 17$ and $CSS_{HIGH} > 17$ respectively.

Baseline characteristics and risk factors stratified across SYNTAX score tertiles are reported in **Table 1** and data pertinent to the procedure and the score calculation are reported in **Table 2**. Patient age was significantly lower in SS_{LOW}; whilst creatinine clearance and left ventricular ejection fraction were significantly lower in SS_{HIGH} . Patients in the high tertile had a significantly higher prevalence of diabetes and multivessel coronary artery disease, with acute coronary syndromes the primary indication for PCI in this subgroup. The numbers of lesions (both overall and the treated ones) were as expected higher in the SS_{MID} and SS_{HIGH} tertiles compared to the SS_{LOW}. Increasing angiographic complexity was reflected by the increased frequency of adverse angiographic characteristics (bi- and trifurcations, total occlusions), and the significantly longer total implanted stent length in patients in the higher tertiles.

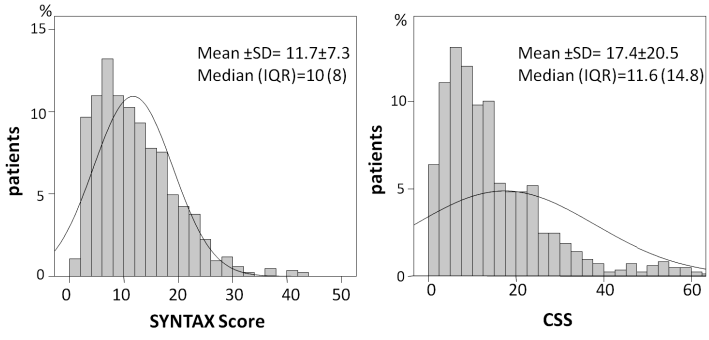


Figure 1: Scores' distribution in the SIRTAX trial population. Histograms of SYNTAX score (left side) and clinical SYNTAX score (CSS-right side) with superimposed normal curves; in both cases the distribution is skewed to the right. Histogram for CSS is truncated at the 98th percentile value. Mean±SD values and median values plus inter-quartile range (IQR) are reported.

Table 1: Baseline clinical characteristics

Characteristic	SS≤7 n=293	7<SS≤14 n=287	SS>14 n=268	P-value
Age (years ±SD)	60.7±10.6	61.4±11.2	63.7±11.3	0.004
Male gender, n (%)	218 (74.4)	219 (76.3)	211 (78.7)	0.48
Body Mass Index ±SD	27.4±4.2	27.4±4.0	27.0±3.8	0.41
Diabetes mellitus, n (%)	45 (15.4)	50 (17.4)	66 (24.6)	0.04
Hypertension, n (%)	171 (58.4)	175 (61.0)	160 (59.7)	0.85
Hyperlipidemia, n (%)	176 (60.1)	159 (55.4)	146 (54.5)	0.66
Current smoking, n (%)	124 (42.3)	100 (34.8)	93 (34.7)	0.41
Previous MI, n (%)	73 (24.9)	78 (27.2)	73 (27.2)	0.56
Previous PCI, n (%)	51 (17.4)	51 (17.8)	48 (17.9)	0.94
Peripheral vascular disease, n (%)	19 (6.5)	17 (5.9)	13 (4.9)	0.84
Stable angina pectoris, n (%)	163 (55.6)	115 (40.1)	108 (40.3)	<0.001
Acute coronary syndromes, n (%)	130 (44.4)	172 (59.9)	160 (59.7)	<0.001
Unstable angina, n (%)	14 (4.8)	23 (8.0)	12 (4.5)	
Non ST-segment elevation MI, n (%)	74 (25.3)	61 (21.3)	63 (23.5)	
ST-segment elevation MI, n (%)	42 (14.3)	88 (30.7)	85 (31.7)	
Multi-vessel coronary artery disease, n (%)	96 (32.8)	107 (58.2)	209 (78.0)	<0.001
Left ventricular ejection fraction ±SD	60.2±9.4	56.8±11.4	53.3±12.6	<0.001
Serum creatinine (mg/dl ±SD)	0.93±0.33	0.95±0.54	1.02±0.83	0.14
Creatinine clearance (ml/min/1.73m2 ±SD)	98.6±34.9	99.5±35.8	91.6±34.8	0.02

MI=myocardial infarction, PCI=Percutaneous coronary intervention, SD=standard deviation, SS= SYNTAX score

Stratified clinical outcome

One-year outcome data across SYNTAX score tertiles is reported in **Table 3**. The primary endpoint (MACE), driven mainly by TLR, was significantly higher in SS_{HIGH} compared to SS_{LOW} (14.2% vs. 6.9%, HR 2.17 [1.27-3.74], *P*<0.01). There was no significant difference in all-cause mortality between SYNTAX score tertiles (overall *P*=0.20). Definite stent thrombosis rates were similar between SS_{MID} and SS_{HIGH}, and not significantly higher compared to SS_{LOW} (*P* value 0.11 and 0.14 respectively).

Five-year outcomes across SYNTAX score tertiles are shown in **Figure 2**. MACE rates were significantly higher in SS_{HIGH} compared to SS_{LOW} (24.2% vs. 12.5%, HR 2.10 [1.40-3.16], *P*<0.01); which was also the case for the endpoints of all-cause mortality, cardiac death, MI and TLR rates. Event rates did not differ significantly between SS_{MID} and SS_{HIGH}; MI and definite stent thrombosis rates were in fact numerically higher in SS_{MID} compared to SS_{HIGH} (8.7% vs. 8.1%, *P*=0.83 and 5.8% vs. 4.2%, *P*=0.43 respectively). There was a clearer separation between Kaplan-Meier curves for all-cause mortality; however the difference between SS_{HIGH} and SS_{MID} did not reach statistical significance (*P*= 0.16).

Stratifying outcomes across CSS tertiles (**Table 4**) led to similar results for the comparisons between high and low score tertiles. However in this analysis, event rates for MACE and TLR were significantly higher in CSS_{HIGH} compared to both CSS_{MID} and CSS_{LOW} at 1- and 5-year follow-up; this held also for all-cause mortality, cardiac death and MI at 5 years. Definite stent thrombosis rates were directionally but not significantly higher in CSS_{HIGH} compared to both CSS_{MID} and CSS_{LOW} at 1- and 5-year follow-up.

Table 2: Procedural characteristics and lesions adjudicated in SYNTAX score (SS)

Characteristics per patient	SS≤7 n=293	7<SS≤14 n=287	SS>14 n=268	P-value
Mean number of lesions ±SD	1.4±0.6	2.1±0.9	2.9±1.2	<0.001
Bifurcation-trifurcation lesions ±SD	0.1±0.3	0.6±0.6	0.9±0.8	<0.001
Total occlusions ±SD	0.1±0.3	0.3±0.5	0.6±0.6	<0.001
Lesions treated ±SD	1.2±0.5	1.4±0.6	1.5±0.6	<0.001
1 lesion treated, n (%)	237 (80.9)	180 (62.7)	150 (56.0)	
2 lesions treated, n (%)	49 (16.7)	91 (31.7)	99 (36.9)	<0.001
3 lesions treated, n (%)	7 (2.4)	16 (5.6)	19 (7.1)	
Mean number of stents ±SD	1.1±0.3	1.2±0.4	1.2±0.6	<0.001
Total stent length ±SD	20.5±11.4	26.9±14.8	30.0±16.8	<0.001
SES usage, n (%)	139 (47.4)	150 (52.3)	137 (51.1)	0.48
PES usage, n (%)	154 (52.6)	137 (47.7)	131 (48.9)	0.48

SD=standard deviation, SES=sirolimus-eluting stent

Table 3: Clinical Events at 1-year follow-up stratified across SYNTAX Score (SS) tertiles (univariate analysis)

	SSLOW n=293, %	SSMID n=287, %	SSHIGH n=268, %	HR [95% CI] SSMID vs. SSLOW	P value	HR [95% CI] SSHIGH vs. SSLOW	P value	P-value overall
Death	1.0	1.4	3.0	1.36 [0.31-6.08]	0.69	2.95 [0.78-11.12]	0.11	0.20
Cardiac death	0.7	0.3	2.6	0.51 [0.05-5.64]	0.58	3.86 [0.80-18.60]	0.09	0.06
Myocardial infarction	1.7	4.2	4.5	2.48 [0.88-7.05]	0.09	2.66 [0.94-7.56]	0.07	0.16
TLR (ID)	5.1	9.5	10.2	1.89 [1.01-3.55]	<0.05	2.06 [1.10-3.88]	0.02	0.06
MACE (ID)	6.9	10.8	14.2	1.63 [0.93-2.85]	0.09	2.17 [1.27-3.74]	<0.01	0.02
Stent thrombosis (definite)	0.7	2.4	2.3	3.60 [0.75-17.35]	0.11	3.32 [0.67-16.46]	0.14	0.26

CI=confidence interval, ID=ischemia driven, MACE=major adverse cardiac events, TLR=target lesion revascularization

Stratified analysis of drug-eluting stents performance

Overall adverse clinical event rates for each treatment arm are reported in **Table 5** for the 848 patients included in this sub-study. Stratified comparisons of PES versus SES for clinical outcome measures at 1 and 5 years follow-up are shown in **Figures 3** and **4**, respectively. Among patients in the higher SYNTAX score tertile, there was an increase in MACE rates with PES compared to SES at 1-year follow-up (20.7% vs. 8.0%, HR 2.76 [1.37-5.56], *P*=0.005), which was mainly driven by increased TLR rates in the PES arm (14.9% vs. 5.9%, HR 2.63 [1.15-6.01], *P*=0.02). Higher MACE rates for the PES arm persisted at 5 years (29.3% vs. 19.3% for SES, HR 1.68 [1.02-2.77], *P*=0.04), whereas differences in TLR rates were no longer significant (19.0% vs. 12.7%, HR 1.60 [0.86-2.98], *P*=0.14). The interaction term between treatment arm and SYNTAX score for all endpoints at 1- and 5-year follow-up had a *P* value consistently

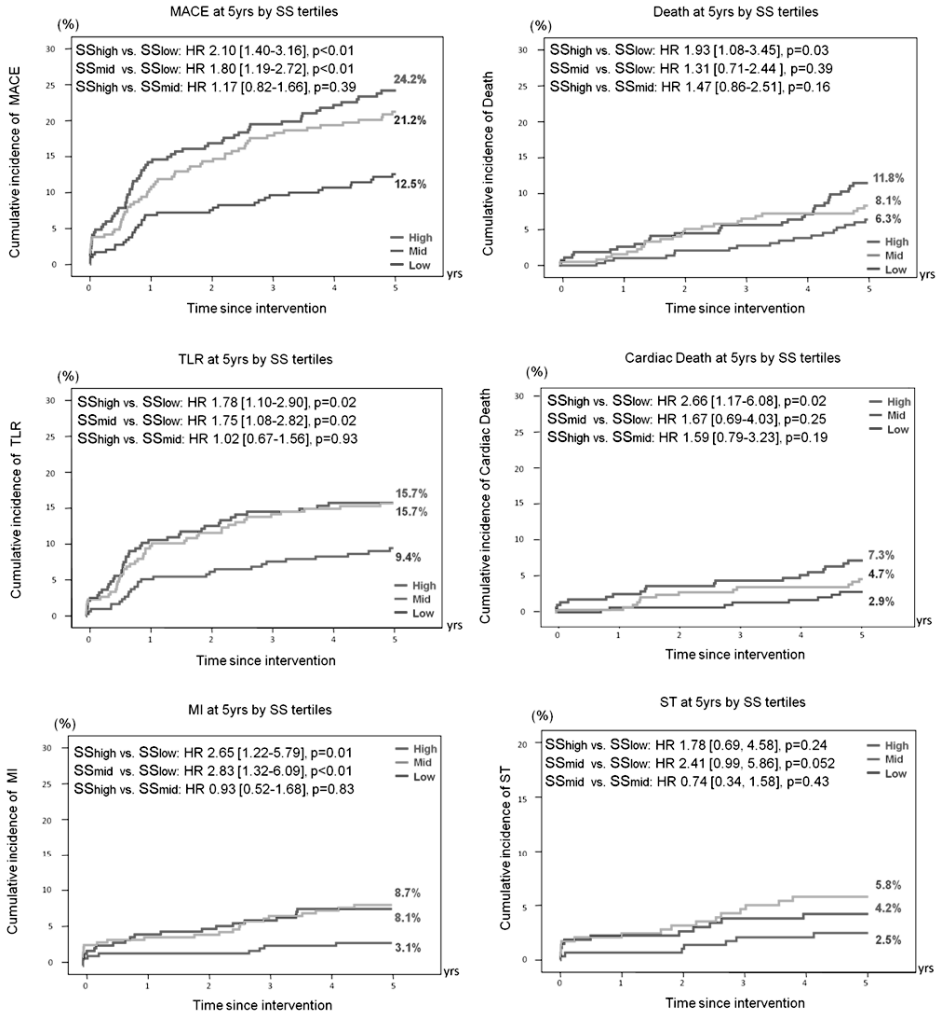


Figure 2: Clinical outcome at 5-year follow-up stratified across SYNTAX score (SS) tertiles. Kaplan-Meier curves are presented for major adverse cardiac events (MACE), ischemia-driven target lesion revascularization (TLR), myocardial infarction, all-cause mortality (death) and cardiac death, and definite stent thrombosis (ST). Tertiles for SYNTAX score were defined as SSLOW≤7, 7<SSMID≤14, SSHIGH>14. Pairwise comparison results are presented as hazard ratios (HR) plus 95% confidence intervals and respective P-values.

larger than 0.05; respective values for MACE, all-cause mortality and TLR were 0.38, 0.39 and 0.69 at 1-year and 0.31, 0.75 and 0.58 at 5-year follow-up, respectively.

Stratifying outcome across CSS tertiles led to the same conclusions regarding the performance of PES vs. SES; in fact differences in MACE and TLR rates at 1- and 5-year follow-up within CSS_{HIGH} were slightly augmented (not shown).

Table 4: Clinical Events at 1- and 5-year follow-up stratified across Clinical SYNTAX Score (CSS) tertiles (univariate analysis)

	CSSLOW n=282, %	CSSMID n=283, %	CSSHIGH n=283, %	HR [95% CI] CSSMID vs. CSSLOW	P value	HR [95% CI] CSSHIGH vs. CSSLOW	P value	P value overall
1-Year								
Death	1.4	0.4	3.5	0.25 [0.03-2.22]	0.21	2.53 [0.79-8.06]	0.12	0.04
Cardiac death	0.7	0.0	2.8	N/A	0.97	4.03 [0.86-18.99]	0.08	0.21
Myocardial infarction	2.1	2.5	5.7	1.16 [0.39-3.46]	0.79	2.71 [1.06-6.92]	0.04	0.048
TLR (ID)	6.1	6.4	12.2	1.05 [0.54-2.04]	0.88	2.10 [1.17-3.75]	0.01	0.01
MACE (ID)	7.8	7.4	16.3	0.95 [0.52-1.72]	0.86	2.19 [1.32-3.64]	0.002	0.001
Stent thrombosis (definite)	1.1	1.4	2.8	1.33 [0.30-5.93]	0.71	2.70 [0.72-10.16]	0.14	0.26
5-Year								
Death	5.8	4.6	15.5	0.80 [0.39-1.67]	0.56	2.82 [1.59-5.00]	<0.001	<0.001
Cardiac death	2.2	2.5	10.0	1.15 [0.39-3.43]	0.80	4.71 [1.94-11.40]	0.001	<0.001
Myocardial infarction	5.1	4.7	9.9	0.93 [0.44-1.97]	0.85	2.02 [1.06-3.85]	0.03	0.03
TLR (ID)	11.3	11.4	17.9	1.03 [0.63-1.69]	0.90	1.71 [1.09-2.67]	0.02	0.03
MACE (ID)	14.1	15.3	28.0	1.10 [0.72-1.70]	0.66	2.18 [1.48-3.20]	<0.001	<0.001
Stent thrombosis (definite)	3.6	3.2	5.5	0.90 [0.37-2.21]	0.82	1.56 [0.70-3.48]	0.27	0.35

CI=confidence interval, ID=ischemia driven, MACE=major adverse cardiac events, TLR=target lesion revascularization

Table 5: Clinical Events at 1- and 5-year follow-up by treatment arm (univariate analysis)

	PES n=422, %	SES n=426, %	HR [95% CI] PES vs. SES	P value
1-year outcome				
Death	2.1	1.4	1.53 [0.54-4.29]	0.42
Cardiac death	1.4	0.9	1.52 [0.43-5.40]	0.51
Myocardial infarction	4.1	2.8	1.44 [0.69-3.02]	0.33
TLR (ID)	10.8	5.7	1.95 [1.19-3.20]	0.008
MACE (ID)	13.6	7.5	1.86 [1.20-2.86]	0.005
Stent thrombosis	1.7	1.9	0.88 [0.32-2.44]	0.81
5-year outcome				
Death	8.4	8.8	0.97 [0.61-1.54]	0.89
Cardiac death	5.1	4.6	1.13 [0.61-2.10]	0.70
Myocardial infarction	7.3	5.8	1.28 [0.75-2.20]	0.36
TLR (ID)	14.8	12.3	1.26 [0.87-1.82]	0.23
MACE (ID)	20.7	17.7	1.22 [0.90-1.67]	0.20
Stent thrombosis	4.2	4.1	1.02 [0.52-2.00]	0.96

CI=confidence interval, ID=ischemia driven, MACE=major adverse cardiac events, PES=paclitaxel-eluting stent, SES=sirolimus-eluting stent, TLR=target lesion revascularization

Multivariate analysis

Independent predictors for MACE and all-cause mortality at 5-year follow-up are reported in **Tables 6** and **7**. If used as a continuous variable, SYNTAX score emerged as an independent predictor of MACE, but not of mortality; CSS did not make it to the final model either for MACE of mortality. Taking the skewness in the SYNTAX score and CSS distribution into consideration, these scores were used as categorical variables (tertile distribution) in multivariate analysis as well. In these models, CSS emerged as an independent predictor of both MACE (P= 0.002) and mortality (P=0.02) at 5-years after the index intervention. The number of lesions treated (HR 1.54 [1.21-1.98], P=0.001) was an independent predictor of MACE, whilst age (HR 1.05 [1.02-1.08] per year, P<0.001) and diabetes mellitus (HR 2.08 [1.27-3.43], P=0.004) were independent predictors of mortality beyond categorical CSS.

SYNTAX Score vs. CSS

The ROC curves for MACE and all-cause mortality at 5-year follow-up are shown in **Figure 5**. The area-under-the-curve for the SYNTAX score and CSS for 5-year MACE was 0.61 and 0.62, and for 5-year mortality 0.58 and 0.66 respectively.

DISCUSSION

The main findings of this study indicate that the SYNTAX score, and to a greater extent the CSS, have an important role to play in the risk stratification of short- and long-term outcomes in patients undergoing PCI, with both scores identified as independent predictors of 5-year mortality and MACE. An additional potential role of the SYNTAX score in the assessment of stent performance was also identified.

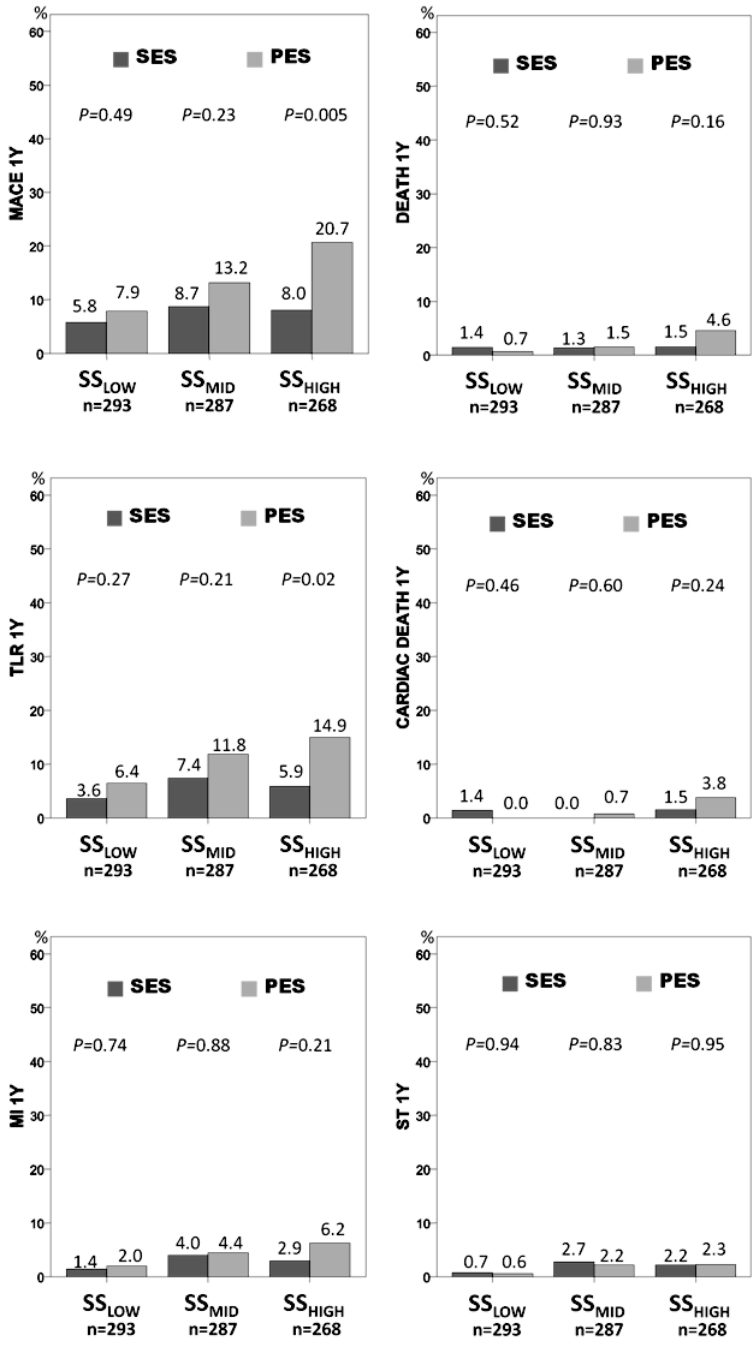


Figure 3: Stratified comparison between sirolimus- and paclitaxel-eluting stents (SES-PES) treatment arms for clinical outcomes at 1-year follow-up. Events are stratified across SYNTAX score tertiles defined as SSLOW≤7, 7<SSMID≤14, SSHIGH>14. Clinical events abbreviations as defined in legend under Figure 2.

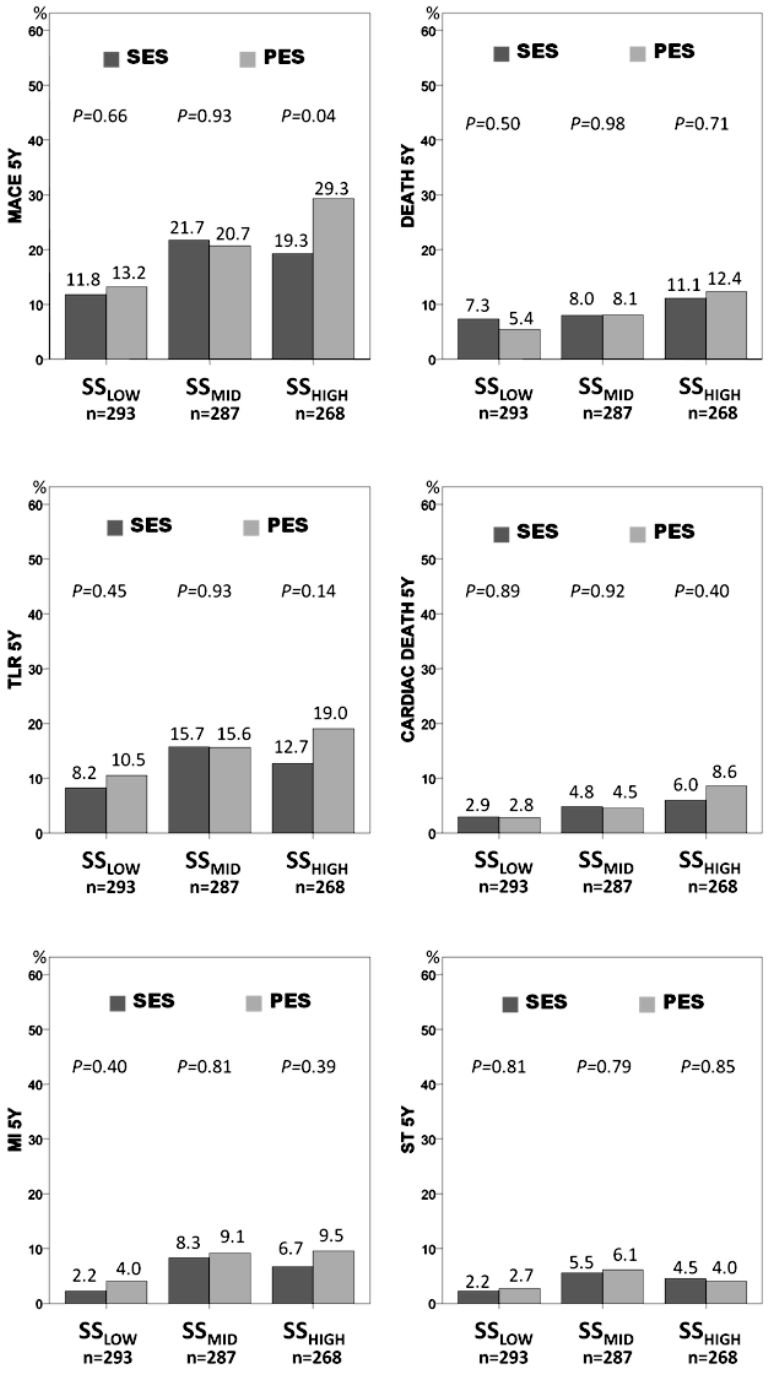


Figure 4: Stratified comparison between sirolimus- and paclitaxel-eluting stents (SES-PES) treatment arms for clinical outcomes at 5-year follow-up. Events are stratified across SYNTAX score tertiles defined as SSLOW≤7, 7<SSMID≤14, SSHIGH>14. Clinical events abbreviations as defined in legend under Figure 2.

Table 6: Univariate and multivariate predictors of MACE at 5-years follow-up.

Variables	Univariate analysis		Multivariate analysis	
	HR [95% CI]	P value	HR [95% CI]	P value
Age*	1.01 [1.00-1.03]	0.06		
Diabetes mellitus	1.46 [1.01-2.11]	0.04		
Peripheral vascular disease	1.69 [0.96-2.99]	0.07		
SYNTAX score*	1.04 [1.02-1.06]	<0.001	1.03 [1.01-1.05]	0.002
Clinical SYNTAX Score*	1.01 [1.01-1.01]	<0.001		
Creatinine clearance*	0.99 [0.99-1.00]	0.06		
LVEF*	0.99 [0.98-1.00]	0.06		
Number of lesions treated	1.67 [1.32-2.11]	<0.001	1.54 [1.20-1.98]	0.001
Total stent length*	1.01 [1.01-1.02]	0.002		

CI=confidence interval, HR=hazard ratio, LVEF=left ventricular ejection fraction, MACE=major adverse cardiac events *per unit increase

Table 7: Univariate and multivariate predictors of mortality at 5-years follow-up.

Variables	Univariate analysis		Multivariate analysis	
	HR [95% CI]	P value	HR [95% CI]	P value
Age*	1.07 [1.04-1.09]	<0.001	1.06 [1.04-1.09]	<0.001
Diabetes mellitus	2.72 [1.66-4.43]	<0.001	2.18 [1.33-3.59]	0.002
Peripheral vascular disease	2.34 [1.12-4.89]	0.02		
Hypertension	2.04 [1.16-3.57]	0.01		
SYNTAX score*	1.04 [1.02-1.06]	<0.001		
Clinical SYNTAX Score*	1.01 [1.01-1.01]	<0.001		
Creatinine clearance*	0.99 [0.98-0.99]	<0.001		
LVEF*	0.98 [0.96-1.00]	0.04		
Number of lesions treated	1.42 [0.99-2.04]	0.06		

CI=confidence interval, HR=hazard ratio, LVEF=left ventricular ejection fraction
*per unit increase

Although the current study employed comparable inclusion criteria to the two most recent all-comers studies, the mean SYNTAX score of 11.7 was lower than the 13.5 and 14.6 seen in the LEADERS and RESOLUTE studies, respectively.[7-8] This observation is not surprising considering the differing time periods when patients were enrolled in the three studies (SIRTAX 2003-2004, LEADERS 2006-2007, RESOLUTE 2008), and the increasing number of co-morbidities now seen in patients presenting for revascularization. Consistent with these differences, were the lower rates of 1-year mortality and MI seen in corresponding tertiles of the SYNTAX score between the present study and the LEADERS study. On the other hand, the only cohort where the CSS had been studied so far is the ARTS II trial population,[14] which enrolled patients during a similar time to the SIRTAX study, however inclusion criteria required patients to have at least two-vessel coronary artery disease.[18] The prevalence of multi-vessel disease in SIRTAX was close to 60%,[15] and therefore the lower mean CSS, and lower CSS tertile cut-offs seen in the current study are entirely expected.

The SYNTAX score has been proven efficient in stratifying risk for adverse clinical outcomes in patient cohorts as diverse as the three-vessel ±left main coronary artery disease PCI population in

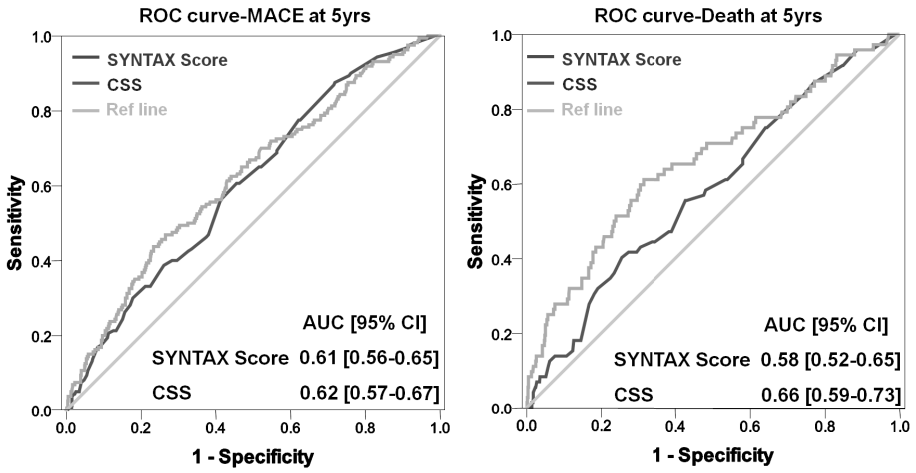


Figure 5: Receiver operating characteristic (ROC) curves for SYNTAX score and clinical SYNTAX score (CSS). Left side: ROC curve for 5-year major adverse cardiac events (MACE) Right side: ROC curve for 5-year all-cause mortality (death). AUC=area-under-the-curve, CI=confidence interval.

the SYNTAX trial,[2-3] a registry of patients with left main disease reported by Capodanno et al,[4] and the aforementioned ARTS-II, LEADERS and RESOLUTE populations.[5-8] As mean SYNTAX score values decrease in a population with less complex disease, one would hypothesize that differences in clinical outcome between individuals would go increasingly undetected by a score solely based on angiographic parameters; clinical variables such as the ones incorporated in the CSS, may therefore compensate for this possible decrease in sensitivity of the SYNTAX score. The current study undertook the stratification of clinical outcome measures by both indices, in order to highlight this effect. Hard qualitative findings observed with analysis using the SYNTAX score, such as the significant difference in event rates between high and low tertiles for MACE at one-and 5-year, were confirmed using the CSS based stratification. However *P*-values for pairwise and overall comparisons over strata for all clinical endpoints became more significant with the CSS; moreover, separation of event rates in the high compared to the mid tertiles reached statistically significance for MACE, mortality, and TLR at 1- and 5-year follow-up, implying a more refined risk stratification with the CSS.

This refinement in stratification resulted in an increased predictive accuracy for the CSS compared to the SYNTAX score, both for MACE but especially for mortality at 5-years, as previously documented in the ARTS-II sub-study by means of C-statistics.[14] Individual components included in MACE, especially TLR, are expected to be more sensitive to measures of angiographic complexity, such as the SYNTAX score. On the other hand, very long-term mortality, as also shown in the multivariate analysis, is expected to be dependent on well-known predictors of outcome after PCI such as age and diabetes mellitus; age is included in the CSS, whilst diabetes mellitus is known to impact on renal function. Similarly, the euroSCORE,[19-20] which has also been shown to be effective in risk stratifying patients undergoing percutaneous or surgical revascularization does not include assessment of diabetic status, but renal function.

An added finding of our study is the differential performance of PES and SES for patients stratified across SYNTAX score and CSS tertiles. It is the second time after the LEADERS trial [21] that the SYNTAX score has been shown to identify a subgroup, where there is a difference in clinical outcomes between devices. In the original SIRTAX trial publication,[15] there was a significant, almost two-fold, increase in the primary endpoint at 9-month follow-up in patients allocated to PES compared to SES; this difference in MACE was mainly driven by the increased TLR rates in the PES treatment arm and was attributed to increased angiographic or procedural complexity. In successive reports from the same group, similarly significant differences in 2-year MACE have been reported between PES and SES, when implanted in vessels with a reference size <2.75mm,[22] or when studied separately in diabetic patients in a pre-specified analysis.[23] In both analyses, differences in MACE were driven by significantly decreased TLR rates with SES. Not unexpectedly, in our study, significantly increased MACE rates with PES were observed at 1- and 5-year follow-up within the subgroup of patients with increased angiographic complexity. Respective hazard ratios were inflated, when MACE was stratified across the CSS tertiles; a plausible reason was the integration of clinical factors such as creatinine clearance and left ventricular ejection fraction in the CSS, which are known to induce adverse outcome after PCI.[11-12] Beyond SIRTAX, there have been conflicting reports comparing PES with SES. Detected differences in late lumen loss favoring the use of SES, usually failed to translate into significant differences in clinical outcome,[24-27] whereas meta-analysis of 16 randomized trials of SES versus PES reported significant reductions in TLR and stent thrombosis rates with SES at a median of 2-year follow-up.[28] Of note, the late catch-up phenomenon[29-30] may have been responsible for limiting the difference in MACE and TLR rates over time observed in our study; however MACE rates remained significantly higher with PES compared to SES in the higher score tertiles at 5-year follow-up. Finally, it should be recognized that this was a subgroup analysis, not pre-specified in the original study, thus the superiority seen with SES could be the result of a type I error.

LIMITATIONS

The current study is limited by its *post-hoc* nature. As the cardiologists adjudicating the diagnostic angiograms were blinded to procedural data, and taking into account the modest reproducibility of SYNTAX score even among experienced cardiologists,[31] a discrepancy in results cannot be ruled out, would the scores have been collected prospectively. However, in the case of the SIRTAX trial, this is purely hypothetical, as the SYNTAX score algorithm had not been developed at the time of patient enrolment.

Well known limitations of the SYNTAX score should also be acknowledged. Patients with prior CABG had to be excluded from the study; moreover, scoring acute coronary occlusions as total occlusions may have resulted in an inflation of the individual scores overestimating the complexity of recanalization. However, it has been recently shown that SYNTAX score values derived after the instrumentation of the infarct-related artery and therefore probably lower compared to the values derived with the standard method, could have resulted in an erroneous risk stratification; it should not be overlooked that the absence of flow itself holds an adverse impact on long-term outcome.[9] Moreover, irrespective of the method used, SYNTAX score for acute MI patients was proven to improve the

discriminatory power of models solely based on clinical variables, such as the TIMI risk score.[32] Lastly, in our study, multivariate analysis for MACE and all-cause mortality adjusted for clinical presentation, rendering continuous SYNTAX score and categorical CSS as independent predictors of outcome.

CONCLUSIONS

The SYNTAX score and the CSS successfully stratified risk for very long-term adverse clinical outcome in an all-comers population receiving drug-eluting stents. Predictive accuracy for 5-year mortality was improved using the CSS. Within the highest score tertiles 5-year MACE increased with use of paclitaxel- compared to sirolimus-eluting stents. This study is yet another step to map the performance of SYNTAX score and CSS in the entire range of coronary artery disease seen in daily clinical practice.

ACKNOWLEDGMENTS

Dr Girasis has received support by the Hellenic Cardiological Society (Athens, Greece), and the Hellenic Heart Foundation (Athens, Greece).

REFERENCES

1. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Van Dyck N, Russell ME, Mohr FW, Serruys PW. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1(2):219-27.
2. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360(10):961-72.
3. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, Van Dyck N, Mack M, Holmes D, Feldman T, Morice MC, Colombo A, Bass E, Leadley K, Dawkins KD, van Es GA, Morel MA, Mohr FW. Assessment of the SYNTAX score in the Syntax study. EuroIntervention 2009;5(1):50-6.
4. Capodanno D, Di Salvo ME, Cincotta G, Miano M, Tamburino C. Usefulness of the SYNTAX score for predicting clinical outcome after percutaneous coronary intervention of unprotected left main coronary artery disease. Circ Cardiovasc Interv 2009;2(4):302-8.
5. Valgimigli M, Serruys PW, Tsuchida K, Vaina S, Morel MA, van den Brand MJ, Colombo A, Morice MC, Dawkins K, de Bruyne B, Kornowski R, de Servi S, Guagliumi G, Jukema JW, Mohr FW, Kappetein AP, Wittebols K, Stoll HP, Boersma E, Parrinello G. Cyphering the complexity of coronary artery disease using the syntax score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. Am J Cardiol 2007;99(8):1072-81.
6. Serruys PW, Onuma Y, Garg S, Vranckx P, De Bruyne B, Morice MC, Colombo A, Macaya C, Richardt G, Fajadet J, Hamm C, Schuijer M, Rademaker T, Wittebols K, Stoll HP. 5-year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. J Am Coll Cardiol 2010;55(11):1093-101.
7. Wykrzykowska JJ, Garg S, Girasis C, de Vries T, Morel MA, van Es GA, Buszman P, Linke A, Ischinger T, Klauss V, Corti R, Eberli F, Wijns W, Morice MC, di Mario C, van Geuns RJ, Juni P, Windecker S, Serruys PW. Value of the SYNTAX score for risk assessment in the all-comers population of the randomized multicenter LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial. J Am Coll Cardiol 2010;56(4):272-7.
8. Garg S, Serruys PW, Silber S, Wykrzykowska J, van Geuns RJ, Richardt G, Buszman PE, Kelbaek H, van Boven AJ, Hofma SH, Linke A, Klauss V, Wijns W, Macaya C, Garot P, Dimario C, Manoharan G, Kornowski R, Ischinger T, Bartorelli A, Ronden J, Bressers M, Gobbens P, Negoita M, van Leeuwen F, Windecker S. The prognostic utility of the SYNTAX score on 1-year outcomes following revascularization with zotarolimus- and everolimus-eluting stents. In press. J Am Coll Cardiol Intv.
9. Garg S, Sarno G, Serruys PW, Rodriguez AE, Bolognese L, Anselmi M, De Cesare N, Colangelo S, Moreno R, Gambetti S, Monti M, Bristot L, Bressers M, Garcia-Garcia HM, Parrinello G, Campo G, Valgimigli M. Prediction of 1-Year Clinical Outcomes Using the SYNTAX Score in Patients With Acute ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention A Substudy of the STRATEGY (Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent Versus Abciximab and Bare-Metal Stent in Acute Myocardial Infarction) and MULTISTRATEGY (Multicenter Evaluation of Single High-Dose Bolus Tirofiban Versus Abciximab With Sirolimus-Eluting Stent or Bare-Metal Stent in Acute Myocardial Infarction Study) Trials. JACC Cardiovasc Interv;4(1):66-75.
10. Feldman DN, Gade CL, Slotwiner AJ, Parikh M, Bergman G, Wong SC, Minutello RM. Comparison of outcomes

of percutaneous coronary interventions in patients of three age groups (<60, 60 to 80, and >80 years) (from the New York State Angioplasty Registry). Am J Cardiol 2006;98(10):1334-9.

11. Keelan PC, Johnston JM, Koru-Sengul T, Detre KM, Williams DO, Slater J, Block PC, Holmes DR, Jr. Comparison of in-hospital and one-year outcomes in patients with left ventricular ejection fractions <or=40%, 41% to 49%, and >or=50% having percutaneous coronary revascularization. Am J Cardiol 2003;91(10):1168-72.

12. Shaw JA, Andrianopoulos N, Duffy S, Walton AS, Clark D, Lew R, Sebastian M, New G, Brennan A, Reid C, Ajani AE. Renal impairment is an independent predictor of adverse events post coronary intervention in patients with and without drug-eluting stents. Cardiovasc Revasc Med 2008;9(4):218-23.

13. Ranucci M, Castelvecchio S, Menicanti L, Frigiola A, Pelissero G. Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony. Circulation 2009;119(24):3053-61.

14. Garg S, Sarno G, Garcia-Garcia HM, Girasis C, Wykrzykowska J, Dawkins KD, Serruys PW. A new tool for the risk stratification of patients with complex coronary artery disease: the Clinical SYNTAX Score. Circ Cardiovasc Interv 2010;3(4):317-26.

15. Windecker S, Remondino A, Eberli FR, Juni P, Raber L, Wenaweser P, Togni M, Billinger M, Tuller D, Seiler C, Roffi M, Corti R, Sutsch G, Maier W, Luscher T, Hess OM, Egger M, Meier B. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. N Engl J Med 2005;353(7):653-62.

16. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115(17):2344-51.

17. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

18. Serruys PW, Ong AT, Morice MC, De Bruyne B, Colombo A, Macaya C, Richardt G, Fajadet J, Hamm C, Dawkins K, O'Malley AJ, Bressers M, Donohoe D. Arterial Revascularisation Therapies Study Part II - Sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. EuroIntervention 2005;1(2):147-56.

19. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999;16(1):9-13.

20. Romagnoli E, Burzotta F, Trani C, Siviglia M, Biondi-Zoccai GG, Niccoli G, Leone AM, Porto I, Mazzari MA, Mongiardo R, Rebuzzi AG, Schiavoni G, Crea F. EuroSCORE as predictor of in-hospital mortality after percutaneous coronary intervention. Heart 2009;95(1):43-8.

21. Wykrzykowska J. All-comers LEADERS Trial: Biolimus-eluting stents reduce mortality in patients with high SYNTAX scores in the 'all-comers' LEADERS trial. . In: EuroPCR. Paris, France, 2010.

22. Togni M, Eber S, Widmer J, Billinger M, Wenaweser P, Cook S, Vogel R, Seiler C, Eberli FR, Maier W, Corti R, Roffi M, Luscher TF, Garachemani A, Hess OM, Wandel S, Meier B, Juni P, Windecker S. Impact of vessel size on outcome after implantation of sirolimus-eluting and paclitaxel-eluting stents: a subgroup analysis of the SIRTAX trial. J Am Coll Cardiol 2007;50(12):1123-31.

23. Billinger M, Beutler J, Taghetchian KR, Remondino A, Wenaweser P, Cook S, Togni M, Seiler C, Stettler C, Eberli FR, Luscher TF, Wandel S, Juni P, Meier B, Windecker S. Two-year clinical outcome after implantation of sirolimus-eluting and paclitaxel-eluting stents in diabetic patients. Eur Heart J 2008;29(6):718-25.

24. Dibra A, Kastrati A, Mehilli J, Pache J, Schuhlen H, von Beckerath N, Ulm K, Wessely R, Dirschinger J, Scho-

mig A. Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. N Engl J Med 2005;353(7):663-70.

25. Kastrati A, Mehilli J, von Beckerath N, Dibra A, Hausleiter J, Pache J, Schuhlen H, Schmitt C, Dirschinger J, Schomig A. Sirolimus-eluting stent or paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. JAMA 2005;293(2):165-71.

26. Morice MC, Colombo A, Meier B, Serruys P, Tamburino C, Guagliumi G, Sousa E, Stoll HP. Sirolimus- vs paclitaxel-eluting stents in de novo coronary artery lesions: the REALITY trial: a randomized controlled trial. JAMA 2006;295(8):895-904.

27. Cosgrave J, Melzi G, Corbett S, Biondi-Zoccai GG, Agostoni P, Babic R, Airoldi F, Chieffo A, Sangiorgi GM, Montorfano M, Michev I, Carlino M, Colombo A. Comparable clinical outcomes with paclitaxel- and sirolimus-eluting stents in unrestricted contemporary practice. J Am Coll Cardiol 2007;49(24):2320-8.

28. Schomig A, Dibra A, Windecker S, Mehilli J, Suarez de Lezo J, Kaiser C, Park SJ, Goy JJ, Lee JH, Di Lorenzo E, Wu J, Juni P, Pfisterer ME, Meier B, Kastrati A. A meta-analysis of 16 randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary artery disease. J Am Coll Cardiol 2007;50(14):1373-80.

29. Aoki J, Abizaid AC, Ong AT, Tsuchida K, Serruys PW. Serial assessment of tissue growth inside and outside the stent after implantation of drug-eluting stent in clinical trials. - Does delayed neointimal growth exist? EuroIntervention 2005;1(3):235-55.

30. Claessen BE, Beijk MA, Legrand V, Ruzyllo W, Manari A, Varenne O, Suttorp MJ, Tijssen JG, Miquel-Hebert K, Veldhof S, Henriques JP, Serruys PW, Piek JJ. Two-year clinical, angiographic, and intravascular ultrasound follow-up of the XIENCE V everolimus-eluting stent in the treatment of patients with de novo native coronary artery lesions: the SPIRIT II trial. Circ Cardiovasc Interv 2009;2(4):339-47.

31. Garg S, Girasis C, Sarno G, Goedhart D, Morel MA, Garcia-Garcia HM, Bressers M, van Es GA, Serruys PW. The SYNTAX score revisited: a reassessment of the SYNTAX score reproducibility. Catheter Cardiovasc Interv 2010;75(6):946-52.

32. Magro M, Nauta S, Simsek C, Onuma Y, Garg S, van der Heide E, van der Giessen WJ, Boersma E, van Domburg RT, van Geuns RJ, Serruys P. Value of the SYNTAX score in patients treated by primary percutaneous coronary intervention for acute ST elevation myocardial infarction – the MI SYNTAXscore study. Am Heart J 2011.

Chapter 6.7

The impact of completeness of revascularization on the five year outcome in PCI and CABG patients (from the ARTS-II study)

Am J Cardiol 2010; 106(10): 1369–1375

Giovanna Sarno, Scot Garg, Yoshinobu Onuma, Juan-Luis Gutiérrez-Chico, Marcel Van den Brand, Benno Rensing, Marie-Angèle Morel, Patrick W. Serruys on behalf of the ARTS-II Investigators

Impact of Completeness of Revascularization on the Five-Year Outcome in Percutaneous Coronary Intervention and Coronary Artery Bypass Graft Patients (from the ARTS-II Study)

Giovanna Sarno, MD, PhD[a], Scot Garg, MB, ChB[a], Yoshinobu Onuma, MD[a], Juan-Luis Gutiérrez-Chico, MD, PhD[a], Marcel J.B.M. van den Brand, MD, PhD[b], Benno J.W.M. Rensing, MD[c], Marie-angele Morel, BSc[b], and Patrick W. Serruys, MD, PhD[a,*] on Behalf of the ARTS-II Investigators

The aim of this study was to compare clinical outcome at 5 years in patients with complete and incomplete revascularization treated with coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) with drug-eluting stents. Baseline and procedural angiograms and surgical case-record forms were centrally assessed for completeness of revascularization. Patients treated with PCI for incomplete revascularization were stratified according to Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score tertiles. Complete revascularization was achieved in 360 of 588 patients (61.2%) in the PCI with sirolimus-eluting stent group and 477 of 567 patients (84.1%) in the CABG group ($p < 0.05$). There was no significant difference in 5-year survival without major adverse cardiac and cerebrovascular events (MACCEs; death, cerebrovascular accident, myocardial infarction, and any revascularization) between patients with complete and incomplete revascularization treated with PCI or CABG. Survival free from MACCEs in patients with incomplete revascularization treated with PCI was significantly lower than those with complete revascularization treated with CABG (hazard ratio 1.66, 0.96 to 1.80, log-rank $p = 0.001$). The 5-year MACCE-free survival in patients with incomplete revascularization treated with PCI stratified according to SYNTAX score tertiles showed a significantly lower MACCE survival in the higher SYNTAX tertile compared to the low (hazard ratio 0.56, 0.32 to 0.96, log-rank $p = 0.04$) and intermediate (hazard ratio 0.50, 0.28 to 0.91, log-rank $p = 0.02$) tertiles, whereas survival between the low and intermediate SYNTAX tertiles was not significantly different (hazard ratio 1.13, 0.60 to 2.13, log-rank $p = 0.71$). In conclusion, this study suggests that patients with complex coronary disease, in whom complete revascularization cannot be achieved with PCI, should be offered surgical revascularization. However, in those patients with less complex disease, PCI is a valid alternative even if complete revascularization cannot be achieved. **(Am J Cardiol 2010;106:1369–1375)**

The aim of this study was to compare differences in clinical outcome at 5-year follow-up in patients with complete and incomplete revascularization treated with coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) with drug-eluting stents (DESs).

Methods

The method of the part-II Arterial Revascularisation Therapies (ARTS-II) study has been published previously.[1] In brief, the study was a multicenter, nonrandomized, open-label trial designed to compare the safety and efficacy of the sirolimus-eluting stent in patients with de novo multivessel coronary artery disease, using the surgical group of the ARTS-I study as historical controls. The ARTS-I and ARTS-II studies used the same inclusion criteria.[1,2]

Patients with stable angina, unstable angina, or silent ischemia who had ≥2 coronary lesions in different major epicardial vessels and/or their side branches (excluding the left main coronary artery) that were potentially amenable to stent implantation were eligible for inclusion. All patients were required to have a lesion with a diameter stenosis >50% in the left anterior descending coronary artery and ≥1 other major epicardial coronary artery.

The goal was to achieve complete anatomic revascularization. One totally occluded major epicardial vessel or side branch could be included. Coronary lesions were required to be amenable to stenting using a sirolimus-eluting stent with diameter of 2.5 to 3.5 mm and length of 13 to 33 mm; there was no restriction on total implanted stent length.

The major exclusion criteria were patients with previous coronary intervention, left main coronary disease, overt congestive heart failure, left ventricular ejection fraction <30%, history of a cerebrovascular accident, transmural myocardial infarction in the preceding week, severe hepatic

[a]Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands; [b]Cardialysis BV, Rotterdam, The Netherlands; and [c]Antonius Hospital, Nieuwegein, The Netherlands. Manuscript received April 4, 2010; revised manuscript received and accepted June 28, 2010.

*Corresponding author: Tel: 31-10-463-5260; fax: 31-10-463-5260.
E-mail address: p.w.j.c.serruys@erasmusmc.nl (P.W. Serruys).

0002-9149/10/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.amjcard.2010.06.069

Table 1
Clinical and angiographic characteristics per patient

Variable	CABG (n = 567)		PCI With DES* (n = 588)	
	Complete (n = 477)	Incomplete (n = 90)	Complete (n = 360)	Incomplete (n = 228)
Men	367 (76.9%)	63 (68.9%)	277 (76.1%)	176 (77.2%)
Age (years), mean ± SD	61 ± 9	62 ± 10	62 ± 10	63 ± 10†
Stable angina pectoris	280 (58.7%)	53 (58.9%)	181 (50.3%)	134 (58.8%)
Unstable angina pectoris	197 (41.3%)	37 (41.1%)	179 (49.7%)	94 (41.2%)
Previous myocardial infarct	33 (36.7%)	204 (46.9%)	116 (32.2%)	82 (36.0%)
Previous percutaneous coronary intervention	10 (2.1%)	3 (3.3%)‡	2 (0.6%)	0 (0.0%)
Previous smoker	221 (46.3%)	33 (48.9%)	151 (41.9%)	91 (39.9%)
Current smoker	127 (26.6%)	17 (18.9%)	70 (19.4%)	46 (20.2%)
Diabetes mellitus	72 (15.0%)	21 (23.3%)	91 (25.3%)	61 (26.8%)
Hypercholesterolemia (>190 mg/dl)	286 (60.0%)	42 (46.7%)‡§	276 (69.7%)	159 (77.1%)
Hypertension (>165/95 mm Hg)	208 (43.6%)	49 (54.4%)	232 (64.4%)	162 (64.4%)
Logistic EuroSCORE (%), mean ± SD	2.02 ± 1.63	2.22 ± 1.64	2.13 ± 1.48	2.21 ± 1.63
SYNTAX score, mean ± SD	—	—	18.8 ± 8.9	23.5 ± 9.6*
Only main branch untreated/patient	—	24/90 (26.7%)	—	3/228 (1.3%)‡
Only side branch untreated/patient	—	63/90 (70.0%)	—	143/228 (62.8%)
Main and side branches untreated/patient	—	3/90 (3.3%)	—	82/228 (35.9%)‡
Number of diseased vessels/patient, mean ± SD	2.30 ± 0.50	2.70 ± 0.50§	2.47 ± 0.49	2.62 ± 0.48*
Number of lesions/patient, mean ± SD	2.60 ± 0.80	3.70 ± 1.10§	3.22 ± 1.11	4.05 ± 1.30*
Number of stents implanted/patient, mean ± SD	—	—	3.62 ± 1.49	3.72 ± 1.52
Total stent length (mm), mean ± SD	—	—	71.20 ± 30.91	73.62 ± 32.72

* Not significant for PCI DES complete versus PCI DES incomplete.
† Post hoc multiple comparison analysis: $p < 0.05$ for PCI DES incomplete versus CABG complete revascularization group.
‡ $p < 0.05$ for CABG incomplete versus PCI DES incomplete.
§ $p < 0.05$ for CABG complete versus CABG incomplete.
EuroSCORE = European System for Cardiac Operative Risk Evaluation.

or renal disease, neutropenia or thrombocytopenia, an intolerance or contraindication to acetylsalicylic acid or thienopyridines, need for concomitant major surgery, and life-limiting major concomitant noncardiac diseases.

Surgical techniques for patients randomized to surgery were also standardized. The left anterior descending coronary artery and/or diagonal branches were revascularized using the left internal mammary artery. Other vessels were bypassed with venous bypass grafts.

This study analyzed clinical outcomes from the 567 patients with CABG from ARTS-I and 588 patients from ARTS-II treated with DESs who had completeness of revascularization assessed.

After the index revascularization procedure an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands) reviewed all diagnostic coronary angiograms to assess completeness of revascularization. The coronary arterial tree was subdivided into 15 segments according to American Heart Association/American College of Cardiology criteria.[3] All lesions with diameter stenosis >50% in a vessel with a reference diameter ≥1.50 mm were scored as potentially amenable to treatment. If all such defined segments had been treated according to the surgical report on the case-record form, the surgical procedure was scored as a complete revascularization. If ≥1 segment was left unbypassed, the patient was considered to have incomplete revascularization. Any patient with grafts bypassing ≥1 nonsignificant lesion and all significant lesions was included in the completely revascularized subgroup. Patients treated with grafts bypassing nonsignificant lesions who also had significant lesions that were left untreated were included in the incompletely revascularized subgroup.

For patients treated with PCI, diagnostic and procedural angiograms were reviewed. Patients were considered to have complete revascularization if all lesions with >50% diameter stenosis had been successfully treated. Those patients in whom attempt was made to treat ≥1 significant lesion or whose treatment resulted in a final diameter stenosis >50% were considered to have incomplete revascularization.

Degree of incompleteness of revascularization with either technique was further specified by dividing coronary artery segments into main and side branches. The proximal left anterior descending coronary artery (segments 6 and 7), proximal left circumflex artery (segment 11 and, in case of left dominance, segment 13), and proximal right coronary artery (segments 1, 2, and 3) were scored as main branches. All other segments were scored as side branches (12). The completeness of revascularization was then scored for the main branches, the side branches, or a combination of such defined vessels.

In addition, a detailed coronary risk score that has been previously published and tested in a subgroup of ARTS-II patients with 3-vessel disease (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery [SYNTAX] score) was used to characterize the complexity of the coronary anatomy.[4] In brief, each coronary lesion producing ≥50% luminal obstruction in vessels ≥1.5 mm

Table 2
Angiographic and procedural characteristics per lesion

Variable	CABG (n = 1,635 lesions)		PCI With DES (n = 2,160 lesions)	
	Complete (n = 1,312 lesions)	Incomplete (n = 323 lesions)	Complete (n = 1,175 lesions)	Incomplete (n = 985 lesions)
Narrowed coronary artery				
Right	397 (30.3%)	84 (26.0%)	353 (30.2%)	275 (27.9%)
Left circumflex	375 (28.6%)	103 (32.8%)	337 (28.7%)	297 (30.2%)
Left anterior descending	540 (41.1%)	133 (41.2%)	483 (41.1%)	413 (41.9%)
Lesion characteristics				
Lesion length (visual) (percent lesions)				
Discrete (<10 mm)	840 (67.2%)	217 (72.3%)*	715 (60.9%)	543 (55.1%)†
Tubular (10–20 mm)	329 (26.3%)	62 (20.7%)*‡	291 (24.8%)	272 (27.6%)
Diffuse (>20 mm)	81 (6.5%)	21 (7.0%)*	125 (10.6%)	120 (12.2%)
Small vessels (<2.5 mm)			71 (6%)	128 (13%)†
Moderate/heavy calcium	177 (14.2%)	52 (17.3%)*	321 (27.3%)	322 (32.7%)†
Thrombus containing lesions	19 (1.5%)	4 (1.3%)*	9 (0.8%)	2 (0.2%)
Long-term total occlusion	76 (5.8%)	23 (7.1%)*	18 (1.5%)	32 (3.2%)†
Bifurcation with side branch involvement	384 (36.0%)	108 (30.7%)	364 (31.0%)	337 (34.2%)

* $p < 0.05$ for CABG incomplete versus PCI incomplete.
† $p < 0.05$ for PCI complete versus PCI incomplete.
‡ $p < 0.05$ for CABG complete versus CABG incomplete.

was separately scored and added to provide the overall SYNTAX score. The SYNTAX score was calculated using a dedicated software that integrates the number of lesions with their specific weighting factors based on the amount of myocardium distal to the lesion according to the score of Leaman et al[5] and the morphologic features of each single lesion, as previously reported.[6] Baseline SYNTAX scores in the ARTS-I study were not calculated because the baseline cine angiograms are no longer available.

Deaths included death from any cause. Cerebrovascular accidents included transient ischemic attacks, reversible neurologic deficits, intracranial hemorrhage, and ischemic stroke.

Myocardial infarction was defined in the first 7 days after the intervention, if there was documentation of new abnormal Q waves and a ratio of serum creatinine kinase-MB isoenzyme to total creatinine kinase that >0.1 or a creatinine kinase-MB value that was 5 times the upper limit of normal. Serum creatinine kinase and creatinine kinase-MB isoenzyme concentrations were measured 6, 12, and 18 hours after the intervention. Commencing 8 days after the intervention (length of hospital stay after surgery), abnormal Q waves or enzymatic changes, as described earlier, were sufficient for a diagnosis of myocardial infarction. Myocardial infarction was confirmed only after the relevant electrocardiograms had been analyzed by the core laboratory and adjudicated by the clinical events committee. Incidence of stent thrombosis was determined according to Academic Research Consortium definitions.[7]

Continuous variables are expressed as mean ± SD and were compared using analysis of variance and Tukey post hoc test for multiple comparisons of all pairs. Categorical data are presented as frequency (percentage) and were compared using chi-square test or Fischer's exact test. Survival curves were constructed for time-to-event variables using Kaplan-Meier estimates and compared by log-rank test.

Results

Angiograms from 1,155 patients (97.4%) were available for central analysis. In the PCI DES group, 588 (96.9%) of 607 angiograms were reviewed, whereas for bypass surgery, 567 (97.9%) of 579 angiograms were available. Complete revascularization was achieved in 360 of 588 patients (61.2%) in the PCI DES group and 477 of 567 patients (84.1%) in the CABG group ($p < 0.05$).

Baseline demographics of patients with complete and incomplete revascularization from the CABG and PCI DES groups are presented in Table 1. Patients in the PCI group whose revascularization was incomplete were significantly older than those treated with CABG whose revascularization was complete.

Angiographic characteristics are presented in Table 2. Number of diseased vessels and number of lesions per patient were significantly higher in the incompletely revascularized groups compared to the completely revascularized groups irrespective of type of revascularization. Patients with incomplete revascularization who were treated with PCI had significantly more lesions that were >20 mm in length and moderately/heavily calcified and totally occluded compared to those with incomplete revascularization treated with CABG. Number of calcified and totally occluded lesions was significantly higher in patients with PCI DESs and incomplete revascularization compared to patients with PCI DES and complete revascularization. Procedural success rate for PCI of calcified and totally occluded lesions was 65.6% (22 of 32).

Five-year Kaplan-Meier curves for major adverse cardiac and cerebrovascular events (MACCEs; composite of death, cerebrovascular accident, myocardial infarction, and any revascularization) after complete and incomplete revascularization with CABG and PCI are shown in Figure 1.

Survival free from MACCEs (Figure 1) in patients with

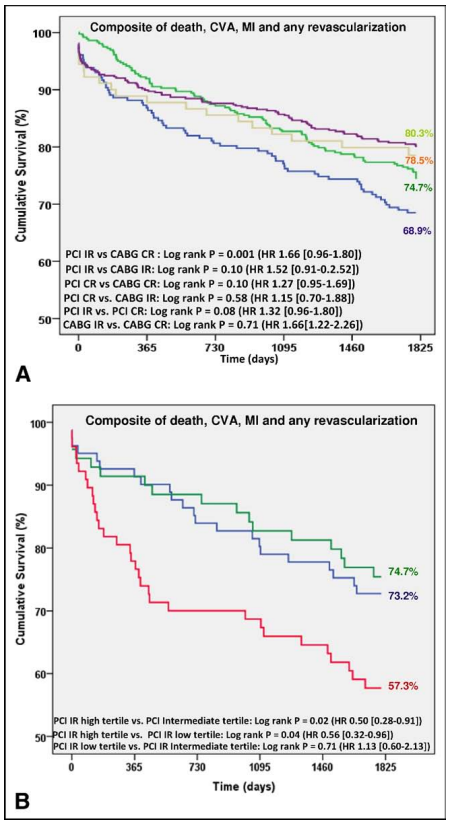


Figure 1. Kaplan-Meier survival curves at 5-year follow-up for composite of death, cerebrovascular accident [CVA], myocardial infarction [MI], and any revascularization *(A)* in the CABG completely revascularized (CR) *(purple line)*, CABG incompletely revascularized (IR) *(yellow line)*, PCI CR *(green line)*, and PCI IR *(blue line)* groups and *(B)* for the incompletely revascularized PCI subgroup stratified according to low (<19) *(blue line)*, intermediate (≥19 to ≤26.5) *(green line)*, and high (>26.5) *(red line)* SYNTAX score tertiles. HR = hazard ratio.

incomplete revascularization and PCI was numerically lower than in patients with incomplete revascularization and CABG (hazard ratio 1.52, 0.91 to 0.2.52, log-rank p = 0.10) and significantly lower than the completely revascularized CABG group (hazard ratio 1.66, 0.96 to 1.80, log-rank p = 0.001). The Kaplan-Meier curve for MACCEs of the PCI DES incompletely revascularized group shows a crossing point with the incompletely revascularized CABG group at 6 months, whereas the survival curve of the PCI DES completely revascularized group diverges from the CABG completely revascularized group after 2 years with a decrease of survival rate free from MACCEs in the PCI completely revascularized group from 87% at 2 years up to 75% at 5-year follow-up.

Figure 1 shows 5-year survival free from MACCEs in the incompletely revascularized PCI DES group stratified according to SYNTAX score tertile distribution. Of note, the 5-year event-free survival in the low (SYNTAX score <19) and intermediate (SYNTAX score ≥19 to ≤26.5) tertiles was significantly better than in the higher tertile (SYNTAX score >26.5) and similar to the completely and incompletely CABG groups or the completely revascularized PCI group.

Five-year Kaplan-Meier curves for death, for the composite of death, cerebrovascular accident, and myocardial infarction, for any revascularization, and for the composite of definite/probable stent thrombosis after complete and incomplete revascularization with CABG and PCI are shown in Figure 2.

Table 3 presents the 5-year cumulative incidence of major adverse events in the 4 subgroups. Need for repeat revascularization and rate of nontarget lesion revascularization in the incompletely revascularized PCI DES group were significantly higher compared to the completely revascularized PCI DES group.

Definite stent thrombosis according to Academic Research Consortium definitions occurred in 6 of 228 patients (2.6%) in the PCI incompletely revascularized group versus 14 of 360 patients (3.9%) in the PCI completely revascularized group (p = 0.45), whereas the composite of definite or probable stent thrombosis occurred in 15 of 228 patients (6.5%) in the PCI incompletely revascularized group versus 31 of 360 patients (8.6%) in the PCI completely revascularized group (p = 0.41).

Discussion

The main finding of this study is that in patients with incomplete revascularization and PCI, only those in the highest SYNTAX score tertile had a higher rate of adverse events at 5 years compared to patients treated with CABG. Conversely, outcomes in patients with incomplete revascularization and PCI with low/intermediate SYNTAX scores were not significantly different from those patients who had complete revascularization with CABG or PCI. These findings reiterate the need for a careful assessment of the anatomic complexity and lesion characteristics in patients with multivessel coronary disease to facilitate the decision on the most appropriate revascularization strategy.

This study provides complementary evidence to recent studies[4,8–10] that have demonstrated that surgical revascularization is the most appropriate method of revascularization in patients with complex anatomy and a high SYNTAX score, a group of patients in whom complete revascularization is least likely to be achieved percutaneously. However, these studies are limited by a relatively short follow-up. To date, there is no study with such long-term outcome (5 years) comparing the effect of completeness of revascularization between CABG and PCI with DESs.

There are many possible explanations why a patient may not have complete revascularization after PCI or CABG. By all intents and purposes, complete revascularization is anticipated when patients undergo surgical revascularization.

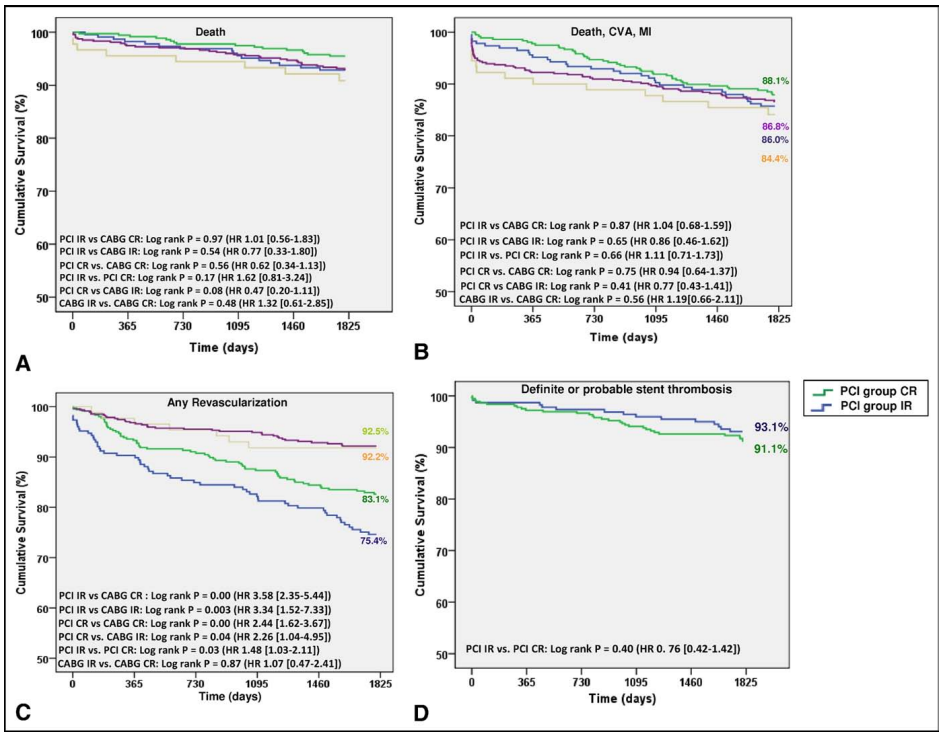


Figure 2. Kaplan-Meier survival curves at 5-year follow-up up for death *(A)*, for the composite of death, cerebrovascular accident, and myocardial infarction *(B)*, for any revascularization *(C)*, and for the composite of definite/probable stent thrombosis *(D)* in the CABG CR *(purple line)*, CABG IR *(yellow line)*, PCI CR *(green line)*, and PCI IR *(blue line)* groups. Abbreviations as in Figure 1.

However, at the time of surgery factors such as a lack of suitable conduits or presence of small native vessels may become apparent that prevent complete revascularization. In addition, previous PCI with stents, particularly in patients with a "full-metal jacket," may limit the location at which bypasses can be attached.

Incomplete percutaneous revascularization may occur unintentionally, for example, after a failed attempt at opening a calcified and totally occluded vessel. Intentionally it may occur if operators have decided to "stage" the PCI, or if procedural time has been prolonged in view of the risk of radiation or after an excessive contrast load. It is likely that these were the main reasons for the incomplete revascularization of patients with PCI in this study. Indeed, the rate of failed calcified and totally occluded vessels was significantly higher in the PCI incompletely revascularized group compared to the PCI completely revascularized group.

In this study use of the SYNTAX score enabled the identification of those patients (SYNTAX score <26.5) with incomplete revascularization who do not develop significant adverse events at long-term follow-up compared to patients with complete revascularization.

The SYNTAX score[6,11] was initially designed to better anticipate the risks of percutaneous or surgical revascularization, taking into account the functional impact of the coronary circulation with all its anatomic components such as bifurcations, total occlusions, thrombus, calcifications, small vessels, etc. Therefore, it is not merely an anatomic score but it also takes into account the functional relevance of a lesion according to its location and relative amount of blood supply to the myocardium. Recent studies have demonstrated that it has also a role in short- and long-term risk stratification of patients having PCI.[1,4,8–10,12,13]

In the study protocol the definition of incomplete revascularization required the presence, after the procedure, of stenosis $>50\%$ in a vessel with a reference diameter >1.5 mm. However, use of only an anatomic definition is limiting to understand the clinical implications when leaving untreated lesions. It is not difficult to recognize that an untreated lesion in a diagonal branch or a distal right coronary

Table 3
Cumulative incidence of major adverse events at five years in the four subgroups

Variable	CABG (n = 567)		PCI With DES* (n = 588)	
	Complete (n = 477)	Incomplete (n = 90)	Complete (n = 360)	Incomplete (n = 228)
Death	33 (6.9%)	8 (8.9%)	16 (4.4%)	16 (6.0%)
Cerebrovascular accident	17 (3.6%)	1 (1.1%)	15 (4.2%)	7 (3.1%)
Myocardial infarction	23 (4.8%)	7 (7.8%)	18 (8.0%)	16 (7.0%)
Death/cerebrovascular accident/myocardial infarction	63 (13.2%)	14 (15.6%)	43 (12.0%)	32 (14.0%)
Any revascularization	36 (7.5%)‡	7 (7.8%)§	61 (16.9%)	56 (25.6%)*†
Target lesion percutaneous coronary intervention	23 (4.8%)	4 (4.4%)§	41 (11.4%)‖	32 (14%)†
Target lesion coronary artery bypass graft	2 (0.4%)	1 (1.1%)	3 (0.8%)	2 (0.9%)
Nontarget lesion percutaneous coronary intervention	14 (2.9%)	3 (3.3%)	25 (6.9%)	28 (12.3%)*
Nontarget lesion coronary artery bypass graft	0 (0.0%)	0 (0.0%)	2 (0.6%)	3 (1.3%)
Major adverse cardiovascular and cerebrovascular events (death/cerebrovascular accident/myocardial infarction/any revascularization)	94 (19.7%)	19 (21.1%)	91 (25.3%)	71 (31.1%)†

Values are numbers of patients (percentages).
* $p < 0.05$ for PCI DES complete versus PCI DES incomplete.
† $p < 0.05$ for PCI DES incomplete versus CABG complete.
‡ $p < 0.05$ for CABG complete versus CABG incomplete.
§ $p < 0.05$ for CABG incomplete versus PCI DES incomplete.
‖ $p < 0.05$ for PCI DES complete versus CABG complete.

artery is less prognostically significant compared to an untreated proximal left anterior descendent artery.[14] The SYNTAX score is able to discriminate between lesions with different vessel location and angiographic characteristics.

The results of this study confirm previous findings of the ARTS-I substudy that showed no significant difference in the safety end point (death, cerebrovascular accident, myocardial infarction) at 1 year between the CABG and PCI groups, whereas the only difference was in need for repeat revascularization at 1 year.[15] The greater requirements for repeat revascularization after PCI compared to CABG are well known.[1,8,12,16,17] Indeed, this study has shown that survival free from any revascularization was significantly lower in the 2 PCI groups compared to the 2 CABG groups, with a steep decrease in survival rate in the 2 PCI groups at 6 months and after 1 year.

Of note, survival rate free from the composite of definite or probable stent thrombosis in the 2 PCI groups showed an early decrease with a further decrease at 1 year. Surprisingly, a further decrease was observed in the PCI completely revascularized group after 2 years with a decrease of survival rate from 97.3% to 91.1%. There is not a clear explanation for this finding and particularly the number of implanted stent per patient was similar in the completely and incompletely revascularized PCI groups.

At variance with previous studies[16,18–21] was the absence of any significant difference in MACCEs and subsequent repeat revascularization rate between the incompletely and completely revascularized CABG groups. This may be the result of the sample size, which was underpowered to detect a significant difference, or because assessment of completeness of revascularization in the CABG group relied on the operation note prepared by the cardiac surgeon and not on coronary angiogram after CABG. Therefore, it is likely that some surgical patients, deemed to have had a complete revascularization according to the surgical report, would have been assigned to the incompletely revascularized group if a coronary angiogram had been obtained after CABG. In a recent study coronary angiography immediately after CABG indicated the presence of significant angiographic defects (conduit defects, anastomotic defects, target vessel errors) in 12% of coronary grafts.[22]

The concept of completeness of revascularization is currently evolving; as reported by Ong et al,[23] several definitions of "completeness of revascularization" (anatomic, functional, numeric, conditional/unconditional, and functional based on jeopardy score) are still in use and it is not straightforward to make definite conclusions on the impact of achieving complete revascularization with PCI or CABG.

The results of this study, showing no significant differences in 5-year outcome between patients with complete and incomplete revascularization in the CABG and PCI groups, highlight the need of a new standardized definition of completeness of revascularization that should take into account the anatomic or functional severity of the lesions and help the clinical decision on the appropriateness of revascularization in patients with multivessel coronary disease. Indeed, PCI of nonhemodynamically significant stenoses has been shown not to improve a patient's prognosis or symptoms while increasing health care costs.[24–26]

The absence of SYNTAX scores in patients treated with CABG is a limitation that otherwise would have allowed a more effective comparison of anatomic complexity in the surgical group.

In addition, ARTS-II was a registry and as such has the inherent limitation of this type of study. Moreover, this cohort of patients represents a subgroup analysis and therefore end points were not adequately powered to provide definitive results.

1. Serruys PW, Ong ATL, Morice M-C, Bruyne BD, Colombo A, Macaya C, Richardt G, Fajadet J, Hamm C, Dawkins K, O'Malley AJ, Bressers M, Dennis D, on behalf of the ARTS II Investigators. Arterial Revascularisation Therapies Study Part II—sirolimus-eluting stents

for the treatment of patients with multivessel de novo coronary artery lesions. *Eurointervention* 2005;1:147–156.
2. Serruys PW, Unger F, van Hout BA, van den Brand MJ, van Herwerden LA, van Es GA, Bonnier JJ, Simon R, Cremer J, Colombo A, Santoli C, Vandormael M, Marshall PR, Madonna O, Firth BG, Breeman A, Morel MA, Hugenholtz PG. The ARTS study (Arterial Revascularization Therapies Study). *Semin Interv Cardiol* 1999;4:209–219.
3. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, McGoon DC, Murphy ML, Roe BB. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation* 1975;51:5–40.
4. Valgimigli M, Serruys PW, Tsuchida K, Vaina S, Morel MA, van den Brand MJ, Colombo A, Morice MC, Dawkins K, de Bruyne B, Kornowski R, de Servi S, Guagliumi G, Jukema JW, Mohr FW, Kappetein AP, Wittebols K, Stoll HP, Boersma E, Parrinello G. Cyphering the complexity of coronary artery disease using the SYNTAX score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. *Am J Cardiol* 2007;99:1072–1081.
5. Leaman DM, Brower RW, Meester GT, Serruys P, van den Brand M. Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. *Circulation* 1981;63:285–299.
6. Serruys P, Onuma Y, Garg S, Sarno G, Van Den Brand M, Kappetein AP, van Dyck N, Mack MJ, Holmes DR Jr, Feldman TE, Morice MC, Colombo A, Bass EJ, Leadley K, Dawkins K, van Es GA, Morel MA, Mohr F. Assessment of the SYNTAX score in the Syntax study. *Eurointervention* 2009;5:50–56.
7. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;115:2344–2351.
8. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;360:961–972.
9. Capodanno D, Di Salvo ME, Cincotta G, Miano M, Tamburino C, Tamburino C. Usefulness of the SYNTAX score for predicting clinical outcome after percutaneous coronary intervention of unprotected left main coronary artery disease. *Circ Cardiovasc Interv* 2009;2:302–308.
10. Capodanno D, Capranzano P, Di Salvo ME, Caggegi A, Tomasello D, Cincotta G, Miano M, Patane M, Tamburino C, Tolaro S, Patane L, Calafiore AM. Usefulness of SYNTAX score to select patients with left main coronary artery disease to be treated with coronary artery bypass graft. *JACC Cardiovasc Interv* 2009;2:731–738.
11. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Van Dyck N, Russell ME, Serruys P. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. *Eurointervention* 2005;1:219–227.
12. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schonberger JP, Buller N, Bonser R, van den Brand MJ, van Herwerden LA, Morel MA, van Hout BA. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med* 2001;344:1117–1124.
13. Singh M, Rihal CS, Gersh BJ, Lennon RJ, Prasad A, Sorajja P, Gullerud RE, Holmes DR Jr. Twenty-five-year trends in in-hospital and long-term outcome after percutaneous coronary intervention: a single-institution experience. *Circulation* 2007;115:2835–2841.
14. Chaitman BR, Ryan TJ, Kronmal RA, Foster ED, Frommer PL, Killip T. Coronary Artery Surgery Study (CASS): comparability of 10 year survival in randomized and randomizable patients. *J Am Coll Cardiol* 1990;16:1071–1078.
15. van den Brand MJ, Rensing BJ, Morel MA, Foley DP, de Valk V, Breeman A, Suryapranata H, Haalebos MM, Wijns W, Wellens F, Balcon R, Magee P, Ribeiro E, Buffolo E, Unger F, Serruys PW. The effect of completeness of revascularization on event-free survival at one year in the ARTS trial. *J Am Coll Cardiol* 2002;39:559–564.
16. Bell MR, Gersh BJ, Schaff HV, Holmes DR Jr, Fisher LD, Alderman EL, Myers WO, Parsons LS, Reeder GS. Effect of completeness of revascularization on long-term outcome of patients with three-vessel disease undergoing coronary artery bypass surgery. A report from the Coronary Artery Surgery Study (CASS) Registry. *Circulation* 1992;86:446–457.
17. Serruys P, Onuma Y, Garg S, Vranckx P, De Bruyne B, Morice MC, Colombo A, Macaya C, Gert R, Fajadet J, Hamm C, Schuijer M, Rademaker T, Wittebols K, Stoll HP, on behalf of the ARTS-II investigators. Five-year clinical outcomes of the arterial revascularisation therapies (ARTS-II) study of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. *J Am Coll Cardiol* 2010;55:1093–1101.
18. Vander Salm TJ, Kip KE, Jones RH, Schaff HV, Shemin RJ, Aldea GS, Detre KM. What constitutes optimal surgical revascularization? Answers from the Bypass Angioplasty Revascularization Investigation (BARI). *J Am Coll Cardiol* 2002;39:565–572.
19. Kleisli T, Cheng W, Jacobs MJ, Mirocha J, Derobertis MA, Kass RM, Blanche C, Fontana GP, Raissi SS, Magliato KE, Trento A. In the current era, complete revascularization improves survival after coronary artery bypass surgery. *J Thorac Cardiovasc Surg* 2005;129:1283–1291.
20. Kozower BD, Moon MR, Barner HB, Moazami N, Lawton JS, Pasque MK, Damiano RJ Jr. Impact of complete revascularization on long-term survival after coronary artery bypass grafting in octogenarians. *Ann Thorac Surg* 2005;80:112–117.
21. Bourassa MG, Yeh W, Holubkov R, Sopko G, Detre KM. Long-term outcome of patients with incomplete vs complete revascularization after multivessel PTCA. A report from the NHLBI PTCA Registry. *Eur Heart J* 1998;19:103–111.
22. Zhao DX, Leacche M, Balaguer JM, Boudoulas KD, Damp JA, Greelish JP, Byrne JG, Ahmad RM, Ball SK, Cleator JH, Deegan RJ, Eagle SS, Fong PP, Fredi JL, Hoff SJ, Jennings HS III, McPherson JA, Piana RN, Pretorius M, Robbins MA, Slosky DA, Thompson A. Routine intraoperative completion angiography after coronary artery bypass grafting and 1-stop hybrid revascularization results from a fully integrated hybrid catheterization laboratory/operating room. *J Am Coll Cardiol* 2009;53:232–241.
23. Ong AT, Serruys PW, Mohr FW, Morice MC, Kappetein AP, Holmes DR Jr, Mack MJ, van den Brand M, Morel MA, van Es GA, Kleijne J, Koglin J, Russell ME. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. *Am Heart J* 2006;151:1194–1204.
24. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, Bar F, Hoorntje J, Koolen J, Wijns W, de Bruyne B. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. *J Am Coll Cardiol* 2007;49:2105–2111.
25. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van't Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;360:213–224.
26. Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, Weintraub WS, O'Rourke RA, Dada M, Spertus JA, Chaitman BR, Friedman J, Slomka P, Heller GV, Germano G, Gosselin G, Berger P, Kostuk WJ, Schwartz RG, Knudtson M, Veledar E, Bates ER, McCallister B, Teo KK, Boden WE. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation* 2008;117:1283–1291.

PART VII

The Impact of Stent Type on Clinical Outcomes in Patients Treated with PCI

Chapter 7.1

Three year clinical follow up of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo coronary artery lesions. The SPIRIT II Trial.

J Am Coll Cardiol Intv 2009; 2(12):1190-1198

Scot Garg, Patrick W. Serruys, Yoshi Onuma, Cecile Dorange, Susan Veldhorf, Katherine Miquel-Hebert, Krishna Sudhir, Jean Boland, Kurt Huber, Eulogio Garcia , Jan AM Rielete on behalf of the SPIRIT II Investigators

3-Year Clinical Follow-Up of the XIENCE V Everolimus-Eluting Coronary Stent System in the Treatment of Patients With De Novo Coronary Artery Lesions

The SPIRIT II Trial (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions)

Scot Garg, MBChB,* Patrick Serruys, MD, PhD,* Yoshinobu Onuma, MD,* Cécile Dorange, MSc,† Susan Veldhof, RN,† Karine Miquel-Hébert, PhD,† Krishnankutty Sudhir, MD, PhD,‡ Jean Boland, MD,§ Kurt Huber, MD,‖ Eulogio Garcia, MD,¶ Jan A. M. te Riele, MD,# on behalf of the SPIRIT II Investigators

Rotterdam and Breda, the Netherlands; Diegem and Liege, Belgium; Santa Clara, California; Vienna, Austria; and Madrid, Spain

Objectives This paper reports the 3-year clinical outcomes of the XIENCE V (Abbott Vascular, Santa Clara, California) everolimus-eluting stent (EES) compared with the TAXUS (Boston Scientific, Natick, Massachusetts) paclitaxel-eluting stent (PES) in the randomized SPIRIT II (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions) study.

Background The Xience V EES is a new-generation drug-eluting stent (DES) that might offer advantages over the first-generation DES in terms of improved clinical outcomes and a better safety profile.

Methods The SPIRIT II trial was a multicenter, prospective, randomized, single-blind, clinical trial, randomizing 300 patients with de novo coronary artery lesions in a ratio of 3:1 to either EES or PES. The primary end point was in-stent late loss at 180 days.

Results At 3-year clinical follow-up cardiac death was numerically lower with EES than PES (0.5% vs. 4.3%, $p = 0.056$). The observed rate of myocardial infarction was 3.6% for EES and 7.2% for PES ($p = 0.31$). The rate of ischemia-driven target lesion revascularization was 4.6% and 10.1% for EES and PES, respectively ($p = 0.14$). Overall, there was a trend for lower major adverse cardiovascular events in the EES group compared with PES (7.2% vs. 15.9%, $p = 0.053$). The rate of stent thrombosis was low and comparable in both groups (EES 1.0% vs. PES 2.9%).

Conclusions The present study reports the favorable 3-year clinical outcomes of the EES, which are consistent with the results from other studies of the EES with shorter follow-up. (J Am Coll Cardiol Intv 2009;2:1190–8) © 2009 by the American College of Cardiology Foundation

From the *Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands; †Abbott Vascular, Diegem, Belgium; ‡Abbott Vascular, Santa Clara, California; §C.H.R. La Citadelle, Liege, Belgium; ‖Wilhelminenspital der Stadt, Vienna, Austria; ¶University Hospital Gregorio Maranon, Madrid, Spain; and the #Amphia Hospital, Breda, the Netherlands. Cécile Dorange, Susan Veldhof, Dr. Miquel-Hébert, and Dr. Sudhir are employees of Abbott Vascular.

Manuscript received May 14, 2009; revised manuscript received September 8, 2009, accepted October 6, 2009.

Drug-eluting stents (DES) revolutionized the field of percutaneous coronary intervention (PCI) after their introduction in 2002, by significantly reducing rates of restenosis (1). After their introduction there was a rapid and unprecedented uptake of their use, such that within 3 years they were used in 80% to 90% of revascularization procedures in the U.S. (2). Recently, concerns have emerged that the first generation of DES, coated with sirolimus and paclitaxel, are associated with an increased risk of very late stent thrombosis (>1 year) when compared with bare-metal stents (BMS) (3). An everolimus-eluting stent (EES) has been developed with the goal of improving the safety of DES.

See page 1236

The FUTURE (The First Use To Underscore restenosis Reduction with Everolimus) I (4,5) and FUTURE II (6) studies were the first to demonstrate the feasibility of using everolimus on a DES. The SPIRIT (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions) FIRST study has subsequently demonstrated clinical safety and efficacy of the EES out to 4 years' follow-up (7). In particular, significantly lower in-stent late loss was demonstrated at 12-month angiographic follow-up, compared with an identical BMS (8).

The assessment of the EES continued with SPIRIT II and the larger SPIRIT III studies. Both involved the randomized comparison of EES to the TAXUS (Boston Scientific, Natick, Massachusetts) paclitaxel-eluting stent (PES) in patients with a maximum of 2 de novo coronary artery lesions. In both studies, there was a significant reduction in major adverse cardiac events (MACE) with EES compared with PES at 12-month follow-up (9,10). A "late loss catch-up" with EES was suggested by the 2-year outcome data from SPIRIT II that showed no significant difference in angiographic and clinical outcomes between the 2 stents (11). The 2-year follow-up data from SPIRIT III, however, has shown promising results with improvements in event-free survival and lower rates of stent thrombosis with the use of an EES (12).

The current study presents the 3-year clinical outcome of patients enrolled in the SPIRIT II study treated with either EES or a PES. This represents the longest available clinical follow-up for EES in a moderately sized population.

Methods

Patient population. The patient population has been described previously (13). In brief, SPIRIT II was a multicenter trial enrolling 300 patients who were randomized in a ratio of 3:1 to receive either an EES, XIENCE V (Abbott Vascular, Santa Clara, California) (n = 223), or a PES (n = 77). Both TAXUS Express[2] (73% of lesions) and TAXUS Liberté (27% of lesions) were used in the control arm. A detailed description of everolimus and the EES is provided elsewhere (13,14). The ethics committee of each participating institution approved the study protocol, and all patients gave written informed consent.

All patients were over the age of 18, with evidence of myocardial ischemia and a maximum of 2 de novo native coronary artery lesions in different major epicardial vessels. For inclusion, on visual estimation, target lesion(s) were required to be: in a vessel with a reference vessel diameter of between 2.5 and 4.25 mm; <28 mm in length; and have a percentage diameter stenosis (DS) of between 50% and 99%, with a Thrombolysis In Myocardial Infarction flow grade >1. Patients with documented evidence of recent (<3 days) myocardial infarction (MI); a left ventricular ejection fraction <30%; waiting heart transplantation; or having a known sensitivity or contraindications to aspirin, heparin, bivalirudin, clopidogrel or ticlopidine, cobalt, chromium, nickel, tungsten, everolimus, paclitaxel, acrylic, and fluoropolymers were excluded. Angiographic lesions involving the left main stem lesion or the aorto-ostial junction; located within 2 mm of the origin of the left anterior descending or left circumflex; that were heavily calcified; or that had associated visible thrombus were also excluded.

Abbreviations and Acronyms

ARC = Academic Research Consortium
BMS = bare-metal stent(s)
CABG = coronary artery bypass graft
CI = confidence interval
CK-MB = creatinine kinase-myocardial band
DES = drug-eluting stent(s)
DS = diameter stenosis
EES = everolimus-eluting stent(s)
HR = hazard ratio
ID-TLR = ischemia-driven target lesion revascularization
IVUS = intravascular ultrasound
MACE = major adverse cardiovascular events
MI = myocardial infarction
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stent(s)
RR = relative risk
SES = sirolimus-eluting stent(s)
ULN = upper limit of normal
TVF = target vessel failure
TVR = target vessel revascularization

Study procedure. Patients were randomized between EES and PES after the identification of suitable lesions on preliminary angiography. Physicians were not blinded, in view of the different packaging for each stent. Standard interventional techniques were used to treat the lesion; in particular predilation was mandatory, and stent implantation was performed at a pressure not exceeding the rated burst pressure. Post-dilation was left to the operator's discretion; however, if post-dilation was performed, balloons were required to be shorter than the length of the deployed stent. In the event of a bailout procedure and the need for an additional stent, the stent was required to be of the same type as the first implanted stent.

In a subset of 152 consecutive patients enrolled in pre-selected centers, intravascular ultrasound (IVUS) was performed after optimal stent placement had been achieved. Periprocedural pharmaceutical treatment was administrated according to standard hospital practice. Procedural anticoagulation was achieved with unfractionated heparin or bivalirudin. The use of glycoprotein IIb/IIIa inhibitors was left to the operator's discretion. All patients enrolled into the study were to receive ≥75 mg of aspirin daily for a minimum of 1 year and clopidogrel 75 mg for a minimum of 6 months after the index procedure.

Follow-up. Patient review was initially planned at 1, 6, 9, 12, and 24 months after the index procedure; however, a subsequent protocol amendment enabled further clinical evaluation to be performed on an annual basis out to 5 years. At outpatient visits, patients were specifically questioned about the development of angina or the occurrence of any adverse events. Angiographic follow-up for all patients was planned at 180 days, with IVUS planned in a subset of 152 consecutive patients (from selected centers). Angiography and IVUS were repeated after 2 years in these 152 consecutive patients.

Study end points. The clinical end point of this 3-year follow-up study was MACE, defined as a composite of cardiac death, MI, and ischemia-driven target lesion revascularization (ID-TLR) by coronary artery bypass graft surgery (CABG) or PCI. Secondary clinical end points included target vessel failure (TVF), a composite of cardiac death, MI, ID-TLR, and non–target lesion ischemia-driven target vessel revascularization (ID-TVR). An independent blinded clinical events committee (CEC) evaluated all clinical end points, and a data and safety monitoring board, not affiliated with the study, ensured the safe conduct of the trial.

Definitions. All deaths were considered cardiac unless an undisputed noncardiac cause was present. The onset of the trial was before the publication of the Academic Research Consortium's (ARC) consensus definitions for DES study end points, and therefore the only cardiac enzymes available in all patients to adjudicate events were creatinine kinase (CK), and creatinine kinase-myocardial band (CK-MB) (15). Q-wave MI was defined as the development of new pathological Q waves. A non–Q-wave MI was defined as a typical rise and fall of CK-MB, with at least 1 of the following: ischemic symptoms; electrocardiographic changes indicative of ischemia (ST-segment elevation or depression); or an associated coronary artery intervention. For a nonprocedural/spontaneous MI the CK-MB was required to be ≥2 times the upper limit of normal (ULN). A CK-MB ≥3 times the ULN or ≥5 times the ULN was

Table 1. Baseline Characteristics of the Patient Population

	EES (n = 223)	PES (n = 77)	All Patients (n = 300)
Age (yrs)	62 ± 10	62 ± 9	62 ± 10
Male (%)	71	79	73
Current smoker (%)	32	30	31
Diabetes (%)	23	24	23
Hypertension-requiring medication (%)	67	65	67
Hyperlipidemia-requiring medication (%)	69	75	70
Prior target vessel intervention (%)	4	4	4
Prior MI (%)	35	25	32
Stable angina (%)	62	62	62
Unstable angina (%)	27	32	28
Target Vessel (%)	**n = 260 Lesions**	**n = 91 Lesions**	**n = 351 Lesions**
Left anterior descending	41	47	42
Left circumflex	29	19	26
Right coronary artery	30	34	31
AHA/ACC lesion class (%)			
A	1	0	1
B1	21	20	21
B2	65	67	66
C	13	13	13
Reference vessel diameter (mm ± SD)	2.70 ± 0.52	2.82 ± 0.58	2.73 ± 0.54
Lesion length (mm ± SD)	13.0 ± 5.7	13.2 ± 6.4	13.0 ± 5.9

There was no significant difference between the everolimus and paclitaxel treatment arms.

AHA/ACC = American Heart Association/American College of Cardiology; EES = everolimus eluting stent(s); MI = myocardial infarction; PES = paclitaxel-eluting stent(s).

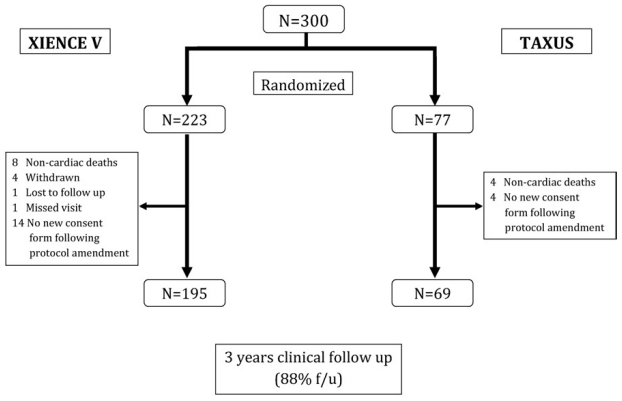


Figure 1. Clinical Follow-Up of Patient Population

Flow chart indicating the flow of patients through the study. In total 264 (88%) patients attended for 3 years of follow-up (f/u). The major reason for the loss of follow-up, which was similar in both groups, was failure to sign a new consent form after the protocol amendment allowing study follow-up to be extended to 5 years.

required for an MI to be defined post-PCI or post-CABG, respectively.

The ID-TLR was defined as revascularization of the target lesion in association with any of the following: a positive test of ischemia, with either exercise testing or fractional/coronary flow reserve; ischemic symptoms and an angiographic DS ≥50% by online quantitative coronary angiography; or DS ≥70% by online quantitative coronary angiography without ischemic symptoms or a positive functional study.

The protocol for stent thrombosis changed after the publication of the ARC definitions for stent thrombosis (15). Those stent thrombotic events occurring before the

Table 2. Hierarchical Subject Counts of Adverse Events Through 3 Years

0–1,095 Days % (n)	EES (n = 223)	PES (n = 77)	Relative Risk (95% CI)	p Value*
MACE	7.2 (14/195)	15.9 (11/69)	0.45 (0.21–0.94)	0.053
TVF	11.8 (23/195)	17.4 (12/69)	0.68 (0.36–1.29)	0.30
Cardiac death	0.5 (1/195)	4.3 (3/69)	0.12 (0.01–1.12)	0.056
MI	3.6 (7/195)	4.3 (3/69)	0.83 (0.22–3.10)	0.72
Q-wave MI	0.0 (0/195)	0.0 (0/69)	NC (NC)	NC
Non–Q-wave MI	3.6 (7/195)	4.3 (3/69)	0.83 (0.22–3.10)	0.72
ID-TLR	3.1 (6/195)	7.2 (5/69)	0.42 (0.13–1.35)	0.16
ID-TLR CABG	0.0 (0/195)	0.0 (0/69)	NC (NC)	NC
ID-TLR PCI	3.1 (6/195)	7.2 (5/69)	0.42 (0.13–1.35)	0.16
ID-TVR (nontarget lesion)	4.6 (9/195)	1.4 (1/69)	3.18 (0.41–24.68)	0.46
ID-TVR CABG	0.5 (1/195)	0.0 (0/69)	NC (NC)	1.00
ID-TVR PCI	4.1 (8/195)	1.4 (1/69)	2.83 (0.36–22.22)	0.45

Intent-to-treat population. Target vessel failure (TVF): composite of cardiac death, myocardial infarction (MI), ischemia-driven target lesion revascularization (ID-TLR), ischemia-driven target vessel revascularization (ID-TVR) (nontarget lesion). All p values displayed are 2-tailed and not from formal hypothesis-testing and are displayed for descriptive purposes only. Subjects are only counted once in the hierarchical order of cardiac death, Q-wave MI, non–Q-wave MI, ID-TLR coronary artery bypass graft surgery (CABG), ID-TLR percutaneous coronary intervention (PCI), ID-TVR CABG, and ID-TVR PCI. This table includes revascularizations on any target vessels(s)/lesion(s) for subjects with 2 target vessels/lesions treated. As per the statistical analysis plan, because the composite TVF and major adverse cardiovascular event (MACE) (cardiac death, MI, ID-TLR) end points included cardiac deaths only, patients with noncardiac deaths were excluded from the denominator. *From Fisher exact test.

CI = confidence interval; NC = not calculable; other abbreviations as in Table 1.

adoption of the ARC definitions were re-adjudicated by the CEC to the new guidelines.

Statistical methods. The rationale for sample size calculations for this study has previously been reported (13). In this article, binary variables are presented as percentages and compared with the Fisher exact test. All analyses are by intention-to-treat with all patients randomized in the study, regardless of the treatment actually received. However, patients who were lost to follow-up, in whom no event had occurred before the follow-up windows, were not included in the denominator for calculations of binary end points. Survival curves were constructed for time-to-event variables with Kaplan-Meier estimates and compared by the log-rank test. Statistical analyses were performed with the SAS statistical package (version 9.1.3, SAS Institute, Cary, North Carolina).

Results

Patient population and lesion characteristics. The baseline demographic, clinical, and angiographic characteristics of both treatment groups have been published previously (16) and are summarized in Table 1. No significant differences were present in any of the parameters listed.

Figure 1 shows the clinical follow-up of patients from enrolment to 3 years, on an intention-to-treat basis. Overall clinical assessment (on the basis of TVF) was available in 264 patients (88%), made up of 195 of the original 223 EES patients (87.4%) and 69 of the original 77 PES patients (89.6%). The reasons for incomplete follow-up are shown in Figure 1. A similar proportion in each stent group were lost because of failure to complete a new consent form, which was required after a change in the initial protocol to allow extended follow-up out to 5 years. Four patients withdrew from the EES group, of which 1 experienced a noncardiovascular event occurring 1-year after PCI; the other 3 patients were all event-free at last contact.

The angiographic outcomes at 6 months and 2 years and the clinical outcomes at 6 months, 1 year, and 2 years have all been presented elsewhere (10,11,16). In brief, at 6

Table 3. Nonhierarchical Subject Counts of Adverse Events Through 3 Years

0–1,095 Days % (n)	EES (n = 223)	PES (n = 77)	Relative Risk (95% CI)	p Value*
All death	4.4 (9/203)	9.6 (7/73)	0.46 (0.18–1.20)	0.14
Cardiac death†	0.5 (1/195)	4.3 (3/69)	0.12 (0.01–1.12)	0.056
MI†	3.6 (7/195)	7.2 (5/69)	0.50 (0.16–1.51)	0.31
Q-wave MI†	0.0 (0/195)	0.0 (0/69)	NC (NC)	NC
Non–Q-wave MI†	3.6 (7/195)	7.2 (5/69)	0.50 (0.16–1.51)	0.31
Any ID-TVR (including ID-TLR)†	9.2 (18/195)	13.0 (9/69)	0.71 (0.33–1.50)	0.36
CABG†	1.0 (2/195)	0.0 (0/69)	NC (NC)	1.00
PCI†	8.7 (17/195)	13.0 (9/69)	0.67 (0.31–1.43)	0.35
All TLR	5.4 (11/203)	12.3 (9/73)	0.44 (0.19–1.02)	0.06
CABG	0.5 (1/203)	0.0 (0/73)	NC (NC)	1.00
PCI	5.4 (11/203)	12.3 (9/73)	0.44 (0.19–1.02)	0.06
ID-TLR†	4.6 (9/195)	10.1 (7/69)	0.45 (0.18–1.17)	0.14
CABG†	0.5 (1/195)	0.0 (0/69)	NC (NC)	1.00
PCI†	4.6 (9/195)	10.1 (7/69)	0.45 (0.18–1.17)	0.14
Non-ID TLR	1.5 (3/203)	5.5 (4/73)	0.27 (0.06–1.18)	0.08
CABG	0.0 (0/203)	0.0 (0/73)	NC (NC)	NC
PCI	1.5 (3/203)	5.5 (4/73)	0.27 (0.06–1.18)	0.08
ID-TVR, nontarget lesion†	5.1 (10/195)	4.3 (3/69)	1.18 (0.33–4.16)	1.00
CABG†	0.5 (1/195)	0.0 (0/69)	NC (NC)	1.00
PCI†	4.6 (9/195)	4.3 (3/69)	1.06 (0.30–3.81)	1.00
Non-ID TVR, nontarget lesion	2.0 (4/203)	1.4 (1/73)	1.44 (0.16–12.66)	1.00
CABG	1.0 (2/203)	0.0 (0/73)	NC (NC)	1.00
PCI	1.0 (2/203)	1.4 (1/73)	0.72 (0.07–7.81)	1.00
Any TVR (including TLR)	11.3 (23/203)	15.1 (11/73)	0.75 (0.39–1.46)	0.41
CABG	2.0 (4/203)	0.0 (0/73)	NC (NC)	0.58
PCI	9.9 (20/203)	15.1 (11/73)	0.65 (0.33–1.30)	0.28

Intent-to-treat population. This table includes revascularizations on any target vessels(s)/lesion(s) for subjects with 2 target vessels/lesions treated. All p values displayed are 2-tailed and not from formal hypothesis testing and are displayed for descriptive purposes only. *From Fisher exact test. †As per the statistical analysis plan, because the composite TVF and MACE end points included cardiac deaths only; patients with noncardiac deaths were excluded from the denominator.

Abbreviations as in Tables 1 and 2.

months EES demonstrated significantly reduced in-stent late loss and percentage volume obstruction when compared with PES ($p < 0.001$). Clinical outcomes in terms of MACE, TVF, MI, cardiac death, and ID-TLR were all better with EES at 6 months, 1 year, and 2 years when compared with PES. Angiographic follow-up at 2 years demonstrated a late increase in neointimal hyperplasia with the EES stent, such that a significant difference was no longer observed between EES and PES for in-stent late loss or percentage volume obstruction.

Clinical outcomes at 3-year follow-up. The hierarchical and non-hierarchical events at 3-year clinical follow-up are shown in Tables 2 and 3, respectively; and Figure 2[6] shows the Kaplan-Meier survival curves for cardiac death, MI, ID-TLR, and MACE.

At 3-year follow-up, the use of EES was associated with nonsignificant reductions in cardiac death, (relative risk [RR]: 0.12, 95% confidence interval [CI]: 0.01 to 1.12, $p = 0.056$) all-cause death (RR: 0.46, 95% CI: 0.18 to 1.20, $p = 0.14$), and MI (RR: 0.50, 95% CI: 0.16 to 1.51, $p = 0.31$). The rates of MI were consistently higher with PES; however, this difference did not reach significance at any time during follow-up.

During the 3-year follow-up period, 7 PES patients (10.1%) and 9 EES patients (4.6%) underwent ID-TLR (RR: 0.45, 95% CI: 0.18 to 1.17, $p = 0.14$). All of these were with PCI, apart from 1 patient in the EES group who underwent CABG. The Kaplan-Meier curve for ID-TLR (Fig. 2B) shows significantly lower ID-TLR with EES at 1-year follow-up; however, this significance was not maintained during long-term follow-up.

The rate of MACE (cardiac death, MI, ID-TLR), which was 7.2% in those patients treated with EES and 15.9% in those treated with PES (RR: 0.45, 95% CI: 0.21 to 0.94, $p = 0.053$), was consistently lower for EES compared with PES; however, the difference between the 2 varied with follow-up. As shown on the Kaplan-Meier curve (Fig. 2), a significant difference in MACE between the 2 stents was observed as early as 12 months (EES vs. PES, 2.7% vs. 9.1%, hazard ratio [HR]: 0.29, 95% CI: 0.10 to 0.87, $p_{logrank} = 0.018$); however, between years 1 and 2 EES seemed to "catch-up." Nevertheless, a significant difference

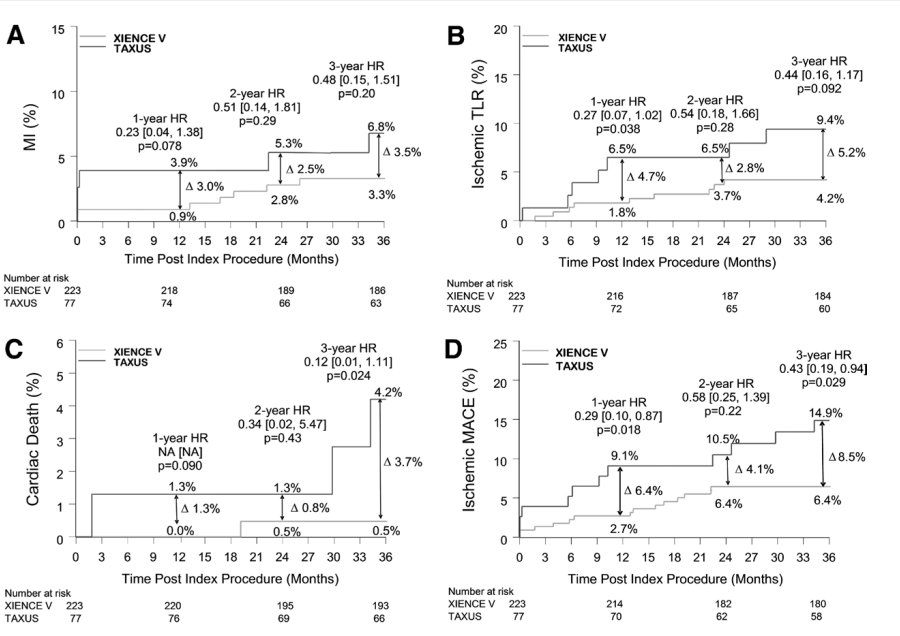


Figure 2. Kaplan-Meier Event Curves at 3-Year Follow-Up

Kaplan-Meier event curves at 3 years follow-up for **(A)** myocardial infarction (MI), **(B)** ischemia-driven target lesion revascularization (TLR), **(C)** cardiac death, and **(D)** major adverse cardiovascular events (MACE). HR = hazard ratio; NA = not applicable.

Table 4. Stent Thrombosis Events by ARC Definitions

Definite and Probable	EES	PES
Acute stent thrombosis (%)	0.0	0.0
Subacute stent thrombosis (%) (24 h–30 days)	0.0	1/77 (1.3)*
Late stent thrombosis (%) (30 days–1 yr)	0.0	1/77 (1.3)*
Very late stent thrombosis (%) (>1 yr)	2/193 (1.0)	1/67 (1.5)
Total stent thrombosis	2/193 (1.0)	2/68 (2.9)

Values are n (%). *Same patient.
ARC = Academic Research Consortium; other abbreviations as in Table 1.

re-emerged by the third year of follow-up (EES vs. PES, 6.4% vs. 14.9%, HR: 0.43, 95% CI: 0.19 to 0.94, $p_{logrank}$ = 0.029), which was the result of 3 additional patients with MACE observed in the PES group, whereas no new patients experienced MACE in the EES group.

The rates of stent thrombosis as per ARC definitions are listed in Table 4. After the 2-year follow-up, no definite/probable stent thrombosis occurred in the EES group, compared with 1 in the PES group. Overall, at 3-year follow-up the rate of stent thrombosis was numerically lower in the EES group (1.0% vs. 2.9%, p = 0.28). The proportion of patients returning for 3-year follow-up, who remained on dual antiplatelet therapy at 3 years, was 14.1% and 21.2% for patients treated with EES and PES, respectively (Fig. 3).

Discussion

This randomized prospective study of the EES has confirmed its favorable clinical outcomes at 3-year follow-up and enhances the work of the previous EES studies (5–8,17).

In the present study, patients randomized to EES experienced fewer MIs, fewer ID-TLR, and had a trend for less cardiac death compared with those patients treated with PES. The overall rates of both MACE and TVF were numerically lower in favor of EES. These 3-year results demonstrate the maintenance of the superior outcomes with EES, which were observed as early as 6 months (13).

Two-year outcome data from SPIRIT II showed the maintenance of the advantage of EES over PES; however, HRs were less prominent than previously observed at 12 months (11). Furthermore, the results of 2-year angiographic follow-up in 97 EES patients demonstrated a 94% increase in the mean in-stent late loss among EES between 6 months and 2 years (0.17 ± 0.32 mm vs. 0.33 ± 0.37 mm), whereas a 3% increase was observed with PES over the same time period (0.33 ± 0.32 mm vs. 0.34 ± 0.34 mm). It is worth noting, however, that angiographic follow-up at 2 years was in a subset and not the entire SPIRIT II population, and as such, an unintended selection bias in this subset cannot be ruled out.

Nevertheless, concerns were raised as to the clinical relevance of this "late-catch up phenomenon" that was observed with EES. The present study, however, confirms that this increase in neointimal hyperplasia did not translate into any clinical events. In fact, between years 2 and 3, 2 ID-TLR were performed for EES (1 of which in a patient who already had ID-TLR before 6 months), and similarly, 2 ID-TLR were performed for PES. The absolute difference in rates of ID-TLR between EES and PES actually increased from 4.7% at 1 year to 5.2% at 3 years (Fig. 2). In addition, no cardiac deaths occurred with EES between years 2 and 3. Of note, the Kaplan-Meier curves for MACE and all its components at 3 years seem to diverge, further supporting the superior performance of the EES with long-term follow-up.

The much larger SPIRIT III trial randomized EES to PES in a 2:1 ratio and enrolled 1,002 patients with similar inclusion and exclusion criteria. The demographic data of both patient populations were similar. The SPIRIT III trial again confirmed the superior performance of EES compared with PES with long-term follow-up with a 45% reduction in MACE at 2 years (7.3% vs. 12.8%; HR: 0.55; 95% CI: 0.36 to 0.83, p = 0.004). Importantly, and unlike in SPIRIT II, there was no reduction in HRs between 1 and 2 years; in fact, the clinical benefits of EES seem to increase (12).

Although the current study is underpowered to make any definitive conclusions regarding stent thrombosis rates between EES and PES, it does confirm low rates of late stent thrombosis with EES (1.0%), which is comparable to published data for sirolimus-eluting stents (SES) and PES, at similar follow-up (18). Historically, first-generation DES have been associated with a persistent risk of very late stent

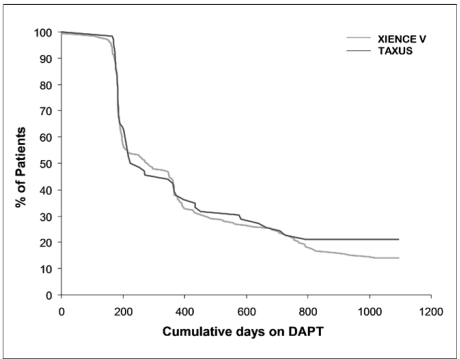


Figure 3. Cumulative Duration of DAPT in Patients With 3-Year Follow-Up

Graph demonstrating the cumulative use of dual antiplatelet therapy (DAPT) among the 264 patients who returned for 3-year follow-up. In total, 14.1% of patients treated with everolimus-eluting stents and 21.2% of patients treated with paclitaxel-eluting stents were still receiving DAPT at 1,080 days of follow-up.

thrombosis, extending out to 4-year follow-up (18); however, this might not be the same for the newer generation of DES such as the XIENCE V. In the current study EES has demonstrated no episodes of acute or late stent thrombosis, 2 episodes (1 definite and 1 probable) of very late stent thrombosis between year 1 and year 2, and no stent thrombosis events after 2 years. Similarly, the SPIRIT III trial demonstrated a low rate of very late (0.3%) and overall stent thrombosis (1.3%) with EES. The relationship of the late loss catch-up, if any, with lower late stent thrombosis is unclear; it is possible that neointimal healing, reflected as a modest increase in late loss over time, might in fact be protective.

The SES has been demonstrated to be the most efficacious first-generation DES (19–21), and therefore, the use of PES in this study might account for the favorable outcomes observed with EES. In principle, because both everolimus and sirolimus inhibit the mammalian target of rapamycin in a similar manner, a comparison between the 2 might demonstrate similar clinical outcomes. Indirect comparisons do support this; for example, similar rates of late loss occurred in the EES arm of the SPIRIT III trial and the SES arm of the SIRIUS (Sirolimus-Eluting Stent in de novo Native Coronary Lesions) trial (EES 0.16 mm vs. SES 0.17 mm) (9,22); however, as yet no randomized head-to-head comparison has been made between the 2 stents. There are, in addition to the antiproliferative coating, other notable differences between the stents, which might result in different clinical outcomes. In brief, EES is made of cobalt chromium, as opposed to stainless steel (PES and SES), which allows comparative radial strength to be achieved with considerably thinner stent struts. This can reduce vascular injury, intimal hyperplasia, and the risk of restenosis (23). Vascular injury and inflammation are also potentially reduced with the use of more biocompatible polymers as found on the EES, compared with the durable and less biocompatible polymers found on the PES and SES.

A clearer picture will be obtained when the results of the prospective, randomized, multicenter EXCELLENT (Efficacy of Xience/promus versus Cypher in rEducing Late Loss after stENTing) trial are available. This study is enrolling approximately 1,400 patients with the aim of comparing the safety and efficacy of the EES and SES and the optimal duration of dual antiplatelet therapy (6 or 12 months). The co-primary end points are the noninferiority of EES compared with SES in inhibiting neointima hyperplasia and preventing late loss at 9 months and TVF at 12 months for comparison of dual antiplatelet therapy duration (24). Furthermore, additional studies of the EES include the SPIRIT IV, SPIRIT V, XIENCE V SPIRIT WOMEN, XIENCE V USA, and XIENCE V INDIA, which are all designed to evaluate the safety and efficacy of the EES in over 14,000 real-world patients.

Study limitations. This study was not powered to detect significant differences in the safety profiles of either stent. In view of the small number of patients recruited and the loss of 8% of patients from follow-up (which was similar in both groups), caution is required when interpreting the differences in events.

Conclusions

The present study reports the favorable 3-year clinical outcomes of the EES, which are consistent with the results from earlier studies with shorter follow-up. In this study, compared with the PES, the EES demonstrated a reduction in cardiac events, clinical restenosis, and overall MACE rate at long-term follow-up. In addition, the overall lower rate of stent thrombosis and absence of stent thrombosis after 2 years with EES is potentially significant and requires additional investigation.

Reprint requests and correspondence: Prof. Patrick Serruys, Ba583a, Thoraxcenter, Erasmus MC,'s-Gravendijkwal 230, 3015 CE Rotterdam, the Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl.

REFERENCES

1. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773–80.
2. Jeremias A, Kirtane A. Balancing efficacy and safety of drug-eluting stents in patients undergoing percutaneous coronary intervention. Ann Intern Med 2008;148:234–8.
3. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. Circulation 2007;115:1440–55, discussion 1455.
4. Costa RA, Lansky AJ, Mintz GS, et al. Angiographic results of the first human experience with everolimus-eluting stents for the treatment of coronary lesions (the FUTURE I trial). Am J Cardiol 2005;95:113–6.
5. Grube E, Sonoda S, Ikeno F, et al. Six- and twelve-month results from first human experience using everolimus-eluting stents with bioabsorbable polymer. Circulation 2004;109:2168–71.
6. Tsuchiya Y, Lansky AJ, Costa RA, et al. Effect of everolimus-eluting stents in different vessel sizes (from the pooled FUTURE I and II trials). Am J Cardiol 2006;98:464–9.
7. Windecker S. Are All New Drug Eluting Stents the Same? Available at: www.europcronline.com/fo/lecture/view_slide.php?id=5455. Accessed April 10, 2009.
8. Serruys PW, Ong ATL, Piek JJ, et al. A randomised comparison of a durable polymer Everolimus-Eluting stent with a bare metal coronary stent: the SPIRIT First trial. Eurointervention 2005;1:58–65.
9. Stone GW, Midei M, Newman W, et al. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. JAMA 2008;299:1903–13.
10. Ruygrok P, Desaga M, van den Branden F, et al. One year clinical follow-up of the XIENCE V Everolimus-eluting stent system in the treatment of patients with de novo native coronary artery lesions: the SPIRIT II study. Eurointervention 2007:315–20.
11. Claessen BE, Beijk MA, Legrand V, et al. Two-year clinical, angiographic, and intravascular ultrasound follow-up of the XIENCE V everolimus-eluting stent in the treatment of patients with de novo native coronary artery lesions: the SPIRIT II trial. Circ Cardiovasc Intervent 2009;2:339–47.
12. Stone GW, Midei M, Newman W, et al. Randomized comparison of everolimus-eluting and paclitaxel-eluting stents: two-year clinical follow-up from the clinical evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions (SPIRIT) III trial. Circulation 2009;119:680–6.

13. Serruys PW, Ruygrok P, Neuzner J, et al. A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent: the SPIRIT II trial. Eurointervention 2006;2:286–94.
14. Farb A, John M, Acampado E, Kolodgie FD, Prescott MF, Virmani R. Oral everolimus inhibits in-stent neointimal growth. Circulation 2002; 106:2379–84.
15. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
16. Serruys PW, Ruygrok P, Neuzner J, et al. A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent: the SPIRIT II trial. Eurointervention 2006;2: 286–94.
17. Tsuchida K, Piek JJ, Neumann F-J, et al. One-year results of a durable polymer everolimus-eluting stent in de novo coronary narrowings (the SPIRIT FIRST trial). Eurointervention 2006;1:266–72.
18. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;369:667–78.
19. Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet 2007;370:937–48.
20. Morice MC, Colombo A, Meier B, et al. Sirolimus- vs paclitaxel-eluting stents in de novo coronary artery lesions: the REALITY trial: a randomized controlled trial. JAMA 2006;295:895–904.
21. Windecker S, Remondino A, Eberli FR, et al. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. N Engl J Med 2005;353:653–62.
22. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–23.
23. Kastrati A, Mehilli J, Dirschinger J, et al. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO) trial. Circulation 2001;103:2816–21.
24. Park KW, Yoon JH, Kim JS, et al. Efficacy of Xience/promus versus Cypher in rEducing Late Loss after stENTing (EXCELLENT) trial: study design and rationale of a Korean multicenter prospective randomized trial. Am Heart J 2009;157:811–7.e1.

Key Words: angioplasty ■ everolimus-eluting stent ■ paclitaxel-eluting stent.

Chapter 7.2

Four year clinical follow up of the XIENCE V Everolimus eluting coronary stent system in the treatment of patients with de novo coronary artery lesions. The SPIRIT II Trial.

Catheter Cardiovasc Interv 2010 Sep 7. [Epub ahead of print]

Scot Garg, Patrick W. Serruys, Katherine Miquel-Hebert on behalf of the SPIRIT II Investigators

Original Studies

Four-Year Clinical Follow-Up of the XIENCE V Everolimus-Eluting Coronary Stent System in the Treatment of Patients With *De Novo* Coronary Artery Lesions: The SPIRIT II Trial

Scot Garg,[1] MB, ChB, MRCP, Patrick W. Serruys,[1*] MD, PhD, and Karine Miquel-Hebert,[2] PhD, on behalf of the SPIRIT II Investigators

This report describes the 4-year clinical outcomes of the SPIRIT II study, which randomized 300 patients to treatment with the XIENCE V everolimus-eluting stent (EES), or the TAXUS paclitaxel-eluting stent. At 4-year clinical follow-up, which was available in 256 (85.3%) patients, treatment with EES lead to a trend for lower rates of ischemia-driven major adverse cardiovascular events, a composite of cardiac death, myocardial infarction, and ischemia-driven target lesion revascularization (EES 7.7% vs. paclitaxel-eluting stent 16.4%, $P = 0.056$). Treatment with EES also resulted in a trend toward lower rates of cardiac death and numerically lower rates of myocardial infarction, ischemia-driven target lesion revascularization, and stent thrombosis. Overall, this study reports numerically fewer clinical events in patients treated with EES at 4-year follow-up, which is consistent with results from earlier follow-up. © 2010 Wiley-Liss, Inc.

Key words: percutaneous coronary intervention (PCI); angiography coronary (ANGO); diagnostic cardiac catheterization (CATH)

INTRODUCTION

Second-generation drug-eluting stents (DES), such as the XIENCE V everolimus-eluting stent (EES; Abbott Vascular, Santa Clara, CA), were developed with the aim of improving the safety profile of DES, after reports of stent thrombosis (ST) with first-generation devices [1]. These newer-generation stents elute everolimus or zotarolimus, use more biocompatible polymers, and have cobalt chromium stent platforms. Current results from randomized studies evaluating the EES indicate favorable clinical outcomes, together with lower rates of ST when compared with first-generation DES; however, results are limited to only medium-term follow-up [2–5]. Ensuring that these benefits are sustained long-term is important, not only because drug elution ceases within 6 months of stent implantation, but also because of the permanence of the stent platform and polymer. Therefore, in this study, we report the 4-year clinical outcomes of patients randomized to treatment with either EES or the TAXUS paclitaxel-eluting stent (PES; Boston Scientific, Natick, MA) in the SPIRIT II study.

METHODS

Study Design

The study design and outcomes at 6-, 12-, 24-, and 36-months follow-up are reported elsewhere [2,6–8]. In brief, this multicenter, prospective, single-blind study randomized 300 patients with up to two *de novo*

[1]Department of Interventional Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands
[2]Abbott Vascular, Diegem, Belgium

Conflict of interest: Karine Miquel-Hebert is an employee of Abbott Vascular. The other authors have no conflicts of interest to report.

Study sponsor: Abbott Vascular

*Correspondence to: Patrick W. Serruys, MD, PhD, Ba583a, Thoraxcenter, Erasmus MC,'s-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl

Received 9 June 2010; Revision accepted 6 August 2010

DOI 10.1002/ccd.22770
Published online in Wiley Online Library (wiley onlinelibrary.com)

coronary artery lesions in a ratio of 3:1 to treatment with either EES ($n = 223$) or PES ($n = 77$). The primary endpoint was in-stent late loss at 180 days.

Endpoints

Clinical endpoints assessed at 4 years included ischemia-driven major adverse cardiac events (ID-MACE), a composite of cardiac death, myocardial infarction (MI), and ischemia-driven target lesion revascularization (ID-TLR) by percutaneous coronary intervention or coronary artery bypass graft surgery, and its individual components. All events up to 4 years were adjudicated by an independent clinical event committee that was blinded to the treatment assignments.

Definitions

Complete definitions are provided elsewhere [2,6–8]. All deaths were considered cardiac unless an undisputed noncardiac cause was present. Q-wave MI was defined as the development of new pathological Q waves. A non-Q-wave MI was defined as a typical rise and fall of creatine kinase myoglobin band (CK-MB), with at least one of the following: ischemic symptoms; electrocardiographic changes indicative of ischemia (ST segment elevation or depression); or an associated coronary artery intervention. For a nonprocedural or spontaneous MI, the CK-MB was required to be ≥ 2 times the upper limit of normal (ULN). A CK-MB ≥ 3 times the ULN or ≥ 5 times the ULN was required for an MI to be defined postpercutaneous coronary intervention or postcoronary artery bypass graft, respectively. ID-TLR was defined as revascularization of the target lesion in association with any of the following: a positive test of ischemia, using either exercise testing, or fractional/coronary flow reserve; ischemic symptoms and an angiographic diameter stenosis $\geq 50\%$ by on-line quantitative coronary angiography (QCA); or a diameter stenosis $\geq 70\%$ by on-line QCA without ischemic symptoms or a positive functional study. ST was classified according to the Academic Research Consortium classification [9].

Statistical Methods

All analyses were conducted according to the intention-to-treat principle. Binary variables are presented as percentages (counts), and compared using the Fisher's exact test. Cumulative events curves were generated using the Kaplan–Meier method, and the two groups were compared using the log-rank test. Hazard ratios with 95% confidence intervals were calculated using the Cox proportional hazards model.

RESULTS

Clinical follow-up was available in 256 (85.3%) patients (EES 192 [86.1%] and PES 64 [83.1%]) with a similar proportion of patients (EES 15 [6.7%] and PES 4 [5.2%]) lost because of failure to complete a new consent form, which was required after a change to the initial protocol to allow extended follow-up to 5 years. Other reasons for incomplete follow-up included death (EES 10 and PES 7), loss to follow-up (EES 2), and withdrawal (EES 4 and PES 2).

Baseline Demographic Data

Baseline demographic, clinical, and angiographic characteristics, which were comparable between both treatment groups are described in full elsewhere [6] and summarized in Table I.

Clinical Outcomes

Clinical outcomes in terms of cardiac death, MI, ID-TLR, all TLR, and ID-MACE at 4-year follow-up are shown in Table II. At 4 years, there was a trend for lower rates of cardiac mortality, all TLR, and ID-MACE in patients treated with EES. Rates of MI and ID-TLR were numerically lower with EES, although these differences were not statistically significant. Kaplan–Meier cumulative curves are shown in Fig. 1A–D.

The rate of definite or probable ST out to 4-year follow-up was 0.9% and 2.8% in patients treated with EES and PES, respectively ($P = 0.27$, Fig. 1E, Table III). Of note, no ST events were observed in the EES arm after 24 months of follow-up, whereas only one ST event was observed in the PES arm around month 30. The proportion of patients returning for 4-year follow-up, who were still taking dual antiplatelet therapy were 17.7% (34 of 192) and 21.9% (14 of 64) for patients treated with EES and PES, respectively. All patients experiencing an ST event were taking aspirin at the time of the event, with only one patient also taking clopidogrel (Table III).

DISCUSSION

This study represents the longest available follow-up of EES in a randomized patient population and, thereby, provides important data on the long-term efficacy and the safety of EES. The assessment of long-term outcomes is particularly important for DES because the elution of antiproliferative agents is largely exhausted within 6 months of stent deployment. Therefore long-term efficacy is not a consequence of drug elution, but more dependent on the stent platform and

Catheterization and Cardiovascular Interventions DOI 10.1002/ccd.
Published on behalf of The Society for Cardiovascular Angiography and Interventions (SCAI).

TABLE I. Baseline Patient Data

	Everolimus stent ($n = 223$)	Paclitaxel stent ($n = 77$)	All patients ($n = 300$)
Age (years)	62 ± 10	62 ± 9	62 ± 10
Male gender (%)	71	79	73
Current smoker (%)	32	30	31
Diabetes (%)	23	24	23
Hypertension requiring medication (%)	67	65	67
Hyperlipidemia requiring medication (%)	69	75	70
Prior target vessel intervention (%)	4	4	4
Prior MI (%)	35	25	32
Stable angina (%)	62	62	62
Unstable angina (%)	27	32	28
Target vessel (%)	No. of lesions = 260	No. of lesions = 91	No. of lesions = 351
Left anterior descending	41	47	42
Left circumflex	29	19	26
Right coronary artery	30	34	31
AHA/ACC lesion class (%)			
A	1	0	1
B1	21	20	21
B2	65	67	66
C	13	13	13
Reference vessel diameter (±SD) (mm)	2.70 ± 0.52	2.82 ± 0.58	2.73 ± 0.54
Lesion length (±SD) (mm)	13.0 ± 5.7	13.2 ± 6.4	13.0 ± 5.9

There was no significant difference between the everolimus and paclitaxel treatment arms.
MI, myocardial infarction; AHA/ACC, American Heart Association/American College of Cardiology.

polymer. Newer-generation DES, such as EES and the Endeavor (Medtronic, Santa Rosa, CA) zotarolimus-eluting stent (ZES), use a cobalt chromium stent platform that enables struts to be thinner, which ultimately can reduce vascular injury, leading to a lower risk of restenosis and ST. In addition, the improvement in the biocompatibility of the stent polymer is designed to improve the stent's safety profile, potentially reducing the risk of ST further [10].

Besides this study, the only other randomized data to support the potential benefits of second- versus first-generation DES at long-term (>3 years) follow-up are the ENDEAVOR III study, which randomized patients to either the Cypher (Cordis, Warren, NJ) sirolimus-eluting stent (SES), or ZES [11]. Although the 6-months results from the ENDEAVOR III study failed to demonstrate noninferiority of ZES with respect of the primary endpoint of in-segment late loss (ZES 0.34 ± 0.44 mm vs. SES 0.13 ± 0.32 mm; $P < 0.001$), long-term results suggest a more durable performance of ZES [12]. In particular, respective rates of death, TLR, target vessel failure, and ST between 1- and 5-year follow-up rose by 4.6%, 1.6%, 5.9%, and 0.7% for ZES, compared with rises of 13.0%, 3.0%, 7.0%, and 0.9% for SES, such that the early superiority of SES was not sustained at final follow-up.

Similarly, this report demonstrates the long-term safety and sustained efficacy of EES, which is consistent with other results observed from the evaluation EES at shorter follow-up [2–5]. It is noteworthy that the long-term efficacy of everolimus was previously called into question after the delayed late-loss observed in the EES angiographic subset of this study at 2 years [8]. Importantly, this delayed late-loss had little effect on reported clinical outcomes at 3-year follow-up, and, reassuringly, this is consistent with the present results, which show absolute differences between EES and PES for cardiac death, MI, ID-TLR, and ID-MACE, which are all at least as good at 4-years follow-up as they were at 1- and 2-year follow-up. Clearly, in the absence of further QCA analyses, it is not possible to definitively state whether these durable clinical results entirely dismiss the significance of the previously observed delayed late-loss. In contrast, in the SIRTAX-LATE study, the delayed late-loss observed with SES

TABLE II. Clinical Outcomes at 4-Year Follow-up

0–1,460 Days, % (n)	EES ($n = 195$)	PES ($n = 67$)	P-value[a]
MACE	7.7 (15)	16.4 (11)	0.056
Cardiac death	0.5 (1)	4.5 (3)	0.053
Myocardial infarction	3.6 (7)	7.5 (5)	0.19
Ischemia-driven TLR	5.1 (10)	10.4 (7)	0.15
All TLR	5.9 (12)	12.7 (9)	0.073

MACE hierarchical, and all others nonhierarchical.
[a]From Fisher's exact test.MACE, major adverse cardiovascular events (a composite of cardiac death, myocardial infarction, and ischemia-driven target lesion revascularization); TLR, target lesion revascularization.

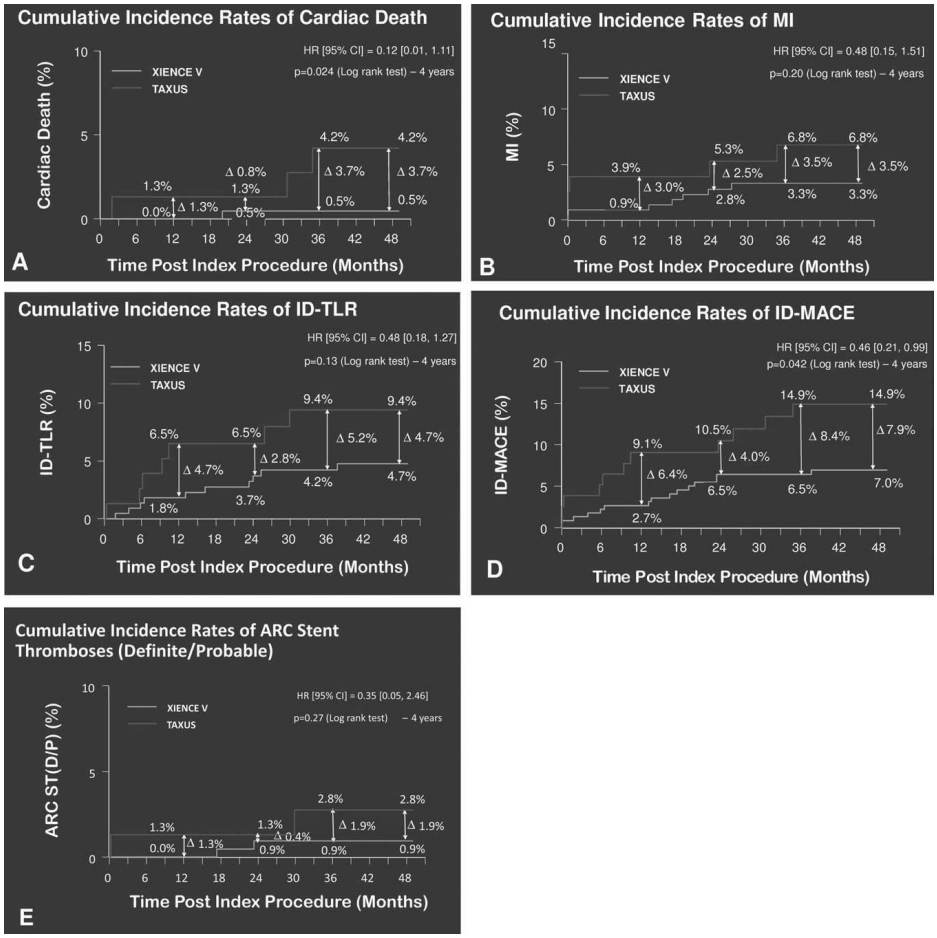


Fig. 1. Cumulative Kaplan–Meier estimates of the rates of key study endpoints. Cumulative risk of events at 1,460 days for (A) cardiac death; (B) myocardial infarction (MI); (C) ischemia-driven target lesion revascularization (ID-TLR); (D) ischemia-driven major adverse cardiac events (ID-MACE), a composite of cardiac death, nonfatal myocardial infarction (MI), and ischemia-driven target lesion revascularization (ID-TLR); and (E) definite/probable stent thrombosis. HR, hazard ratio.

(Δ 0.18 mm between 1 and 5 years) was associated with the absolute difference in TLR between SES and PES falling from 3.5% at 1 year to 3.0% at 5 years [13]. With both EES and SES, drug elution is complete within 6 months, reiterating that other factors such as the type of stent platform and polymer biocompatibility are important factors in influencing the long-term efficacy of DES.

Ultimately, the concerns over ST were one of the main driving forces behind the development of second-generation DES. EES has an acrylic fluorinated polymer, which is considered to be more biocompatible than that found on SES and PES; however, at present, no published study has been adequately powered to make any definitive conclusions regarding rates of ST between DESs. In this study, despite a lower

Catheterization and Cardiovascular Interventions DOI 10.1002/ccd.
Published on behalf of The Society for Cardiovascular Angiography and Interventions (SCAI).

TABLE III. Definite and Probable Stent Thrombosis Events Out to 4-Year Follow-up

Days to ST	Stent	Stented vessel	Antiplatelet therapy use throughout the study period	Events at time of ST	Worst hierarchical outcome
Definite ST					
9[a]	PES	Mid LAD	Aspirin throughout the study period; clopidogrel throughout the study period	Day 8: non-Q-wave MI; day 9: ID-TLR	Day 56: cardiac death
521	EES	Mid RCA	Aspirin throughout the study period; clopidogrel for 1 year, restarted on day 521 and stopped on day 956	Day 521: Non Q-wave MI	Day 521: non-Q-wave MI
897	PES	Distal RCA	Aspirin until day 1,026; clopidogrel for 6 months, restarted on day 1,009 and continued throughout the study period	Day 896: ID-TLR PCI	Day 1: non-Q-wave MI
Probable ST					
54[a]	PES	Mid LAD	Aspirin throughout the study period; clopidogrel throughout the study period	Day 54: non-Q-wave MI	Day 56: cardiac death
721	EES	Distal RCA	Aspirin throughout the study period; clopidogrel for 190 days	Day 700: non-Q-wave MI; day 721: ID-TLR	Day 700: non-Q-wave MI

[a]Same patient.
ST, stent thrombosis; PES, paclitaxel-eluting stent; EES, everolimus-eluting stent; LAD, left anterior descending artery; RCA, right coronary artery; MI, myocardial infarction; ID-TLR, ischemia-driven target lesion revascularization.

proportion of patients taking dual antiplatelet therapy with EES at the time of follow-up, rates of ST remain numerically lower with EES, with no ST observed over the last 2 years of follow-up. The small sample size of this study must be taken into account; however, the absence of very late ST events during prolonged follow-up is important nevertheless. It will be of great interest to observe whether similar findings are seen during long-term follow-up of the more complex patient groups enrolled in the SPIRIT III and IV studies.

Limitations

The loss of patients during clinical follow-up, which was largely because of the failure of some patients to complete a new consent form that was required after a protocol amendment increasing follow-up of the study from 2 to 5 years, impacts on the power of the study to detect differences in clinical events. Moreover, interpretation of the current clinical results must take into account that the study was powered for in-stent late loss at 6-month follow-up and, therefore, not specifically designed to detect differences in clinical outcomes or ST.

CONCLUSIONS

This study reports numerically fewer clinical events at 4-year follow-up in patients treated with EES compared with the PES, which is consistent with other randomized studies of EES albeit at shorter follow-up. Overall, ST rates were low, with the absence of recent ST events remaining an important observation requiring careful surveillance.

REFERENCES

1. Stettler C, Wandel S, Allemann S, Kastrati A, Morice MC, Schomig A, Pfisterer ME, Stone GW, Leon MB, de Lezo JS, et al. Outcomes associated with drug-eluting and bare-metal stents: A collaborative network meta-analysis. Lancet 2007;370: 937–948.
2. Garg S, Serruys PW, Onuma Y, Dorange C, Veldhof S, Miquel-Hebert K, Sudhir K, Boland J, Huber KC, Garcia E, et al. Three year clinical follow up of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo coronary artery lesions. The SPIRIT II Trial. J Am Coll Cardiol Intv 2009;2:1190–1198.
3. Stone GW. The XIENCE V-PROMUS everolimus-eluting stent: Comprehensive update of the clinical trial program. Presented at the Transcatheter Cardiovascular Therapeutics, September 21, 2009. Available at: www.tctmd.com/txshow.aspx?tid=939082&id=84006&trid=938634. Accessed October28, 2009.
4. Kedhi E, Joesoef KS, McFadden E, Wassing J, van Mieghem C, Goedhart D, Smits PC. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): A randomised trial. Lancet . 2010;375:201–209.
5. Stone GW, Rizvi A, Newman W, Mastali K, Wang JC, Caputo R, Doostzadeh J, Cao S, Simonton CA, Sudhir K, et al. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med 2010;362:1663–1674.
6. Serruys PW, Ruygrok P, Neuzner J, Piek JJ, Seth A, Schofer JJ, Richardt G, Wiemer M, Carrie D, Thuesen L, et al. A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent: The SPIRIT II trial. Eurointervention 2006;2:286–294.
7. Ruygrok P, Desaga M, van den Branden F, Rasmussen K, Suryapranata H, Dorange C, Veldhof S, Serruys PS II. One year clinical follow-up of the XIENCE V everolimus-eluting stent system in the treatment of patients with de novo native coronary artery lesions: The SPIRIT II study. Eurointervention 2007;3: 315–320.
8. Claessen BE, Beijk MA, Legrand V, Ruzyllo W, Manari A, Varenne O, Suttorp MJ, Tijssen JGP, Miquel-Hebert K, Veldhof S, et al. Two-year clinical, angiographic, and intravascular ultrasound follow-up of the XIENCE V everolimus-eluting stent in

Catheterization and Cardiovascular Interventions DOI 10.1002/ccd.
Published on behalf of The Society for Cardiovascular Angiography and Interventions (SCAI).

the treatment of patients with de novo native coronary artery lesions: The SPIRIT II trial. Circ Cardiovasc Interv 2009;2: 339–347.
9. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, et al. Clinical end points in coronary stent trials: A case for standardized definitions. Circulation 2007;115:2344–2351.
10. Holmes DR Jr, Kereiakes D, Garg S, Serruys PW, Dehmer GJ, Ellis SG, Williams DO, Kimura T, Moliterno D. Stent thrombosis. J Am Coll Cardiol, in press.
11. Kandzari DE, Leon MB, Popma JJ, Fitzgerald PJ, O'Shaughnessy C, Ball MW, Turco M, Applegate RJ, Gurbel PA, Midei MG, et al. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease: A randomized controlled trial. J Am Coll Cardiol 2006;48: 2440–2447.
12. Kandzari D, Mauri L, Popma J, Turco M, O'Shaughnessy C, Gurbel P, Fitzgerald P, Leon MB. ENDEAVOR III: 5 year final outcomes. Presented at the American College of Cardiology Scientific Sessions, Atlanta, GA, March 14–16, 2010.
13. Raber L. SIRTAX-LATE: Five-year clinical and angiographic follow-up from a prospective randomized trial of sirolimus-eluting and paclitaxel-eluting stents. Presented at the Transcatheter Cardiovascular Therapeutics, San Francisco, CA, September 22, 2009.

Chapter 7.3

Comparison of zotarolimus-eluting and everolimus-eluting coronary stents

N Engl J Med 2010; 363 (2):136-146

Patrick W. Serruys, Sigmund Silber, Scot Garg, Robert Jan van Geuns, Gert Richardt, Pawel E. Buszman, Henning Kelbæk, Adrianus Johannes van Boven, Sjoerd H. Hofma, Axel Linke, Volker Klauss, William Wijns, Carlos Macaya, Philippe Garot, Carlo DiMario, Ganesh Manoharan, Ran Kornowski, Thomas Ischinger, Antonio Bartorelli, Jacintha Ronden, Marco Bressers, Pierre Gobbens, Manuela Negoita, Frank van Leeuwen, Stephan Windecker

ORIGINAL ARTICLE

Comparison of Zotarolimus-Eluting and Everolimus-Eluting Coronary Stents

Patrick W. Serruys, M.D., Ph.D., Sigmund Silber, M.D., Ph.D., Scot Garg, M.B., Ch.B., M.R.C.P., Robert Jan van Geuns, M.D., Ph.D., Gert Richardt, M.D., Pawel E. Buszman, M.D., Ph.D., Henning Kelbæk, M.D., Adrianus Johannes van Boven, M.D., Ph.D., Sjoerd H. Hofma, M.D., Ph.D., Axel Linke, M.D., Ph.D., Volker Klauss, M.D., Ph.D., William Wijns, M.D., Ph.D., Carlos Macaya, M.D., Ph.D., Philippe Garot, M.D., Carlo DiMario, M.D., Ph.D., Ganesh Manoharan, M.B., B.Ch., M.D., F.R.C.P., Ran Kornowski, M.D., Thomas Ischinger, M.D., Ph.D., Antonio Bartorelli, M.D., Jacintha Ronden, Ph.D., Marco Bressers, M.Sc., Pierre Gobbens, B.Sc., Manuela Negoita, M.D., Frank van Leeuwen, M.D., and Stephan Windecker, M.D.

ABSTRACT

BACKGROUND

New-generation coronary stents that release zotarolimus or everolimus have been shown to reduce the risk of restenosis. However, it is unclear whether there are differences in efficacy and safety between the two types of stents on the basis of prospectively adjudicated end points endorsed by the Food and Drug Administration.

METHODS

In this multicenter, noninferiority trial with minimal exclusion criteria, we randomly assigned 2292 patients to undergo treatment with coronary stents releasing either zotarolimus or everolimus. Twenty percent of patients were randomly selected for repeat angiography at 13 months. The primary end point was target-lesion failure, defined as a composite of death from cardiac causes, any myocardial infarction (not clearly attributable to a nontarget vessel), or clinically indicated target-lesion revascularization within 12 months. The secondary angiographic end point was the extent of in-stent stenosis at 13 months.

RESULTS

At least one off-label criterion for stent placement was present in 66% of patients. The zotarolimus-eluting stent was noninferior to the everolimus-eluting stent with respect to the primary end point, which occurred in 8.2% and 8.3% of patients, respectively ($P<0.001$ for noninferiority). There were no significant between-group differences in the rate of death from cardiac causes, any myocardial infarction, or revascularization. The rate of stent thrombosis was 2.3% in the zotarolimus-stent group and 1.5% in the everolimus-stent group ($P=0.17$). The zotarolimus-eluting stent was also noninferior regarding the degree (±SD) of in-stent stenosis (21.65±14.42% for zotarolimus vs. 19.76±14.64% for everolimus, $P=0.04$ for noninferiority). In-stent late lumen loss was 0.27±0.43 mm in the zotarolimus-stent group versus 0.19±0.40 mm in the everolimus-stent group ($P=0.08$). There were no significant between-group differences in the rate of adverse events.

CONCLUSIONS

At 13 months, the new-generation zotarolimus-eluting stent was found to be noninferior to the everolimus-eluting stent in a population of patients who had minimal exclusion criteria. (ClinicalTrials.gov number, NCT00617084.)

From Erasmus Medical Center (P.W.S., S.G., R.J.G.) and Cardialysis (J.R., M.B., P. Gobbens) — both in Rotterdam; and Medisch Centrum Leeuwarden, Leeuwarden (A.J.B., S.H.H.) — all in the Netherlands; Kardiologische Praxis und Praxisklinik (S.S.), University Hospital Munich (Innenstadt) (V.K.) and Hospital Bogenhausen (T.I.) — all in Munich; Herz-Kreislauf-Zentrum, Segeberger Kliniken, Bad Segeberg (G.R.); and Herzzentrum Leipzig, Leipzig (A.L.) — all in Germany; Medical University of Silesia, Katowice, Poland (P.E.B.); Rigshospitalet, Copenhagen (H.K.); Onze Lieve Vrouw Ziekenhuis, Aalst, Belgium (W.W.); Hospital Universitario, Madrid (C.M.); Institut Cardiovasculaire Paris-Sud, Quincy, France (P. Garot); Royal Brompton Hospital, London (C.D.); Royal Victoria Hospital, Belfast, United Kingdom (G.M.); Rabin Medical Center, Tel Aviv University, Tel Aviv (R.K.); Centro Cardiologico Monzino, Milan (A.B.); Medtronic, Santa Rosa, CA (M.N., F.L.); and Bern University Hospital, Bern, Switzerland (S.W.). Address reprint requests to Dr. Serruys at the Department of Cardiology, Erasmus Medical Center, Molewaterplein 40, Ba-583, 3015 GD Rotterdam, the Netherlands, or at p.w.j.c.serruys@erasmusmc.nl.

This article (10.1056/NEJMoa1004130) was published on June 16, 2010, at NEJM.org.

N Engl J Med 2010;363:136-46.

The use of early drug-eluting stents consisting of a metal platform and the controlled release of a therapeutic agent from a durable polymer matrix has partially addressed the problem of restenosis.[1,2] Although these first-generation polymers were considered biocompatible, they have been associated with allergic reactions and inflammation, which in combination with incomplete strut endothelialization have led to early and late stent thrombosis.[3]

New-generation polymer coatings aim more specifically at mimicking the endothelial lining in order to prevent thrombotic complications. In addition, basic research has shown that some of these polymeric materials could potentially upregulate genes related to thrombosis, inflammation, and vasoconstriction.[4] The polymer used with the Resolute zotarolimus-eluting stent (Medtronic CardioVascular) is a mixture of a hydrophilic biocompatible component that faces the endoluminal surface and a hydrophobic component that is attached to the metal stent surface and serves as a drug reservoir, enabling sustained release of zotarolimus to control neointimal hyperplasia in patients with complex conditions and subgroups of lesions, as shown by encouraging early results.[5-9]

The purpose of this study, called the Resolute All Comers trial, was to compare the Resolute zotarolimus-eluting stent with an everolimus-eluting stent (Xience V, Abbott Vascular Devices) in an unrestricted, multicenter, open-label, randomized, controlled, noninferiority trial in patients undergoing percutaneous coronary intervention (PCI) in everyday clinical practice.

Methods

Patients

From April 30, 2008, to October 28, 2008, we recruited 2292 adult patients with chronic, stable coronary artery disease or acute coronary syndromes, including myocardial infarction with or without ST-segment elevation. Patients were eligible if they had at least one coronary lesion with stenosis of more than 50% in a vessel with a reference diameter of 2.25 to 4.0 mm. No restriction was placed on the total number of treated lesions, treated vessels, lesion length, or number of stents implanted. The exclusion criteria were a known intolerance to a study drug, metal alloys, or contrast media; planned surgery within 6 months after the index procedure; childbearing potential; and participation in another trial before reaching the primary end point.

At least one off-label criterion was present in 1520 patients (66.3%). Off-label use included the placement of a stent in patients with at least one of the following clinical or lesion characteristics: renal insufficiency (creatinine level, ≥140 μmol per liter [1.6 mg per deciliter]), an ejection fraction of less than 30%, the occurrence of acute myocardial infarction within the previous 72 hours, more than one lesion per vessel, at least two vessels with stents, a lesion measuring more than 27 mm, bifurcations, bypass grafts, in-stent restenosis, unprotected left main artery (without a functioning bypass graft), lesions with thrombus, or total occlusion.

The study complied with the provisions of the Declaration of Helsinki, and the study protocol was approved by the institutional review board at each study center. All patients provided written informed consent.

Study Design

Patients were randomly assigned to undergo PCI with a coronary stent releasing either zotarolimus or everolimus. A subgroup of patients (20%) was randomly assigned to undergo angiographic follow-up at 13 months. The study-group assignments were unknown to members of the independent clinical events committee, steering committee, data-management committee, Academic Research Organization (Cardialysis), and the sponsor (Medtronic CardioVascular). The principal investigator and the coprincipal investigators designed the study, in collaboration with the sponsor. The verification of data collection was performed by an independent monitoring organization (Premier Research Group). The independent group of statisticians at Academic Research Organization performed the analyses. Members of the steering committee wrote the first draft of the manuscript and vouch for the completeness and accuracy of the data gathering and analysis. The study was conducted in accordance with the trial protocol.

Study Procedures

The zotarolimus-eluting stent was available in diameters of 2.25, 2.50, 2.75, 3.00, 3.50, and 4.00 mm and in lengths of 8 mm and 14 mm for stents with a diameter of 2.75 mm or less, 9 mm and 15 mm for stents with a diameter of 3.00 mm or more, and 12, 14, 18, 24, and 30 mm for all

available stent diameters. The everolimus-eluting stent was available in diameters of 2.25, 2.50, 2.75, 3.00, 3.50, and 4.00 mm, with each available in lengths of 8, 12, 15, 18, 23, and 28 mm.

Balloon angioplasty and stent implantation were performed according to standard techniques; direct stenting (without previous balloon dilatation) was allowed. The aim was to obtain full lesion coverage with one or multiple stents. No mixture of type of stents was permitted for a given patient unless the operator was unable to insert the study stent, in which case crossover to another nonstudy device of the operator's choice was possible. The aim was to treat all coronary lesions in one session; however, staged procedures (defined as procedures planned at the time of the index procedure and performed within 6 weeks with the same type of study stent) were permitted. In the case of unplanned revascularization procedures requiring stent implantation, it was recommended that physicians use the same type of study stent.

Procedural anticoagulation was achieved with unfractionated heparin at a dose of 5000 IU or 70 to 100 IU per kilogram of body weight to maintain an activated clotting time of more than 250 seconds; the use of glycoprotein IIb/IIIa inhibitors was left to the operator's discretion. All patients who were enrolled in the study received at least 75 mg of acetylsalicylic acid before the procedure. A loading dose of 300 to 600 mg of clopidogrel was administered only if the patient had received no clopidogrel during the previous 7 days. All patients were discharged with a prescription for at least 75 mg of acetylsalicylic acid indefinitely and for 75 mg of clopidogrel for a minimum of 6 months after the index procedure.

At baseline, we evaluated all patients with a scoring system developed for the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) study (ClinicalTrials.gov number, NCT00114972) to characterize the coronary vasculature regarding the number of lesions and their function, location, and complexity.[10] The SYNTAX scale can range from 0 to 115, with a higher score indicating more complex disease.

FOLLOW-UP

Patients were followed up by telephone or hospital visit at 1, 6, and 12 months and will continued to be followed annually for 5 years. At outpatient visits, patients were specifically questioned about the occurrence of angina or any adverse event. Angiographic follow-up in 455 patients was planned at 13 months.

QUANTITATIVE CORONARY ANGIOGRAPHY

Findings on quantitative coronary angiography (QCA), which was performed with the use of the Cardiovascular Angiography Analysis System (CAAS) II (Pie Medical Imaging), were centrally assessed at one angiographic core laboratory (Cardialysis).[11] QCA scans from patients returning for any repeat angiography within 14 days after the index procedure were not used in the follow-up QCA analysis, since the need for repeat revascularization in this period was not related to neointimal hyperplasia but rather to an acute response of the lesion to the procedure. These methods are consistent with those used in previous coronary stent trials, such as the Sirolimus Eluting Stent in de Novo Coronary Lesions (SIRIUS) trial (NCT00232765), and the Endeavor stent clinical trial program (Mauri L, Harvard Clinical Research Institute: personal communication). In addition, data from QCA analysis for patients returning for any repeat angiography later than 450 days (15 months) were also excluded from the statistical analysis, since they were outside the time limit for angiographic follow-up stipulated in the protocol. Additional methods and definitions with respect to QCA are provided in the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org.

PRIMARY AND SECONDARY END POINTS

The primary end point was target-lesion failure, defined as a composite of death from cardiac causes, any myocardial infarction (not clearly attributable to a nontarget vessel), or clinically indicated target-lesion revascularization at 12 months. Secondary clinical end points were a composite of death from any cause, any myocardial infarction (Q-wave or non–Q-wave), or any revascularization (either a percutaneous or surgical procedure with either a clinical or nonclinical indication), as well as the individual components of the composite; definite, probable, possible, and overall stent thrombosis, defined according to the Academic Research Consortium definition[12]; and acute procedure, device, and lesion success. (Definitions of all study end points are provided in the Methods section in the Supplementary Appendix.) Quantitative angiographic end points included in-stent and in-segment percent stenosis, rate of binary

restenosis, minimal lumen diameter, and late lumen loss.

STATISTICAL ANALYSES

This trial was powered for noninferiority testing of the primary end point at 12 months on an intention-to-treat basis. Full details of the sample-size calculation for the noninferiority primary and secondary end points are provided in the Methods section in the Supplementary Appendix.

Descriptive statistics for the secondary clinical end points are provided. Categorical variables are reported as counts and percentages, and between-group differences were assessed with the use of Fisher's exact test. Continuous variables are presented as means ±SD and were compared with the use of a two-sample t-test. The Kaplan–Meier method was used to calculate the time to clinical end points, and the log-rank test was used to compare between-group differences. Unless otherwise specified, a two-sided P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

PATIENTS

A total of 2292 patients with 3366 lesions were randomly assigned to receive either zotarolimus-eluting stents (1140 patients with 1661 lesions) or everolimus-eluting stents (1152 patients with 1705 lesions) (Fig. 1 in the Supplementary Appendix). A total of 21 patients (1.8%) in the zotarolimus-stent group and 26 (2.3%) in the everolimus-stent group were lost to follow-up or withdrew consent before the 12-month cutoff date, leaving 1119 patients in the zotarolimus-stent group and 1126 in the everolimus-stent group for inclusion in the intention-to-treat analysis.

Baseline clinical and angiographic characteristics were similar in the two study groups (Tables 1 and 2). Total stent lengths per patient and per lesion were significantly higher in the everolimus-stent group (Table 2). However, this factor had no detrimental effect on 12-month clinical outcomes (Table 3, and Table 1 in the Supplementary Appendix).

The primary end point of target-lesion failure — a composite of death from cardiac causes, any myocardial infarction, or target-lesion revascularization — occurred in 92 patients (8.2%) in the zotarolimus-stent group and 94 patients (8.3%) in the everolimus-stent group (Table 3 and Fig. 1A). We confirmed noninferiority of the zotarolimus-eluting stent, with an absolute risk difference of −0.1% and the upper limit of the one-sided 95% confidence interval of 1.8% ($P<0.001$ in one-sided noninferiority analysis). The rates for the individual components of the primary end point were similar to those for the composite end point (Fig. 1B, 1C, and 1D). The findings for the primary end point were consistent across prespecified stratified analyses (Fig. 2 in the Supplementary Appendix).

Patients in the zotarolimus-stent group, as compared with the everolimus-stent group, had significantly reduced rates of death from any cause while they were hospitalized (0.1% vs. 0.8%, $P=0.02$) and at 30 days (0.2% vs. 0.9%, $P=0.04$) because of a nonsignificant increased rate of death at 30 days in the everolimus-eluting stent group from both cardiac causes (0.2% vs. 0.7%, $P=0.11$) and noncardiac causes (0% versus 0.2%, $P=0.50$). At 12 months, the between-group difference in the rate of death from any cause was no longer significant (1.6% vs. 2.8%, $P=0.08$) (Table 3).

At 12 months, the rate of definite stent thrombosis was significantly higher in the zotarolimus-stent group (1.2%) than in the everolimus-stent group (0.3%, $P=0.01$), which was primarily related to a higher rate of definite stent thrombosis at 30 days in the zotarolimus-stent group (0.8%) than in the everolimus-stent group (0.1%, $P=0.01$). Rates of probable or possible stent thrombosis and of the composite of definite, probable, or possible stent thrombosis were similar in the two groups at all time points (Table 3, and Table 1 in the Supplementary Appendix). A temporal breakdown of all definite and probable episodes of stent thrombosis, along with the worst hierarchical outcome during a 12-month period, is shown in Figure 2 (for details, see the Results section and Table 2 in the Supplementary Appendix).

The secondary angiographic end point, the in-stent percent stenosis at 13 months, was determined at a median of 401 days (interquartile range, 394 to 420) in the zotarolimus-stent group and 409 days (interquartile range, 395 to 426) in the everolimus-stent group. The percent stenosis achieved the prespecified criterion for noninferiority, with 21.65±14.42% in the zotarolimus-stent group versus 19.76±14.64% in the everolimus-stent group, a difference of 2.03% measured as a least-square mean with an upper limit of

Table 1. Characteristics of the Patients at Baseline.*

Variable	Zotarolimus-Eluting Stent (N=1140)	Everolimus-Eluting Stent (N=1152)	Difference (95% CI)†
Age — yr	64.4±10.9	64.2±10.8	0.2 (−0.7 to 1.1)
Male sex — no. (%)	874 (76.7)	889 (77.2)	−0.5 (−4.0 to 2.9)
Coexisting condition — no. (%)			
Diabetes mellitus	268 (23.5)	270 (23.4)	0.1 (−3.4 to 3.5)
Arterial hypertension	810 (71.1)	821 (71.3)	−0.2 (−3.9 to 3.5)
Hyperlipidemia	729 (63.9)	780 (67.7)	−3.8 (−7.6 to 0.1)
Cardiac risk factor			
Current smoker — no. (%)	302 (26.5)	305 (26.5)	0.0 (−3.6 to 3.6)
Premature coronary artery disease in first-degree relative — no./total no. (%)	327/960 (34.1)	361/983 (36.7)	−2.7 (−6.9 to 1.6)
Previous myocardial infarction — no./total no. (%)	324/1122 (28.9)	341/1120 (30.4)	−1.6 (−5.4 to 2.2)
Previous percutaneous coronary intervention — no. (%)	363 (31.8)	370 (32.1)	−0.3 (−4.1 to 3.5)
Previous coronary-artery bypass grafting — no. (%)	114 (10.0)	110 (9.5)	0.5 (−2.0 to 2.9)
Previous revascularization for angina or myocardial infarction — no. (%)	996 (87.4)	1022 (88.7)	−1.3 (−4.0 to 1.3)
Clinical characteristic			
Stable angina — no. (%)	382 (33.5)	416 (36.1)	−2.6 (−6.5 to 1.3)
Unstable angina — no. (%)	221 (19.4)	218 (18.9)	0.5 (−2.8 to 3.7)
Myocardial infarction — no. (%)	393 (34.5)	388 (33.7)	0.8 (−3.1 to 4.7)
Left ventricular ejection fraction <30% — no./total no. (%)	17/610 (2.8)	13/608 (2.1)	0.7 (−1.1 to 2.4)
Multivessel disease — no. (%)	666 (58.4)	682 (59.2)	−0.8 (−4.8 to 3.2)
Target-vessel location — no. (%)			
Left main artery	25 (2.2)	29 (2.5)	−0.3 (−1.6 to 0.9)
Left anterior descending artery	600 (52.6)	560 (48.6)	4.0 (−0.1 to 8.1)
Left circumflex artery	376 (33.0)	379 (32.9)	0.1 (−3.8 to 3.9)
Right coronary artery	425 (37.3)	476 (41.3)	−4.0 (−8.0 to 0.0)
Bypass graft — no. (%)	28 (2.5)	28 (2.4)	0.0 (−1.2 to 1.3)
Complexity of coronary artery disease			
No. of treated lesions per patient	1.46±0.73	1.48±0.77	−0.02 (−0.08 to 0.04)
SYNTAX score‡	14.8±9.3	14.6±9.2	0.2 (−0.6 to 1.0)
At least one small vessel (reference vessel diameter, ≤2.75 mm) — no./total no. (%)	652/962 (67.8)	656/973 (67.4)	0.4 (−3.8 to 4.5)
At least one lesion length >18 mm — no./total no. (%)	175/962 (18.2)	206/973 (21.2)	−3.0 (−6.5 to 0.6)
At least one bifurcation or trifurcation — no./total no. (%)	190/1126 (16.9)	202/1139 (17.7)	−0.9 (−4.0 to 2.3)
At least one total occlusion — no./total no. (%)	184/1127 (16.3)	197/1145 (17.2)	−0.9 (−4.0 to 2.2)
At least one in-stent restenosis — no./total no. (%)	91/1126 (8.1)	91/1139 (8.0)	0.1 (−2.1 to 2.3)
Off-label stent use — no. (%)§	764 (67.0)	756 (65.6)	1.4 (−2.5 to 5.3)

* Plus–minus values are means ±SD. CI denotes confidence interval.
† The value is the difference in the zotarolimus-stent group, as compared with the everolimus-stent group.
‡ The SYNTAX score can range from 0 to 115, with higher scores indicating a greater complexity of disease.
§ Off-label stent use included the placement of a stent in a patient with at least one of the following clinical or lesion characteristics: renal insufficiency (creatinine level, ≥140 μmol per liter [1.6 mg per deciliter]), an ejection fraction of less than 30%, the occurrence of acute myocardial infarction within the previous 72 hours, more than one lesion per vessel, at least two vessels with stents, a lesion measuring more than 27 mm, bifurcation, bypass grafts, in-stent restenosis, unprotected left main artery, lesions with thrombus, or total occlusion.

Table 2. **Characteristics of Revascularization Procedures.***

	Zotarolimus-Eluting Stent (N=1140)	Everolimus-Eluting Stent (N=1152)	Difference (95% CI)†	P Value
Before index procedure				
Lesion length — mm				
Mean	11.89±7.50	12.15±7.86	0.26 (−0.83 to 0.32)	
Range	0.1–73.3	1.3–67.8		
Reference vessel diameter — mm	2.63±0.57	2.63±0.58	0.00 (−0.04 to 0.05)	
Minimum lumen diameter — mm	0.95±0.54	0.93±0.52	0.02 (−0.02 to 0.06)	
Percent stenosis — %	63.59±18.41	64.18±18.19	−0.58 (−1.84 to 0.67)	
Thrombus — no./total no. (%)	80/1518 (5.3)	75/1551 (4.8)	0.4 (−1.1 to 2.0)	
Moderate or heavy calcification — no./total no. (%)	351/1599 (22.0)	323/1634 (19.8)	2.2 (−0.6 to 5.0)	
TIMI score of 0 or 1 — no./total no. (%)	249/1635 (15.2)	264/1672 (15.8)	−0.6 (−3.0 to 1.9)	
After index procedure				
No. of stents				
Per patient	1.90±1.21	2.02±1.34	−0.12 (−0.23 to −0.02)	0.02
Per lesion	1.15±0.42	1.18±0.45	−0.03 (−0.06 to −0.01)	0.02
Total stent length — mm				
Per patient	34.42±24.49	36.98±26.49	−2.56 (−4.65 to −0.47)	0.02
Per lesion	20.87±9.76	21.68±10.16	−0.81 (−1.44 to 0.18)	0.01
Balloon dilatation — no./total no. (%)	780/1122 (69.5)	799/1138 (70.2)	−0.7 (−4.5 to 3.1)	0.75
Received study stent only — no./total no. (%)	1117/1140 (98.0)	1116/1152 (96.9)	1.1 (−0.2 to 2.4)	0.11
Minimum lumen diameter — mm				
No. of lesions	1638	1674		
In-stent	2.36±0.52	2.38±0.53	−0.01 (−0.05 to 0.02)	0.46
In-segment	2.06±0.54	2.06±0.55	0.00 (−0.04 to 0.03)	0.89
Diameter stenosis — %				
In-stent	14.59±10.59	14.19±10.57	0.40 (−0.32 to 1.12)	0.28
In-segment	23.30±11.71	22.99±11.65	0.30 (−0.49 to 1.10)	0.46
Acute gain — mm				
No. of lesions	1531	1557		
In-stent	1.42±0.58	1.46±0.60	−0.04 (−0.08 to 0.01)	0.10
In-segment	1.11±0.59	1.13±0.62	−0.03 (−0.07 to 0.02)	0.22
Successful outcome — no./total no. (%)‡				
Lesion	1869/1889 (98.9)	1946/1963 (99.1)	−0.2 (−0.8 to 0.4)	0.62
Device	1820/1876 (97.0)	1888/1954 (96.6)	0.4 (−0.7 to 1.5)	0.52
Procedure	1060/1121 (94.6)	1063/1128 (94.2)	0.3 (−1.6 to 2.2)	0.79

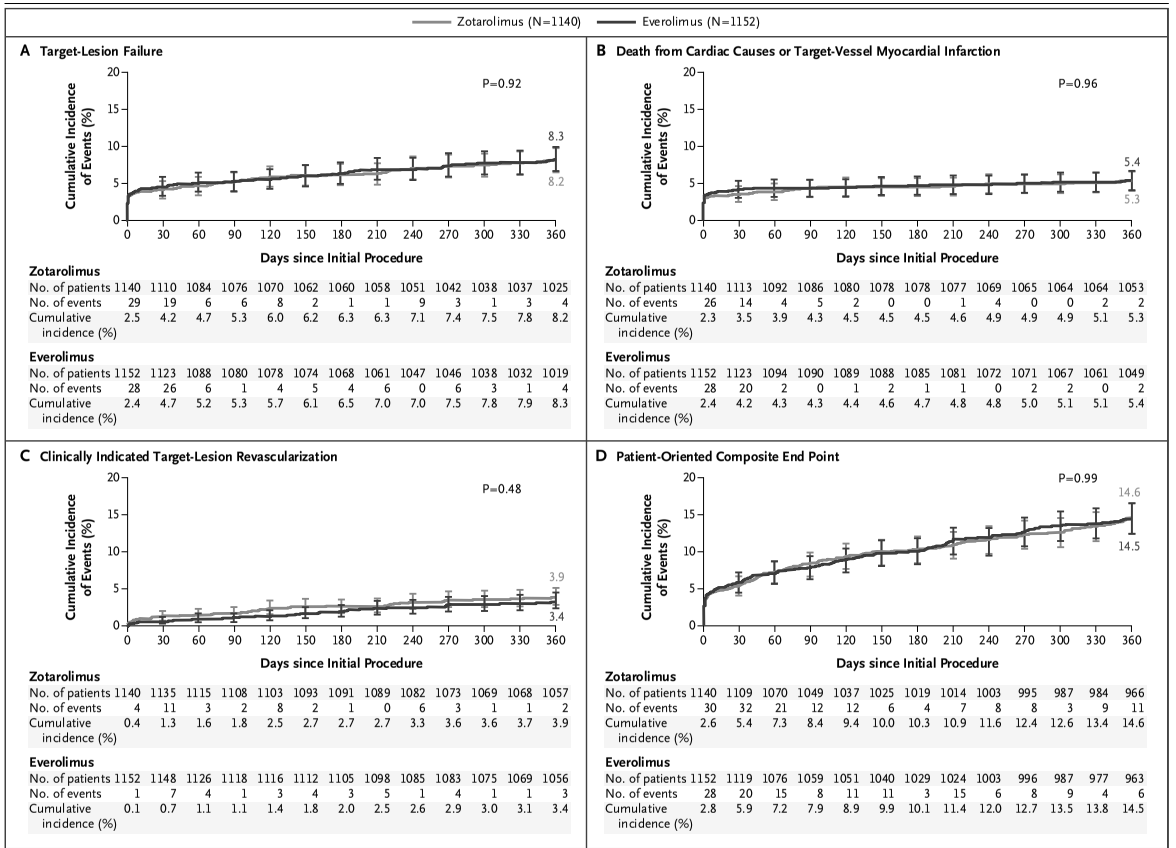
* Plus–minus values are means ±SD. CI denotes confidence interval, and TIMI Thrombolysis in Myocardial Infarction.
† The value is the difference in the zotarolimus-stent group, as compared with the everolimus-stent group.
‡ Definitions for lesion, device, and procedural success are provided in the Methods section in the Supplementary Appendix.

4.73 for the one-sided 95% confidence interval (P=0.04 for noninferiority). Of note, there was a significant difference in in-segment late loss in favor of the everolimus-eluting stent, with 0.15±0.43 mm in the zotarolimus-stent group versus 0.06±0.40 mm in the everolimus-stent group (P=0.04), whereas no significant between-group differences were observed for in-stent late loss (0.27±0.43 mm vs. 0.19±0.40 mm, P=0.08), in-segment binary restenosis (5.2% vs. 6.5%,

Table 3. Clinical Outcomes at 12 Months in the Intention-to-Treat Population.*

Outcome	Zotarolimus-Eluting Stent (N=1119)	Everolimus-Eluting Stent (N=1126)	Difference (95% CI)†	P Value
	no. (%)			
Target-lesion failure‡	92 (8.2)	94 (8.3)	−0.1 (−2.4 to 2.2)	0.94
Death				
From any cause	18 (1.6)	31 (2.8)	−1.1 (−2.4 to 0.1)	0.08
From cardiac cause	15 (1.3)	19 (1.7)	−0.3 (−1.4 to 0.7)	0.61
Target-vessel myocardial infarction§				
Any	47 (4.2)	46 (4.1)	0.1 (−1.5 to 1.8)	0.92
Q-wave	8 (0.7)	5 (0.4)	0.3 (−0.4 to 0.9)	0.42
Non–Q-wave	40 (3.6)	41 (3.6)	−0.1 (−1.6 to 1.5)	1.00
Clinically indicated target-lesion revascularization				
Any	44 (3.9)	38 (3.4)	0.6 (−1.0 to 2.1)	0.50
Coronary-artery bypass grafting	6 (0.5)	8 (0.7)	−0.2 (−0.8 to 0.5)	0.79
Percutaneous coronary intervention	38 (3.4)	31 (2.8)	0.6 (−0.8 to 2.1)	0.39
Myocardial infarction¶	151 (13.5)	153 (13.6)	−0.1 (−2.9 to 2.7)	0.95
Clinically indicated target-vessel revascularization				
Any	55 (4.9)	54 (4.8)	0.1 (−1.7 to 1.9)	0.92
Coronary-artery bypass grafting	7 (0.6)	9 (0.8)	−0.2 (−0.9 to 0.5)	0.80
Percutaneous coronary intervention	48 (4.3)	48 (4.3)	0.0 (−1.6 to 1.7)	1.00
Death from cardiac causes or target-vessel myocardial infarction§	60 (5.4)	61 (5.4)	−0.1 (−1.9 to 1.8)	1.00
Major adverse cardiac event‖	97 (8.7)	109 (9.7)	−1.0 (−3.4 to 1.4)	0.42
Target-vessel failure**	101 (9.0)	108 (9.6)	−0.6 (−3.0 to 1.8)	0.66
Patient-oriented composite end point††	163 (14.6)	164 (14.6)	0.0 (−2.9 to 2.9)	1.00
Definite stent thrombosis (0–360 days)				
All patients	13 (1.2)	3 (0.3)	0.9 (0.2 to 1.6)	0.01
Acute (0–1 day)	4 (0.4)	1 (0.1)	0.3 (−0.1 to 0.7)	0.22
Subacute (2–30 days)	5 (0.4)‡‡§§	0	0.4 (0.1 to 0.8)	0.03
Late (31–360 days)	5 (0.4)‡‡	2 (0.2)	0.3 (−0.2 to 0.7)	0.29
Probable stent thrombosis (0–360 days)				
All patients (0–360 days)	6 (0.5)	5 (0.4)	0.1 (−0.5 to 0.7)	0.77
Acute (0–1 day)	1 (0.1)§§	1 (0.1)	0.0 (−0.2 to 0.2)	1.00
Subacute (2–30 days)	3 (0.3)	4 (0.4)	−0.1 (−0.5 to 0.4)	1.00
Late (31–360 days)	2 (0.2)	0	0.2 (−0.1 to 0.4)	0.25
Stent thrombosis (0–360 days)				
Possible	9 (0.8)	9 (0.8)	0.0 (−0.7 to 0.7)	1.00
Definite or probable	18 (1.6)	8 (0.7)	0.9 (0.0 to 1.8)	0.05
Definite, probable, or possible	26 (2.3)	17 (1.5)	0.8 (−0.3 to 1.9)	0.17

* This trial was powered for noninferiority testing of the primary end point at 12 months on an intention-to-treat basis.
† The value is the difference in the zotarolimus-stent group, as compared with the everolimus-stent group.
‡ Target-lesion failure was defined as death from cardiac causes, any myocardial infarction (not clearly attributable to a nontarget vessel), or clinically indicated target-lesion revascularization.
§ Myocardial infarction was determined on the basis of the extended historical definition.[13]
¶ Myocardial infarction was determined on the basis of the Academic Research Consortium definition.[12]
‖ Major adverse cardiac events included a composite of death, myocardial infarction (Q-wave and non–Q wave), emergent coronary-artery bypass surgery, or repeat clinically indicated target-lesion percutaneous or surgical revascularization.
** Target-vessel failure was defined as death from cardiac causes, any myocardial infarction (not clearly attributable to a nontarget vessel), or clinically indicated target-vessel revascularization.
†† The patient-oriented composite end point was death from any cause, any myocardial infarction (Q-wave and non–Q wave), or any revascularization.
‡‡ One patient had a definite stent thrombosis on both day 4 and day 31.
§§ One patient had a probable stent thrombosis on day 0 and a definite stent thrombosis on day 5.



Zotarolimus

No. of patients	1140	1110	1084	1076	1070	1062	1060	1058	1051	1042	1038	1037	1025
No. of events	29	19	6	6	8	2	1	1	9	3	1	3	4
Cumulative incidence (%)	2.5	4.2	4.7	5.3	6.0	6.2	6.3	6.3	7.1	7.4	7.5	7.8	8.2

Everolimus

No. of patients	1152	1123	1088	1080	1078	1074	1068	1061	1047	1046	1038	1032	1019
No. of events	28	26	6	1	4	5	4	6	0	6	3	1	4
Cumulative incidence (%)	2.4	4.7	5.2	5.3	5.7	6.1	6.5	7.0	7.0	7.5	7.8	7.9	8.3

Zotarolimus

No. of patients	1140	1113	1092	1086	1080	1078	1078	1077	1069	1065	1064	1064	1053
No. of events	26	14	4	5	2	0	0	1	4	0	0	2	2
Cumulative incidence (%)	2.3	3.5	3.9	4.3	4.5	4.5	4.5	4.6	4.9	4.9	4.9	5.1	5.3

Everolimus

No. of patients	1152	1123	1094	1090	1089	1088	1085	1081	1072	1071	1067	1061	1049
No. of events	28	20	2	0	1	2	1	1	0	2	2	0	2
Cumulative incidence (%)	2.4	4.2	4.3	4.3	4.4	4.6	4.7	4.8	4.8	5.0	5.1	5.1	5.4

Zotarolimus

No. of patients	1140	1135	1115	1108	1103	1093	1091	1089	1082	1073	1069	1068	1057
No. of events	4	11	3	2	8	2	1	0	6	3	1	1	2
Cumulative incidence (%)	0.4	1.3	1.6	1.8	2.5	2.7	2.7	2.7	3.3	3.6	3.6	3.7	3.9

Everolimus

No. of patients	1152	1148	1126	1118	1116	1112	1105	1098	1085	1083	1075	1069	1056
No. of events	1	7	4	1	3	4	3	5	1	4	1	1	3
Cumulative incidence (%)	0.1	0.7	1.1	1.1	1.4	1.8	2.0	2.5	2.6	2.9	3.0	3.1	3.4

Zotarolimus

No. of patients	1140	1109	1070	1049	1037	1025	1019	1014	1003	995	987	984	966
No. of events	30	32	21	12	12	6	4	7	8	8	3	9	11
Cumulative incidence (%)	2.6	5.4	7.3	8.4	9.4	10.0	10.3	10.9	11.6	12.4	12.6	13.4	14.6

Everolimus

No. of patients	1152	1119	1076	1059	1051	1040	1029	1024	1003	996	987	977	963
No. of events	28	20	15	8	11	11	3	15	6	8	9	4	6
Cumulative incidence (%)	2.8	5.9	7.2	7.9	8.9	9.9	10.1	11.4	12.0	12.7	13.5	13.8	14.5

Figure 1. **Kaplan–Meier Estimates for Primary and Secondary End Points over 360 Days of Follow-up.**

Kaplan–Meier curves show the cumulative incidence of target-lesion failure (the primary end point), a composite of death from cardiac causes, any myocardial infarction (not clearly attributable to a nontarget vessel), or target-vessel revascularization (Panel A); death from cardiac causes or target-vessel myocardial infarction (Panel B); clinically indicated target-lesion revascularization (Panel C); and the patient-oriented composite end point (death from any cause, any myocardial infarction, or any revascularization) (Panel D).

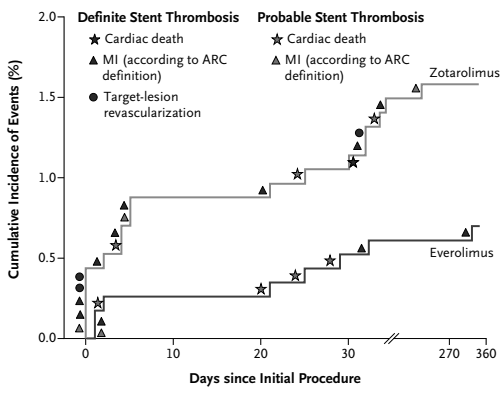


Figure 2. Cumulative Incidence of Definite or Probable Stent Thrombosis. Shown is the incidence of definite stent thrombosis (red) or probable stent thrombosis (blue) among 18 patients in the zotarolimus-stent group and 8 patients in the everolimus-stent group, along with the worst hierarchical clinical outcome, over 360 days of follow-up. ARC denotes Academic Research Consortium, and MI myocardial infarction.

P=0.67), or in-stent binary restenosis (4.2% vs. 3.8%, P=1.00) (Table 3 and Fig. 3 in the Supplementary Appendix). The primary and secondary end points that were calculated on a per-protocol basis are reported in the Results section in the Supplementary Appendix.

DISCUSSION

This study met the primary clinical end point by showing the noninferiority of the zotarolimus-eluting stent, as compared with the everolimus-eluting stent, when used in a population with minimal exclusion criteria. Historically, inclusion criteria for enrollment in randomized trials of coronary stents have included patients with "on-label" indications, including those with single de novo lesions of 27 mm or less in length in vessels with a reference diameter of 2.5 to 3.5 mm. Among patients who were commonly excluded from such studies were those with coexisting illnesses, acute myocardial infarction, and multivessel disease.

In 2006, a Food and Drug Administration panel formally recognized the biohazard of late stent thrombosis, a phenomenon that was observed with increased frequency in the populations who had not been tested in previous randomized trials of coronary stents. The use and the risk of drug-eluting stents in patients in whom the placement of such stents was considered to be off-label for the device became a major concern.[14,15] It was recommended that future trials should address a broad, unselected patient population, which would be more representative of everyday clinical practice. The lack of stringent exclusion criteria in our study resulted in the enrollment of a large proportion of patients with acute myocardial infarction, multivessel intervention, small-vessel disease, long lesions, or bifurcations or trifurcations — patients who represented those undergoing PCI in contemporary practice. Of note, results were consistent across all predefined subgroups.

In our study, we closely monitored the recruitment of patients, which showed that 44% of all patients undergoing PCI were enrolled in the trial. Therefore, we consider that our findings are highly generalizable to patients in everyday clinical practice.

Given the overall complexity of the patient population, the event rates were low and compared favorably with rates in previous "all-comer" studies, despite a somewhat higher mean SYNTAX score.[16] Although the patient-oriented composite end point that was recommended by the Academic Research Consortium,[13] which included all cardiovascular events, had an event rate of 14.6% in the two stent groups, this rate was lower than the rate of 18.3% reported in the angiographic group in the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) study (NCT00267774) in the context of a similar SYNTAX score.[17]

Using historical definitions of myocardial infarction, we compared rates in our trial with those in other all-comer trials.[18-20] Before the start of the trial, it was decided that investigators should collect data on both creatine kinase and troponin levels, but the sponsor and the steering committee, in agreement with the data and safety monitoring board, decided to use the historical World Health Organization definitions of myocardial infarction, which were modified for an all-comer population.[13] This decision was made to ensure that the trial results could be compared with historical coronary-stent studies. The measurement of troponin indeed resulted in a tripling of the rate of diagnosis of myocardial infarction. In the upcoming years, the increased sensitivity of the detection of troponin release will

have to be carefully weighed against the reduced specificity for device-related coronary events.

Overall in our study, rates of stent thrombosis were low and similar to those in previous studies involving all comers or patients with acute coronary syndromes.[18-22] Although we observed no significant between-group difference in overall rates of stent thrombosis, there were differences in rates of subacute definite events. We observed no significant between-group difference in the use of antiplatelet therapy, but there was a preponderance of stenting in the left anterior descending coronary artery and coexisting illnesses in patients with stent thrombosis. It is noteworthy that these episodes of stent thrombosis did not result in an excessive rate of myocardial infarction or death in the zotarolimus-stent group. Although our findings are hypothesis-generating and require additional investigation, definitive conclusions will be obtained only from longer-term follow-up in large patient populations in studies that have sufficient statistical power to detect differences in rates of stent thrombosis.

In designing this trial, we wanted to subrandomize a population for angiographic follow-up, and in order to prevent revascularization that was not clinically indicated, we postponed angiographic follow-up for 4 weeks after the final clinical follow-up. This resulted in a decline in compliance for angiographic follow-up, since the majority of asymptomatic patients who were reassured at the last clinic visit did not want to undergo repeat hospitalization for invasive angiography 4 weeks later. A similar observation was noted in the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial (NCT00433966).[21] Despite this reduced compliance, the power of the angiographic follow-up study was maintained at more than 80% and can be interpreted with confidence. In view of the results of the in-stent and in-segment late loss, we concluded that there was no substantial difference between zotarolimus and everolimus in inhibitory effect on the neointima. Previously, the late loss observed with the zotarolimus stent was 0.12 mm, 0.22 mm, and 0.27 mm at 4, 9, and 13 months, respectively.[5,6] Similarly, the previous late loss with the everolimus stent was 0.10 mm, 0.16 mm, 0.19 mm, and 0.34 mm at 6, 8, 13, and 24 months, respectively.[23-25] If there is a difference in inhibition of neointimal hyperplasia, it must be underscored that these values of late loss are far from clinically relevant, as confirmed by the low and similar rates of binary restenosis.

In conclusion, the new-generation zotarolimus-eluting stent was found to be as safe and effective as the everolimus-eluting stent in a group of patients for whom the procedure was considered to be predominantly off-label.

Supported by Medtronic CardioVascular.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Serruys PW, Kutryk MJB, Ong ATL. Coronary-artery stents. N Engl J Med 2006; 354:483-95.
2. Garg S, Serruys PW. Coronary stents — current status. J Am Coll Cardiol (in press).
3. Cook S, Ladich E, Nakazawa G, et al. Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. Circulation 2009;120:391-9.
4. Hezi-Yamit A, Sullivan C, Wong J, et al. Novel high-throughput polymer biocompatibility screening designed for SAR (structure-activity relationship): application for evaluating polymer coatings for cardiovascular drug-eluting stents. Comb Chem High Throughput Screen 2009;12: 664-76.
5. Meredith IT, Worthley S, Whitbourn R, et al. The next-generation Endeavor Resolute stent: 4-month clinical and angiographic results from the Endeavor Resolute first-in-man trial. EuroIntervention 2007;3:50-3.
6. Meredith IT, Worthley S, Whitbourn R, et al. Clinical and angiographic results with the next-generation resolute stent system a prospective, multicenter, first-in-human trial. JACC Cardiovasc Interv 2009;2:977-85.
7. Meredith IT, Worthley S, Whitbourn R, et al. Long-term clinical outcomes with the next generation Resolute Stent System: a report of the two-year follow-up from the RESOLUTE clinical trial. EuroIntervention 2010;5:692-7.
8. Udipi K, Chen M, Cheng P, et al. Development of a novel biocompatible polymer system for extended drug release in a next-generation drug-eluting stent. J Biomed Mater Res A 2008;85:1064-71.
9. Hezi-Yamit A, Sullivan C, Wong J, et al. Impact of polymer hydrophilicity on biocompatibility: implication for DES polymer design. J Biomed Mater Res A 2009;90:133-41.
10. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1: 219-27.
11. Serruys PW, Foley D, De Feyter PJ, eds. Quantitative coronary angiography in clinical practice. Dordrecht, the Netherlands: Springer, 1994.
12. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-51.
13. Vranckx P, Cutlip DE, Mehran R, et al. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity: addendum to the historical IM definitions used in stent studies. EuroIntervention 2010;5:871-4.
14. Farb A, Boam AB. Stent thrombosis redux — the FDA perspective. N Engl J Med 2007;356:984-7.
15. Serruys P. FDA panel, 7 and 8 December 2006 — the impact on our practice

and research. EuroIntervention 2007;2: 405-7.
16. Wykrzykowska J, Garg S, Girasis C, et al. Value of SYNTAX score (SX) for risk assessment in all-comers population of the randomized LEADERS trial. J Am Coll Cardiol (in press).
17. Tonino PAL, De Bruyne B, Pijls NHJ, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360: 213-24.
18. Windecker S, Remondino A, Eberli FR, et al. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. N Engl J Med 2005;353:653-62.
19. Garg S, Sarno G, Serruys PW, et al. The twelve-month outcomes of a biolimus eluting stent with a biodegradable polymer compared with a sirolimus eluting stent with a durable polymer. EuroIntervention (in press).
20. Kedhi E, Joesoef KS, McFadden E, et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet 2010;375:201-9.
21. Stone GW, Lansky AJ, Pocock SJ, et al. Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. N Engl J Med 2009;360:1946-59.
22. Wiviott SD, Braunwald E, McCabe CH, et al. Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomised trial. Lancet 2008;371:1353-63.
23. Serruys PW, Ruygrok P, Neuzner J, et al. A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent: the SPIRIT II trial. EuroIntervention 2006;2: 286-94.
24. Claessen BE, Beijk MA, Legrand V, et al. Two-year clinical, angiographic, and intravascular ultrasound follow-up of the XIENCE V everolimus-eluting stent in the treatment of patients with de novo native coronary artery lesions: the SPIRIT II trial. Circ Cardiovasc Interv 2009;2:339-47.
25. Stone GW, Midei M, Newman W, et al. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. JAMA 2008;299:1903-13.

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Contents

I. SUPPLEMENTARY METHODS

Quantitative Coronary Angiographic (QCA)

All available QCA data for independent variables such as percent diameter stenosis and binary restenosis were calculated using unmatched data, whilst matched paired QCA data was used in the analysis of serial angiographic endpoints. All angiographic measurements of the target lesion were obtained in the "in-stent" zone, within 5 mm proximal and distal to each stent edge, and over the entire segment ("in-segment" zone). The following QCA parameters were calculated: minimal lumen diameter, reference vessel diameter, percent diameter stenosis (difference between the reference vessel diameter and minimal lumen diameter/reference vessel diameter x 100) and late lumen loss (difference between the post-procedure and follow-up minimal lumen diameter). Binary restenosis was defined as stenosis of 50 percent or greater in the target lesion or segment at angiographic follow-up.

Definitions

All deaths were considered cardiac unless an undisputed non-cardiac cause was present. Myocardial infarction was defined according to an extended historical protocol definition and according to ARC definitions.[1-2] A Q-wave myocardial infarction required, in the absence of cardiac enzyme data, a history of chest pain or other acute symptoms consistent with myocardial ischemia together with new pathological Q waves in two or more contiguous ECG leads as assessed by the core lab or clinical events committee. In the presence of elevated cardiac enzymes, new pathological Q waves in two or more contiguous ECG leads as assessed by the core lab or clinical events committee were sufficient to diagnose a Q-wave myocardial infarction. In the absence of an ECG, a Q-wave myocardial infarction could be adjudicated on the basis of the clinical scenario and appropriate cardiac enzyme data. A target lesion revascularization was considered clinically indicated if angiography during follow-up showed a diameter stenosis greater than 50 percent (core laboratory QCA assessment) and if one of the following occurred: (1) a positive history of recurrent angina pectoris, presumably related to the target vessel; (2) objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent), presumably related to the target vessel; (3) abnormal results of any invasive functional diagnostic test (e.g. fractional flow reserve); (4) a target lesion revascularization with a diameter stenosis greater than 70% even in the absence of the above-mentioned ischemic signs or symptoms. Device success was defined as the attainment at the target site of a final residual diameter stenosis of less than 50 percent using only the assigned study device. Lesion success was defined as the attainment of a final residual diameter stenosis of less than 50 percent using any percutaneous method. Procedure success was defined as the attainment at the target site of a final residual diameter stenosis of less than 50 percent, together with the absence of any in-hospital major adverse cardiac events.

Statistical Methods

Hypothesis of Non-Inferiority for Primary Clinical Endpoint

Based on the event rates from previously reported all comer studies,3-4 we predicted composite endpoint rates at 12 months for both treatment groups to be 8%. Based on a non-inferiority margin of 0.035 (3.5%) as the acceptable difference between the Resolute zotarolimus-eluting stent and the Xience-V everolimus-eluting stent groups (claiming the former to be non-inferior) and a one-sided type I error of 0.05, a total of 2300 patients (1150 patients in each group) will yield at least 90% power to detect non-inferiority. Non-inferiority will be achieved if the upper limit of the one sided 95% confidence interval of the difference is less than the margin.

Non-Inferiority for Secondary Angiographic Endpoint Analysis

This trial was also powered for non-inferiority testing of the angiographic endpoint in-stent percent diameter stenosis. It was anticipated that 1.5 lesions per patient would be treated. Therefore, a mixed

model analysis of variance was used, allowing for the correlation of multiple lesions within patients, using patients as a random effect. The mean in-stent percent diameter stenosis was expected to be equal (16%) in both treatment groups, with a common standard deviation of 16%. With a non-inferiority margin of 5% and a one-sided type I error of 0.05, it is estimated that 460 patients (with on average 1.5 lesion per patient) will yield a power of at least 90% to detect non-inferiority, assuming an attrition rate of 20%.

II. SUPPLEMENTARY RESULTS

Stent Thrombosis (Supplementary Table 2)

Thirteen patients (1.2%) allocated to zotarolimus-eluting stents had a definite stent thrombosis, of whom 12 were on dual antiplatelet therapy at the time of the event, whilst one patient had discontinued therapy. Stent thrombosis was associated with seven (54%) ARC defined myocardial infarctions, and 12 (92%) target lesion revascularizations. The majority (10/13, 77%) of stent thrombosis events occurred in the left anterior descending artery. Conversely, three (0.3%) patients allocated to everolimus-eluting stents had a definite stent thrombosis, all of whom were on dual antiplatelet therapy at the time of the event. Stent thrombosis was associated with a non-fatal ARC defined myocardial infarction in all patients (100%), and a subsequent target lesion revascularization in two patients (67%).

Per Protocol Analysis

The main results of the study are reported on an intention-to-treat basis. Importantly, analysis using only those patients who had all their lesions treated with a study stent (i.e. per protocol) does not result in any changes to the overall conclusions of the study, as the pre-specified criterion for non-inferiority for both the clinical and angiographic endpoint is still achieved. For the record, per protocol, the rate of the primary clinical end point, target lesion failure (a composite of cardiac death, myocardial infarction [not clearly attributable to a non-target vessel], and clinically-indicated target lesion revascularization), occurred in 84 (7.7%) patients treated with the zotarolimus-eluting stent and 84 (7.6%) patients treated with the everolimus-eluting stent (absolute risk difference 0.1%, upper limit of the one-sided 95% CI at 1.9%, one-sided $P_{non\text{-}inferiority}$=0.001). Similarly, the in-stent percent diameter stenosis at 13-months follow-up on a per protocol basis was 21.65±14.42% for the zotarolimus-eluting stent and 19.75±14.68% for everolimus-eluting stent (difference in least square means 2.05%, upper limit of the one-sided 95% CI 4.75, one-sided Pnon-inferiority=0.04).

Adverse Events

No serious adverse events were noted with any unusual frequency, or preponderance to a particular stent.

Supplementary Table 1. Additional Clinical Outcomes at 12 Months on an Intention-to-treat Basis

	ZES (N=1119)	EES (N=1126)	Difference (95% CI)	P value for Difference
Clinical Outcomes				
Target Lesion Failure#	8.2% (92)	8.3% (94)	-0.1% [-2.4%, 2.2%]	0.94
Death (all)	1.6% (18)	2.8% (31)	-1.1% [-2.4%, 0.1%]	0.08
Cardiac	1.3% (15)	1.7% (19)	-0.3% [-1.4%, 0.7%]	0.61
MI (all)*	4.6% (51)	4.4% (49)	0.2% [-1.5%, 1.9%]	0.84
Q-wave	0.9% (10)	0.5% (6)	0.4% [-0.3%, 1.1%]	0.33
Non-Q-wave	3.8% (42)	3.8% (43)	-0.1% [-1.6%, 1.5%]	1.00
Target Vessel MI*	4.2% (47)	4.1% (46)	0.1% [-1.5%, 1.8%]	0.92
Q-wave	0.7% (8)	0.4% (5)	0.3% [-0.4%, 0.9%]	0.42
Non-Q-wave	3.6% (40)	3.6% (41)	-0.1% [-1.6%, 1.5%]	1.00
MI†	13.5% (151)	13.6% (153)	-0.1% [-2.9%, 2.7%]	0.95
Q-wave	0.9% (10)	0.5% (6)	0.4% [-0.3%, 1.1%]	0.33
Non-Q-wave	12.8% (143)	13.1% (147)	-0.3% [-3.1%, 2.5%]	0.85
Any repeat revascularization‡	10.5% (117)	9.1% (102)	1.4% [-1.1%, 3.9%]	0.29
CABG	1.3% (14)	1.1% (12)	0.2% [-0.7%, 1.1%]	0.70
PCI	9.5% (106)	8.3% (93)	1.2% [-1.1%, 3.6%]	0.34
Any TVR	7.2% (81)	6.1% (69)	1.1% [-1.0%, 3.2%]	0.31
CABG	0.9% (10)	0.9% (10)	0.0% [-0.8%, 0.8%]	1.00
PCI	6.3% (71)	5.5% (62)	0.8% [-1.1%, 2.8%]	0.42
Clinically indicated TVR	4.9% (55)	4.8% (54)	0.1% [-1.7%, 1.9%]	0.92
CABG	0.6% (7)	0.8% (9)	-0.2% [-0.9%, 0.5%]	0.80
PCI	4.3% (48)	4.3% (48)	0.0% [-1.6%, 1.7%]	1.00
Any TLR	5.3% (59)	3.8% (43)	1.5% [-0.3%, 3.2%]	0.11
CABG	0.7% (8)	0.7% (8)	0.0% [-0.7%, 0.7%]	1.00
PCI	4.6% (51)	3.2% (36)	1.4% [-0.2%, 3.0%]	0.10
Clinically indicated TLR	3.9% (44)	3.4% (38)	0.6% [-1.0%, 2.1%]	0.50
CABG	0.5% (6)	0.7% (8)	-0.2% [-0.8%, 0.5%]	0.79
PCI	3.4% (38)	2.8% (31)	0.6% [-0.8%, 2.1%]	0.39
Cardiac Death or TV MI*	5.4% (60)	5.4% (61)	-0.1% [-1.9%, 1.8%]	1.00
Death or TV MI*	5.6% (63)	6.4% (72)	-0.8% [-2.7%, 1.2%]	0.48
MACE§	8.7% (97)	9.7% (109)	-1.0% [-3.4%, 1.4%]	0.42
Target Vessel Failure††	9.0% (101)	9.6% (108)	-0.6% [-3.0%, 1.8%]	0.66
Patient Composite End Point¶	14.6% (163)	14.6% (164)	0.0% [-2.9%, 2.9%]	1.00
Stent Thrombosis –				
Definite stent thrombosis				
Acute (0-1 day)	0.4% (4)	0.1% (1)	0.3% [-0.1%, 0.7%]	0.22
Sub-acute (2-30 days)	0.4% (5)**††	0.0% (0)	0.4% [0.1%, 0.8%]	0.03
Late (31-360 days)	0.4% (5)**	0.2% (2)	0.3% [-0.2%, 0.7%]	0.29
All (0-360 days)	1.2% (13)	0.3% (3)	0.9% [0.2%, 1.6%]	0.01
Probable stent thrombosis				
Acute (0-1 day)	0.1% (1)††	0.1% (1)	0.0% [-0.2%, 0.2%]	1.00
Sub-acute (2-30 days)	0.3% (3)	0.4% (4)	-0.1% [-0.5%, 0.4%]	1.00
Late (31-360 days)	0.2% (2)	0.0% (0)	0.2% [-0.1%, 0.4%]	0.25
All (0-360 days)	0.5% (6)	0.4% (5)	0.1% [-0.5%, 0.7%]	0.77
Possible stent thrombosis				
Acute (0-1 day)	0.0% (0)	0.0% (0)	0.0% [-]	No p value
Sub-acute (2-30 days)	0.0% (0)	0.0% (0)	0.0% [-]	No p value
Late (31-360 days)	0.8% (9)	0.8% (9)	0.0% [-0.7%, 0.7%]	1.00
All (0-360 days)	0.8% (9)	0.8% (9)	0.0% [-0.7%, 0.7%]	1.00
Definite or probable stent thrombosis				
Acute (0-1 day)	0.4% (5)††	0.2% (2)	0.3% [-0.2%, 0.7%]	0.29

Sub-acute (2-30 days)	0.7% (8)**††	0.4% (4)	0.4% [-0.2%, 1.0%]	0.26
Late (31-360 days)	0.6% (7)**	0.2% (2)	0.4% [-0.1%, 1.0%]	0.11
All (0-360 days)	1.6% (18)	0.7% (8)	0.9% [0.0%, 1.8%]	0.05
Definite, probable or possible stent thrombosis				
Acute (0-1 day)	0.4% (5)††	0.2% (2)	0.3% [-0.2%, 0.7%]	0.29
Sub-acute (2-30 days)	0.7% (8)**††	0.4% (4)	0.4% [-0.2%, 1.0%]	0.26
Late (31-360 days)	1.3% (15)**	1.0% (11)	0.4% [-0.5%, 1.2%]	0.49
All (0-360 days)	2.3% (26)	1.5% (17)	0.8% [-0.3%, 1.9%]	0.17

Data expressed as percent (number of events).
MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TLR, target lesion revascularization; TVR, target vessel revascularization; TV=Target vessel

Target Lesion Failure: cardiac death, myocardial infarction* (not clearly attributable to a non-target vessel) and clinically indicated target lesion revascularization

* Extended historical definition[2]

† Defined according to the ARC[1]

‡ Includes all staged target vessel procedures[2]

§ MACE: major adverse cardiac events, a composite of death, myocardial infarction (Q-wave and non-Q wave), emergent coronary artery bypass surgery, or repeat clinically indicated target lesion revascularization by percutaneous or surgical revascularization.

|| Target Vessel Failure: cardiac death, myocardial infarction* (not clearly attributable to a non-target vessel) and clinically indicated target vessel revascularization

¶ Patient Composite End Point: all-cause mortality, myocardial infarction (Q- and non-Q wave) or any revascularization.

** One patient had a definite stent thrombosis at day 4 and day 31

†† One patient had a probable stent thrombosis on day 0 and a definite stent thrombosis on day 5.

.

Supplementary Table 2: Detailed Information on Definite and Probable Stent Thrombosis Events out to 12-month Follow-up

Days to Stent Thrombosis	Stent	Stented Vessel	Compliance to DAPT at Time of Stent Thrombosis	Events at Time of Stent Thrombosis§	Worst Hierarchical Outcome at 12-months (days to outcome) §
Definite Stent Thrombosis					
0	ZES	LAD	Yes	Non-Q-wave MI, TLR	Non-Q-wave MI (0)
0	ZES	LAD	Yes	Q-wave MI, TLR	Q-wave MI (0)
0	ZES	LAD	Yes	No event at time of stent thrombosis	TLR (111)
0	ZES	LAD	Yes	TLR	TLR (0)
1	EES	LAD	Yes	Q-wave MI, TLR	Q-wave MI (1)
2	ZES	LAD	Yes	TLR	Q-wave MI (1)
4*	ZES	LAD	Yes	TLR	Non-Q-wave MI (0)
5#	ZES	LAD	Yes	Non-Q-wave MI TLR, Non-TVR	Q-wave MI (10)
5¶	ZES	LAD	Yes	Q-wave MI, TLR	Q-wave MI (5)
10#	ZES	LAD	Yes	Q-wave MI, TLR, Non-TVR	Q-wave MI (10)
21	ZES	LCx	Yes	Q-wave MI, TLR	Q-wave MI (21)
31*	ZES	LAD	Yes	Non-Q-wave MI, TLR	Non-Q-wave MI (0)
31	ZES	LCx	Yes	Q-wave MI, TLR, Non-TVR	Cardiac Death (58)
71	ZES	LAD	No	Non-Q-wave MI, TLR	Non-Q-wave MI (71)
73	ZES	LAD	Yes	TLR	TLR (73)
81†	EES	RCA	Yes	Non-Q-wave MI, TLR	Non-Q-wave MI (79)
124	ZES	RCA	Yes	TLR, TVR	Non-Q-wave MI (111)
279†	EES	RCA	Yes	Non-Q-wave, TLR	Non-Q-wave MI (79)
341	EES	SVG	Yes	Non-Q-wave MI	Non-Q-wave MI (341)
Probable Stent Thrombosis					
0¶	ZES	LAD	Yes	Q-wave MI	Q-wave MI(5)
1	EES	LAD	Yes	Non-Q-wave MI	Non-Q-wave MI (1)
2	EES	LMS	Yes	Q-wave MI, Cardiac death	Cardiac Death(2)
4	ZES	LAD/RCA	Unknown	Cardiac death	Cardiac Death (4)
5	ZES	LCx	Unknown	Non-Q-wave MI	Non-Q-wave MI(5)
21	EES	RCA	Unknown	Q-wave MI, Cardiac death	Cardiac death(21)
25	EES	RCA	Unknown	Cardiac death	Cardiac death (25)
25	ZES	LAD	Unknown	Cardiac death	Cardiac death(25)
29	EES	RCA	Unknown	Cardiac death	Cardiac Death(29)
108	ZES	SVG	Unknown	Cardiac death	Cardiac death (108)
214	ZES	Cx	Yes	Q-wave MI	Q-wave MI(214)

*,#,†,¶ indicates the same patient having the event

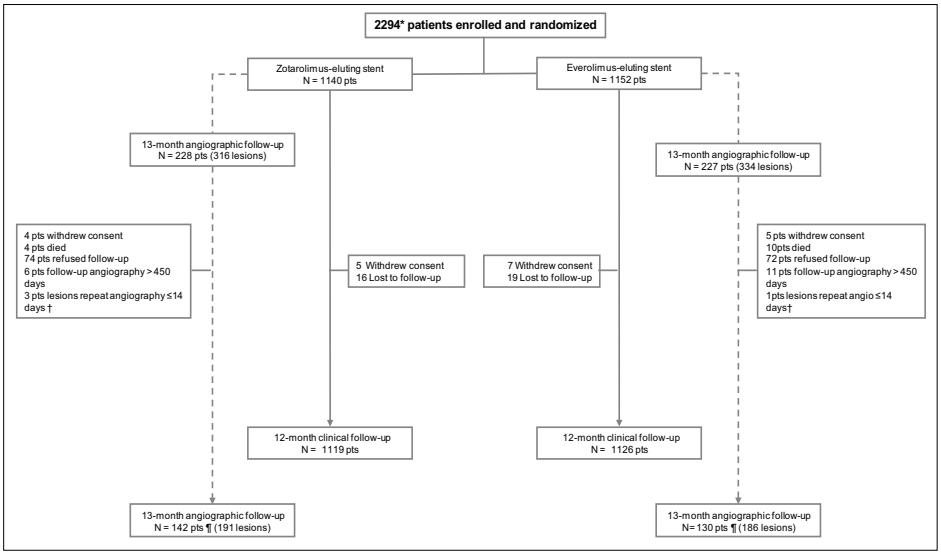
ZES, zotarolimus-eluting stent; EES, everolimus-eluting stent; LAD, left anterior descending coronary artery; RCA, right coronary artery; LCx, circumflex artery; SVG, saphenous vein graft; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization

§Events adjudicated according to the Academic Research Consortium.[1]

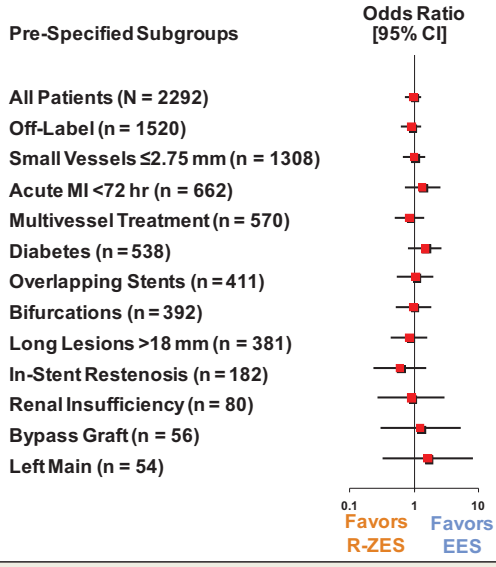
Supplementary Table 3. Angiographic Follow-up on an Intention-to-treat Basis

	ZES	EES	Difference [95% CI]	P value
Unmatched Angiographic Analysis				
13-months				
Diameter stenosis (%)	(N_L =191)	(N_L=186)		
In-stent	21.65±14.42	19.76±14.64	1.89 [-1.05, 4.83]	0.21
In-segment	26.51±14.01	25.50±15.02	1.01 [-1.93, 3.95]	0.50
Binary restenosis (%)	(N_L =191)	(N_L=186)		
In-stent	4.2% (8)	3.8% (7)	0.4% [-3.5%, 4.4%]	1.00
In-segment	5.2% (10)	6.5% (12)	-1.2% [-6.0%, 3.5%]	0.67
Matched Paired Angiographic Analysis				
Post Procedure	(N_L =183)	(N_L=177)		
Minimum lumen diameter (mm)				
In-stent	2.46±0.53	2.42±0.50	0.05 [-0.06, 0.15]	0.39
In-segment	2.18±0.56	2.06±0.49	0.12 [0.01, 0.23]	0.03
13-months				
Minimum lumen diameter (mm)	(N_L =183)	(N_L=177)		
In-stent	2.20±0.62	2.23±0.59	-0.03 [-0.16, 0.10]	0.64
In-segment	2.03±0.61	2.01±0.56	0.03 [-0.09, 0.15]	0.65
Late loss (mm)				
In-stent	0.27±0.43	0.19±0.40	0.08 [-0.01, 0.16]	0.08
In-segment	0.15±0.43	0.06±0.40	0.09 [0.01, 0.18]	0.04

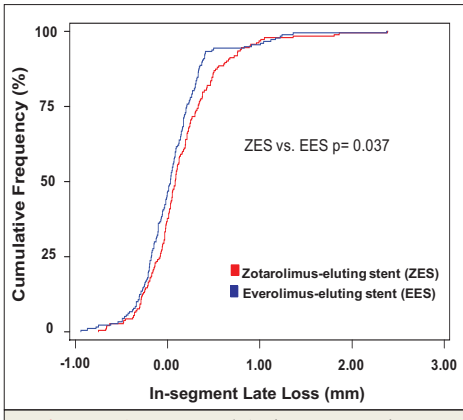
Data are presented as mean±standard deviation and percent (number of events).



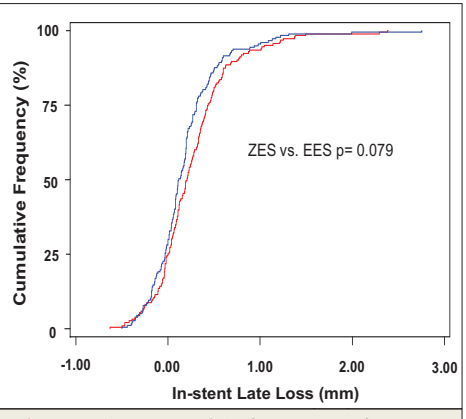
Supplementary Figure 1: Patient Flow
*2 patients randomized to zotarolimus-eluting stents were not included in analysis because no PCI was performed for medical reasons, and consent was subsequently withdrawn.
¶ Number of patients do not add up, as some patients had multiple lesions, that were not all excluded.
† Clinical events in these patients are still included in the final clinical results.
Pts, patients



Supplementary Figure 2: Odd ratio plot for the primary end point in pre-specified sub-groups



Supplementary Figure 3A: Cumulative frequency curves for In-segment late lumen loss.



Supplementary Figure 3B: Cumulative frequency curves for In-stent late lumen loss.

V. Trial Appendix

Sponsor:
Medtronic CardioVascular, Santa Rosa, California, USA

Principal Investigator:
Patrick W. Serruys, Erasmus Medisch Centrum, Rotterdam, The Netherlands

Co-Principal Investigators:
Sigmund Silber, Kardiologische Praxis und Praxisklinik, Munich, Germany
Stephan Windecker, Bern University Hospital, Bern, Switzerland

Steering Committee:
Patrick W. Serruys, Principal Investigator and Chairman, Rotterdam, The Netherlands
Sigmund Silber, Kardiologische Praxis und Praxisklinik, Munich, Germany
Stephan Windecker, Bern University Hospital, Bern Switzerland

Data Safety Monitoring Board (DSMB):
J..P.G. Tijssen
U. Sigwart
M. E. Bertrand

Clinical Events Committee (CEC):
E. Mc Fadden,
C. Hanet,
H.H. Tilsted Hansen
J.P.R. Herrman
V. Legrand
P.W. Radke
W. Rutsch
G. Ducrocq
M. Valgimigli
W. Bocksch

Data Management - Angiographic Core Laboratories:
Cardialysis BV, Rotterdam, The Netherlands

VI. Supplementary References

1. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-51.

2. Vranckx P, Cutlip DE, Mehran R, et al. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. EuroIntervention 2010;5:871-4.

3. Lemos PA, Serruys PW, van Domburg RT, et al. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. Circulation 2004;109:190-5.

4. Windecker S, Remondino A, Eberli FR, et al. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. N Engl J Med 2005;353:653-62.

Chapter 7.4

A randomised comparison of novolimus-eluting and zotarolimus-eluting coronary stents: 9-month follow-up results of the EXCELLA II study

EuroIntervention 2010; 6 (2):195-205

Patrick W. Serruys, Scot Garg*, Alexandre Abizaid, John Ormiston, Stephan Windecker, Stefan Verheye, Christophe Dubois, Jim Stewart, Karl E. Hauptmann, Joachim Schofer, Karl Stangl, Bernhard Witzenbichler, Marcus Wiemer, Emanuele Barbato, Ton de Vries, Anne-Marie den Drijver, Hiromasa Otake, Lynn Meredith, Sara Toyloy, Peter Fitzgerald*

**Equal contributors*

EuroIntervention

A randomised comparison of novolimus-eluting and zotarolimus-eluting coronary stents: 9-month follow-up results of the EXCELLA II study

Patrick W. Serruys[1]*, MD, PhD; Scot Garg[1], MBChB, MRCP; Alexandre Abizaid[2], MD, PhD; John Ormiston[3], MD; Stephan Windecker[4], MD; Stefan Verheye[5], MD, PhD; Christophe Dubois[6], MD; Jim Stewart[3], MD; Karl E. Hauptmann[7], MD; Joachim Schofer[8], MD, PhD; Karl Stangl[9], MD, PhD; Bernhard Witzenbichler[10], MD; Marcus Wiemer[11], MD; Emanuele Barbato[12], MD, PhD; Ton de Vries[13], MSc; Anne-Marie den Drijver[13], PhD; Hiromasa Otake[14], MD; Lynn Meredith[15], MPH; Sara Toyloy[15], Peter Fitzgerald[14], MD, PhD

1.Erasmus Medisch Centrum, Rotterdam, The Netherlands; 2. Instituto Dante Pazzanese, Sao Paulo, Brazil; 3. Mercy Angiography Unit, Auckland, New Zealand; 4. University Hospital Bern, Bern, Switzerland; 5. Academisch Ziekenhuis Middelheim, Antwerpen, Belgium; 6. Universitair Ziekenhuis Gasthuisberg, Leuven, Belgium; 7. Krankenhaus der Barmherzigen Brüder, Trier, Germany; 8. Universitäres Herz-und Gefäßzentrum, Hamburg, Germany; 9. Charité, University Clinic Berlin, Campus Charite Mitte, Berlin, Germany; 10. Charité, University Clinic Berlin, Campus Benjamin-Franklin, Berlin, Germany; 11. Herz-und Diabeteszentrum Nordrhein-Westfalen, Bad Oeynhausen, Germany; 12. Onze Lieve Vrouw Ziekenhuis, Aalst, Belgium; 13. Cardialysis, Rotterdam, The Netherlands; 14. Stanford Cardiovascular Core Analysis Laboratory, Stanford University, CA, USA; 15. Elixir Medical Corp., Sunnyvale, CA, USA

Both PW Serruys and S Garg contributed equally to this article. L. Meredith and S. Toyloy are employees of Elixir Medical. The other authors have no conflicts of interest to declare. This study was sponsored by Elixir Medical Corporation.
Guest Editor: Thomas F. Lüscher, MD, PhD, Cardiovascular Center, University Hospital Zurich, Zurich, Switzerland.

KEYWORDS
Novolimus eluting stent, zotarolimus eluting stent, angioplasty

Abstract

Aims: Novolimus, a macrocyclic lactone with anti-proliferative properties, has a similar efficacy to currently available agents; however it requires a lower dose, and less polymer, and is therefore conceivably safer.
Methods and results: The EXCELLA II study was a prospective, multicentre, single-blind, non-inferiority clinical trial which randomised 210 patients with a maximum of two *de novo* coronary artery lesions in two different epicardial vessels in a ratio of 2:1 to treatment with either the Elixir DESyne Novolimus Eluting Coronary Stent System (NES n=139, Elixir Medical, Sunnyvale, CA, USA) or the Endeavor zotarolimus eluting stent (ZES n=71, Medtronic, Santa Rosa, CA, USA). The primary endpoint was in-stent mean late lumen loss (LLL) at 9-months follow-up. In-stent percent volume obstruction (%VO) was measured in a sub-group of 65 patients having 9-month intravascular ultrasound (IVUS) follow-up. Clinical secondary endpoints included a device orientated composite of cardiac death, target vessel myocardial infarction (MI), and clinically indicated target lesion revascularisation (CI-TLR) assessed at 9-months follow-up. At 9-months, the in-stent LLL was 0.11±0.32 mm in the NES arm, as compared to 0.63±0.42 mm in the ZES ($p<0.0001$ non-inferiority, $p<0.0001$ superiority). In-stent%VO was 4.5±5.1% and 20.9±11.3% for NES and ZES, respectively ($p<0.001$). There was no significant difference between stent groups in the device orientated composite endpoint (NES 2.9% vs. ZES 5.6%, –2.8% [-8.8%, 3.3%], p=0.45) or its individual components of cardiac death, target vessel MI and CI-TLR.
Conclusions: This non-inferiority randomised study not only met its primary endpoint, but also demonstrated superiority of NES compared to the ZES in terms of in-stent LLL.

** Corresponding author: Ba583a, Thoraxcentre, Erasmus MC,'s-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands*
E-mail: p.w.j.c.serruys@erasmusmc.nl

Abbreviations

BMS	Bare metal stent
CABG	Coronary artery bypass graft
CI-TLR	Clinically indicated target lesion revascularisation
CK-MB	Creatinine kinase myoglobin fraction
DES	Drug eluting stents
DS	Diameter stenosis
EES	Everolimus eluting stent
IVUS	Intravascular ultrasound
LLL	Late lumen loss
MI	Myocardial infarction
MLD	Minimal lumen diameter
NES	Novolimus eluting stent
NQWMI	Non-Q-wave myocardial infarction
PCI	Percutaneous coronary intervention
PES	Paclitaxel eluting stent
QCA	Quantitative coronary angiography.
RVD	Reference vessel diameter
SES	Sirolimus eluting stent
TIMI	Thrombolysis in Myocardial Infarction
TVR	Target vessel revascularisation
ULN	Upper limit of normal
ZES	Zotarolimus eluting stent

Introduction

Drug eluting stents (DES) have revolutionised the field of percutaneous coronary intervention (PCI) since their inception in 2002.[1] However, despite their undeniable efficacy at reducing neointimal proliferation and repeat revascularisation compared to their bare metal stent predecessors,[2-5] they have been unable to completely eliminate restenosis, and in more recent times have been dogged by continued concerns over their long-term safety.[6,7] These unresolved issues have prompted design modifications to historical DES systems, in an attempt to develop new DES systems which are both safer, and more efficacious.

The most widely used anti-proliferative agents on current DES systems such as sirolimus, zotarolimus and everolimus are all derived from macrocyclic lactones, and ultimately function through the inhibition of the mammalian target of rapamycin (mTOR), resulting in arrest of the cell cycle. Previous clinical studies have demonstrated the overall superiority, in terms of both reduced late lumen loss, and repeat revascularisation of coronary stents which elute mTOR inhibiting drugs when compared to those eluting paclitaxel.[8]

Novolimus is a metabolite of sirolimus that has been specifically developed for the Elixir DESyne Novolimus Eluting Coronary Stent System (NES, Elixir Medical, Sunnyvale, CA, USA). This modification was aimed at creating a new anti-proliferative drug, which had similar efficacy to currently available agents, but required a lower dose, and lower polymer load and therefore was conceivably safer. The feasibility of using novolimus on a DES has been assessed in the 15-patient first-in-man EXCELLA study, which reported an angiographic in-stent late loss of 0.31±0.25 mm, and a percent volume obstruction on intravascular ultrasound (IVUS) of 6.0±4.4% at 8-months follow-up, together with no major adverse cardiovascular events (MACE) through 12 months,[9] and one MACE event at 24 months, which included a patient death wherein the patient had numerous other cardiovascular co-morbidities.[10]

Further assessment of the NES has been performed in the single-blind, prospective EXCELLA-II study, which randomised patients to treatment with either NES or the Endeavor (Medtronic, Santa Rosa, CA, USA) zotarolimus eluting stent (ZES). The current study reports the 9-month angiographic, IVUS and clinical outcomes of patients enrolled in the EXCELLA-II study, which represents the first, and largest randomised assessment of a coronary stent eluting novolimus.

Methods

Patient population

The EXCELLA-II study was a prospective, single blind, multi-centre trial enrolling 210 patients who were randomised in a ratio of 2:1 to receive either an Elixir NES (n=139), or an Endeavor ZES (n=71). All patients were over the age of 18, with evidence of myocardial ischaemia (as defined by the Canadian Cardiovascular society classification, or documented silent ischaemia or a positive functional test), and a maximum of two *de novo* native coronary artery lesions in different major epicardial vessels. For inclusion, on visual estimation, target lesion(s) were required to be: in a vessel with a reference vessel diameter between 2.5-3.5 mm; <24 mm in length; with a percentage diameter stenosis (DS) between 50-99%, and a Thrombolysis In Myocardial Infarction (TIMI) flow grade ≥1 by visual estimation.

Patients with documented evidence of recent (<3 days) myocardial infarction (creatinine kinase [CK]>2 times the upper normal limit [ULN]); a left ventricular ejection fraction <25%; a serum creatinine>2 mg/dl; those waiting heart transplantation; females of child-bearing age; those who would not consent to follow-up angiography; those with limited life expectancy due to concomitant disease; or those having a known sensitivity or contraindications to aspirin, ticlopidine, clopidogrel, mTOR inhibitor class drugs, cobalt chromium alloy, methacrylate or sensitivity to contrast which could not be adequately pre-medicated were excluded.

Angiographic lesions involving the left main stem; the aorto-ostial junction; those located within 5 mm of the origin of the left anterior descending or left circumflex artery; involving a side branch >2 mm in diameter; located within 10 mm of a previous stent; with heavy proximal calcification; requiring a staged procedure within 9-months; with a lesion with DS>40% proximal or distal to the target lesion; likely to require adjunctive therapy or which had associated visible thrombus were also all excluded. The ethics committee of each participating institution approved the study protocol, and all patients provided written informed consent.

Novolimus eluting stent

STENT PLATFORM

The Elixir DESyne Novolimus Eluting Coronary Stent System is comprised of the Elixir Core Coronary Stent System, which has received CE Mark approval in the European Union, and a novolimus eluting polymer coating. The Elixir core stent is a balloon

expandable stent developed utilising a medical grade cobalt chromium alloy with a nominal strut thickness of 0.0032" (80 microns) including a 6-crown (2.5 mm stent diameter) and an 8-crown (3.0 and 3.5 mm stent diameter) two-link pattern designed to optimise vessel coverage, flexibility and deliverability.

POLYMER

The NES polymer is a durable poly n-butyl methacrylate (PBMA) polymer, which is similar to that currently in clinical use on medical devices including vascular implants and other DES systems such as the Cypher sirolimus eluting stent (SES, Cordis, Warren, NJ, USA) and the XIENCE V everolimus eluting stent (EES, Abbott Vascular, Santa Clara, CA, USA). Importantly the polymer undergoes substantial processing to purify it from unwanted impurities, thereby resulting in a reduction in its overall monomer content. The drug-polymer matrix is applied to the surface of the stent, without a primer polymer coating underneath, using a proprietary spray resulting in a coating thickness of <3 μm, which is thinner than that found on other currently available durable polymer DES (4.1 μm on ZES, 7.6 μm on EES). The polymer facilitates controlled release of novolimus, such that 80% of the drug is released over 12 weeks, with elution complete by 6-months (data on file at Elixir Medical).

NOVOLIMUS

Novolimus is a macrocyclic lactone which has been developed by removal of a methyl-group from carbon C16 (data on file at Elixir medical). Notably this differs from the other macrocyclic lactone agents that are used in DES, which have all been developed through modifications on the carbon C40 of the macrocyclic ring. Nevertheless, in a similar fashion to these other agents, novolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12), to generate an immunosuppressive complex, which binds to and inhibits the activation of the regulatory kinase mTOR. This inhibition suppresses cytokine-driven cell proliferation, inhibiting the progression from the G1 to the S phase of the cell cycle. Novolimus has been shown in *in vitro* studies to have a high potency to inhibit human smooth muscle cells (IC_{50} of 0.5 nM), which is comparable to that of sirolimus (data on file at Elixir Medical). The dose of Novolimus used on the DESyne stent is 5 μg/mm of stent length (compared to 10 μg/mm on ZES, and EES).

Study procedure

Patients were randomised by central telephone randomisation service in a ratio of 2:1 between NES and ZES after the identification of suitable lesions on preliminary angiography. Randomisation was stratified on a site level using random permuted block assignments. Physicians were not blinded, in view of the different packaging for each stent.

NES were available in diameters of 2.5, 3.0 and 3.5 mm and in lengths of 14, 18 and 28 mm, whilst ZES were available in diameters of 2.5, 3.0 and 3.5 mm and in lengths of 14, 18 and 30 mm.

Standard interventional techniques were used to treat the lesion, in particular pre-dilatation was mandatory, and stent implantation was performed at a pressure not exceeding the rated burst pressure. Each stent was required to be long enough to cover the lesion, and pre-dilated area including 2 mm on either side. Post-dilatation was left to the operator's discretion; however, if performed, balloons were required to be shorter than the length of the deployed stent. In the event of a bailout procedure and the need for an additional stent, this was required to be of the same type as the first implanted stent if possible. If not, then a stent comprised on the same base material and drug family was recommended. In patients with two *de novo* lesions, attempts at the second lesion were only permitted if an optimal result defined as a residual DS<20%, TIMI 3 flow, absence of thrombus or edge dissection was seen after PCI of the first lesion. In a subset of 65 (43 NES, 22 ZES) consecutive patients enrolled in pre-selected centres IVUS was performed after optimal stent placement had been achieved. Periprocedural pharmaceutical treatment was administered according to standard hospital practice. Procedural anticoagulation was achieved with unfractionated heparin or bivalirudin. The use of glycoprotein IIb/IIIa inhibitors was left to the operator's discretion. All patients enrolled into the study were to receive ≥75 mg of aspirin daily for a minimum of one year, and clopidogrel 75 mg for a minimum of twelve months following the index procedure.

Follow-up

Patient clinical status review by telephone or hospital visit was planned at 1 (±14 days), 6, 9, and 12 months, and will be followed by annual review out to 5-years (±1 month). At outpatient visits, patients were specifically questioned about the development of angina or the occurrence of any adverse events. Angiographic follow-up for all patients was planned at 9-months (±1 month), with IVUS follow-up planned in a subset of 65 consecutive patients (from selected centres). Prior to follow-up angiography physicians were required to clinically evaluate the patients and prospectively record in the case record form whether any revascularisation, if required, was clinically indicated.

QCA

Quantitative coronary angiography (QCA) was performed using the CAAS II analysis system (Pie Medical BV, Maastricht, The Netherlands).[11] In each patient, the stented segment and the peri-stent segments (defined as a length 5 mm proximal and distal to the stent edge) were analysed. The following QCA parameters were calculated: minimal lumen diameter (MLD), reference vessel diameter (RVD) obtained by an interpolated method, and DS%. Binary restenosis was defined in every segment as a DS≥50% at follow-up. Late lumen loss (LLL) was calculated as the difference between the post-procedure and follow-up MLD. Angiography films were centrally assessed at one angiographic core laboratory (Cardialysis, Rotterdam, The Netherlands) with assessors unaware of the allocated stent.

IVUS

IVUS assessments were performed immediately post-stent implantation and at the 9-month follow-up time frame in a subset of 65 patients. Standard IVUS procedures were followed including a motorised pullback at 0.5 mm/sec from the distal reference segment, to at least 10 mm proximal to the lesion/stent border. Quantitative IVUS parameters included the minimum lumen area,

and volume data for the neointimal hyperplasia, vessel, stent, and lumen. To standardise for different lengths, the volume index was calculated as volume divided by length. The Cardiovascular Core Analysis Laboratory (CCAL) at Stanford University Medical Centre, Stanford, CA, USA performed the independent analysis of the lesions.

Study endpoints

The primary endpoint of the study was in-stent LLL as assessed by QCA at 9-months follow-up. Secondary QCA/IVUS endpoints included: MLD and DS% post-procedure and at 9-months; 9-month in-segment LLL; 9-month in-stent and in-segment binary angiographic restenosis DS≥50%; and in the subset having 9-month IVUS follow-up, in-stent percentage volume obstruction (%VO). In-stent was defined within the margins of the stent, while in-segment was defined as located within the margins of the stent and 5 mm proximal or distal to the stent.

Secondary clinical endpoints, collected at 1, 6, and 9 months, and will be collected annually to 5-years included the device-orientated composite endpoint defined as cardiac death, MI not clearly attributable to a non-intervened vessel (World Health Organisation [WHO] definition), and clinically indicated target-lesion revascularisation (CI-TLR) by PCI or bypass surgery. Other secondary clinical endpoints were CI-TLR, clinically indicated target vessel revascularisation (CI-TVR), stent thrombosis defined according to the Academic Research Consortium (ARC) definition,[12] and acute success including both clinical device and clinical procedural success.

An independent blinded clinical events committee (CEC) evaluated all clinical endpoints, and a Data and Safety Monitoring Board, neither of which were affiliated with the study, ensured the safe conduct of the trial.

Definitions

All deaths were considered cardiac unless an undisputed non-cardiac cause was present. MI was defined according to the WHO definition[13] wherein Q-wave MI was defined as the development of new pathological Q-waves in association with a rise in CK ≥2 times the ULN. A non-Q-wave MI (NQWMI) was defined as a CK elevation ≥2 times the ULN together with an elevation in CK-MB. A target lesion revascularisation was considered clinically indicated if angiography at follow-up showed a DS<50% (core lab QCA assessment) and if one of the following occurred: (1) a positive history of recurrent angina pectoris, presumably related to the target vessel; (2) objective signs of ischaemia at rest (ECG changes) or during exercise test (or equivalent), presumably related to the target vessel; (3) abnormal results of any invasive functional diagnostic test (e.g., fractional flow reserve); (4) A TLR with a diameter stenosis ≥70% even in the absence of the above-mentioned ischaemic signs or symptoms. Device success was defined as the attainment at the target site of a final residual DS<20% using only a NES or ZES stent alone. Procedure success was defined as the attainment at the target site of a final residual DS<50% using a NES or ZES stent alone, together with the absence of any in-hospital device orientated composite endpoints.

Statistical methods

The sample size for this study was calculated based on the planned analysis of the primary endpoint using a one-tailed *t*-test to show non-inferiority of the test arm compared to the control arm at the 0.05 significance level. Assuming the in-stent late lumen loss at nine months was equivalent between the test and control, using a common standard deviation of 0.5 and a margin of equivalence (delta) of 0.20, in order to have an 80% probability (i.e., 0.80 power) a minimum of 118 test and 59 control patients were required for the study. To allow for an approximate 15% patient dropout/lost-to-follow-up rate, approximately 210 patients of which 139 were test and 71 control patients were enrolled.

Binary variables are presented as percentages, and compared using the Fisher's exact test. Continuous variables were compared using the t-test, apart from the non-inferiority primary endpoint of in-stent LLL which was analysed using SAS v8 Proc Mixed which took into account the within-patient correlation structure of these data. The hypothesis testing for the primary endpoint was performed using a one-sided non-inferiority test with asymptomatic test statistic. If non-inferiority was shown, superiority analysis was planned using a two-sided t-test at the 5% alpha level. Clinical outcomes were analysed on an intention to treat basis using all patients randomised in the study, regardless of the treatment actually received. QCA data was analysed on a modified intention to treat basis, where patients were only included if at least one study stent was implanted, and lesions were only included if they were treated with a study stent. Statistical analyses were performed using the SAS statistical package (version 9.1.3, SAS Institute, Cary, NC, USA).

Results

The EXCELLA II study screened 622 patients over 21 sites, of whom 210 (33.8%) were randomised to treatment with NES (n=139) and ZES (n=71) between 28 October 2008 and 5 March 2009. At 9-month follow-up clinical assessment, as shown in Figure 1, was available in 207 patients (98.6%), made up of 137 of the initial 139 NES patients (98.6%) and 70 of the original 71 ZES patients (98.6%). Of the two patients failing to complete 9-month follow-up in the NES group, one was lost to follow-up after 6-months, whilst one withdrew consent prior to the 9-month follow-up angiogram. A single patient in the ZES was lost to follow-up after 4-weeks. Importantly no patient experienced any events up to last patient contact. Overall angiographic follow-up on a modified intention to treat basis was available in 88.6% of patients (89.9% NES, 85.9% ZES), with the reasons for incomplete follow-up shown in Figure 1.

Patient population and lesion characteristics

Baseline patient and angiographic characteristics are shown in Table 1. Overall, both groups had similar baseline risk profiles, and comparable lesion characteristics. Clinical device success occurred in the 137 out of 156 lesions in the NES arm (87.8%), and 70 out of 76 lesions in the ZES arm (92.1%). Of the 19 NES device failures, four were the result of implantation of a non-study stent, whilst 15 occurred because QCA deemed the residual DS to be >20% (mean±SD: 22.3±2.0%). Of note in 12 of these patients the

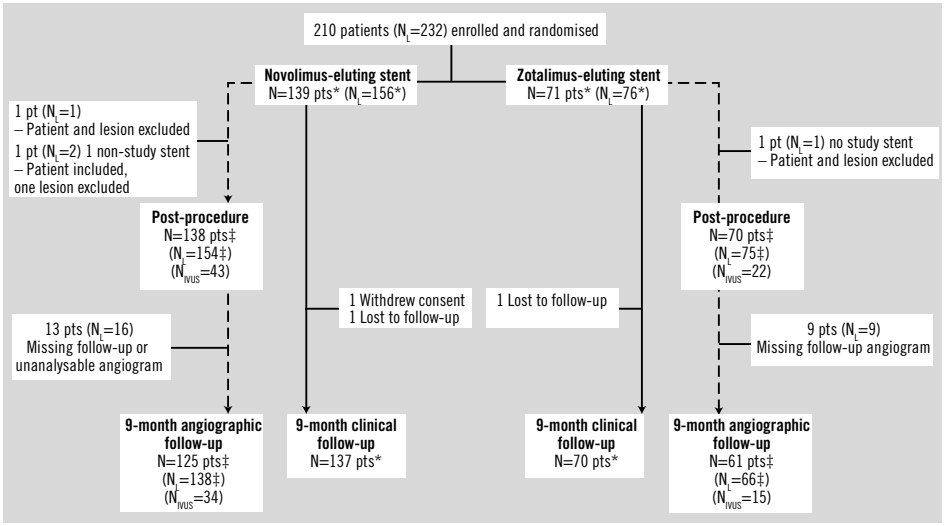


*Figure 1. Clinical and angiographic follow up of patient population. Pts: patients; N_L: number of lesions; IVUS: intra-vascular ultrasound; *Intention to treat analysis; ‡ Modified intention to treat: lesions with at least 1 study stent*

investigator reported the residual DS to be 0%. Similarly in the ZES arm, one non-study stent was implanted, whilst five lesions had a residual DS on QCA of >20% (22.4±1.9%); all of these had been deemed to have a DS of 0% by the investigator. The rates of procedural success were NES 97.8%, and ZES 98.6%, (–0.7% [–4.4%, 2.9%], p=1.00).

QCA analysis

Angiographic data at 9-months were available in 186 patients (204 lesions), and are summarised in Table 2. The RVD, MLD and DS% pre- and post procedure were all comparable between both study arms. At 9-months follow-up however, there was a larger RVD, a significantly larger MLD, and both a significantly lower DS% and rate of in-stent binary restenosis following treatment with NES. At 9-months, the primary endpoint of mean in-stent LLL was significantly lower for NES compared to the ZES, (0.11±0.32 mm vs. 0.63±0.42 mm, non-inferiority p<0.0001, superiority p<0.0001). The cumulative frequency distribution of in-stent LLL and DS% is displayed in Figure 2.

IVUS analysis

Baseline and follow-up IVUS data, which was obtained in 50 patients, including 39 serial sets of data (24 NES, 15 ZES) are shown in Table 3. At follow-up, there were no significant differences between NES and ZES with respect to the absolute vessel, lumen or stent volume indexes. Volumetric analysis indicated significantly less neointimal hyperplasia, (0.3±0.5 vs. 1.6±0.9, p<0.001) and %volume obstruction (4.5±5.1 vs. 20.9±11.3, p<0.001) with NES compared to ZES.

Incomplete stent apposition post procedure was evident in 9/41 (22%) NES lesions, three of which were post-dilated; and 2/23

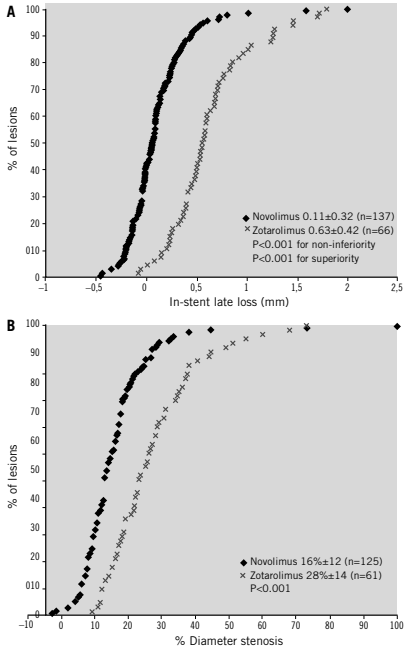


Figure 2. Cumulative frequency of (A) in-stent late loss, (B) % diameter stenosis at 9-month follow-up.

Table 1. Baseline characteristics of the patient population.

%(n) unless stated	Novolimus	Zotarolimus
Baseline patient characteristics	N=139	N=71
Age, years (±SD)	64.7±9.6	62.7±9.7
Male	76.3% (106/139)	78.9% (56/71)
Diabetes mellitus	23.7% (33/139)	23.9% (17/71)
Smoking		
Never smoked	42.8% (59/138)	25.4% (18/71)
Previous smoking	41.3% (57/138)	52.1% (37/71)
Currently smoking	15.9% (22/138)	22.5% (16/71)
Renal insufficiency	1.4% (2/139)	1.4% (1/71)
Hypercholesterolaemia	85.5% (118/138)	76.1% (54/71)
Hypertension	76.3% (106/139)	71.8% (51/71)
Family history	48.6% (67/138)	47.9% (34/71)
Stroke	2.9% (4/139)	4.2% (3/71)
Congestive heart failure	0.0% (0/139)	5.6% (4/71)
Previous myocardial infarction	26.6% (37/139)	31.0% (22/71)
Q-wave	10.8% (15/139)	16.9% (12/71)
Non-Q-wave	17.3% (24/139)	14.1% (10/71)
Previous CABG	3.6% (5/139)	5.6% (4/71)
Previous PCI	33.8% (47/139)	35.2% (25/71)
Peripheral vascular disease	4.3% (6/139)	9.9% (7/71)
Anginal status		
Unstable angina	25.2% (35/139)	31.0% (22/71)
Stable angina	64.0% (89/139)	64.8% (46/71)
Silent ischaemia only	10.8% (15/139)	4.2% (3/71)
Cardiac related medication	97.8% (136/139)	98.6% (70/71)
Ejection fraction,% (±SD)*	67.2±11.1	64.4±13.0
Baseline lesion characteristics	**No. of lesions=154**	**No. of lesions=75**
Target vessel		
Left anterior descending	40.3% (62/154)	50.7% (38/75)
Left circumflex	27.3% (42/154)	14.7% (11/75)
Right coronary artery	32.5% (50/154)	34.7% (26/75)
AHA/ACC Lesion class		
A	2.6% (4/154)	1.3% (1/75)
B1	42.9% (66/154)	48.0% (36/75)
B2	48.1% (74/154)	37.3% (28/75)
C	6.5% (10/154)	13.3% (10/75)
TIMI flow		
0	0.0% (0/154)	0.0% (0/75)
1	1.3% (2/154)	0.0% (0/75)
2	3.9% (6/154)	4.0% (3/75)
3	94.8% (146/154)	96.0% (72/75)
Lesion length, mm (±SD)	11.1±5.6	12.3±6.5
Discrete (<10 mm)	83.1% (128/154)	81.3% (61/75)
Tubular (10-20 mm)	15.6% (24/154)	17.3% (13/75)
Diffuse (>20 mm)	1.3% (2/154)	1.3% (1/75)
Eccentric lesion	97.4% (150/154)	96.0% (72/75)
Excessive tortuosity	1.9% (3/154)	4.0% (3/75)
Moderate/severe lesion angulation	2.6% (4/154)	5.3% (4/75)
Ostial lesion	0.0% (0/154)	1.3% (1/75)
Moderate to heavy calcification	14.3% (22/154)	17.3% (13/75)
Thrombus	3.2% (5/154)	1.3% (1/75)
Bifurcation	10.4% (16/154)	12.0% (9/75)

* Ejection fraction available in 98 Elixir patients, and 50 Endeavor patients; MI: myocardial infarction; CABG: coronary artery bypass surgery; PCI: percutaneous coronary intervention; AHA/ACC: American Heart Association/American College of Cardiology

(8.7%) ZES lesions, both of which were post-dilated. Serial analysis indicated that incomplete stent apposition at 9-months was persistent or resolved in 3/31 (9.7%) and 2/31 (6.5%) NES lesions, and 1/19 (5.3%) and 1/19 (5.3%) ZES lesions, respectively. There were no cases of late acquired incomplete stent apposition.

Clinical outcomes

Hierarchical and non-hierarchical clinical outcomes are shown in Table 4. Overall, there was no significant difference between stent groups in the device orientated composite endpoint (NES 2.9% vs. PES 5.6%, –2.8% [–8.8%, 3.3%], p=0.45) or its individual components of cardiac death, target vessel MI and CI-TLR. In total four MIs (two Q-wave and two NQWMI) were recorded in the study population, all of which were attributable to the study vessel. All TVR, which was performed in 6.5% and 7.0% of patients receiving NES and ZES respectively, was performed with PCI.

Specific to the Q-wave MI patients, one patient experienced a spiral dissection of the LAD during implantation of the first stent, and in the process of treating the dissection the operator implanted three more study stents. At the end of the procedure there was TIMI 2 flow in the target vessel, but within 4-hours, repeat angiography performed due to chest pain revealed an occlusion of the LAD, which required additional treatment with thrombus aspiration and balloon dilatation. The distal segment of the LAD remained occluded. This patient was adjudicated by the CEC as having had a Q-wave MI, a TLR due to DS100%, and a definite acute stent thrombosis. The other Q-wave MI was decided by default, after the CEC could not decide whether the patient had experienced a Q-wave or NQWMI. In this case the procedure itself went without incident, however a CK rise of 614, and CK-MB of 48.3 was recorded post intervention. In the two NQWMI patients, one had an unremarkable procedure, whilst the other had clear evidence of distal embolisation.

Stent thrombosis rates, as shown in Table 4, were low, with only two ST events in patients treated with NES (one early definite, and one late probable), and no ST observed with ZES. The definite ST event was an acute ST, occurring within four hours of the index PCI procedure, which was complicated by a spiral dissection necessitating the implantation of three additional study stents as described earlier. The ST in this case was attributed to procedural complications. The probable ST occurred in a patient still on dual antiplatelet therapy, who was admitted with dyspnoea and no chest pain, however the patient was found to have an elevated troponin, and had ischaemic ECG changes in the territory of the stent implanted at the index PCI 68 days earlier.

Discussion

The main findings from this study are that a specifically designed DES eluting novolimus has a significantly lower 9-month in-stent LLL compared to a ZES, with comparable clinical outcomes at 9-months.

Novolimus represents a specifically manufactured macrocyclic lactone, which is a metabolite of sirolimus that advantageously results in lower concentrations of drug (and consequently polymer) being needed to inhibit neointimal proliferation. The dose of drug and polymer thickness on NES are 5 µg/mm and <3 µm respectively, compared to 10 µg/mm and 4.1 µm for ZES; 10 µg/mm and 7.6 µm for the EES; 10 µg/mm and 16 µm for the TAXUS paclitaxel eluting stent (PES, Boston Scientific, Natick, MA, USA); and 14 µg/mm and 12.6 µm for SES. Although the NES utilises a methacrylate polymer that is similar to that used in other

Table 2. Results of sub-segmental quantitative coronary angiographic analysis.

	In-segment analysis				In-stent analysis			
	Novolimus	Zotarolimus	Difference [95% CI]	P value	Novolimus	Zotarolimus	Difference [95% CI]	P value
RVD. mm								
Pre-procedure*	2.74±0.48	2.74±0.47	0.01 [−0.13, 0.14]	0.93				
Post-procedure†	2.77±0.46	2.83±0.43	−0.06 [−0.19, 0.06]	0.34	2.84±0.43	2.91±0.38	−0.08 [−0.19, 0.04]	0.20
At 9-months‡	2.78±0.46	2.68±0.43	0.11 [−0.03, 0.24]	0.12	2.82±0.44	2.70±0.42	0.12 [−0.01, 0.25]	0.06
MLD/LL (mm)								
MLD Pre-procedure†	1.12±0.35	1.12±0.32	0.00 [−0.09, 0.10]	0.97				
Post-procedure†	2.20±0.45	2.25±0.44	−0.05 [−0.17, 0.08]	0.45	2.48±0.39	2.57±0.37	−0.09 [−0.20, 0.02]	0.10
At 9-months§	2.10±0.52	1.88±0.48	0.22 [0.07, 0.37]	0.004	2.36±0.48	1.95±0.48	0.41 [0.27, 0.55]	<0.001
Acute gain#	1.07±0.45	1.14±0.38	−0.07 [−0.19, 0.05]	0.27	1.36±0.40	1.47±0.36	−0.11 [−0.22, −0.00]	0.047
Acute gain (%)#	38.03±13.75	38.22±11.78	−0.19 [−3.86, 3.48]	0.92	46.48±11.65	47.51±11.13	−1.03 [−4.24, 2.18]	0.53
LL at 9-months‡	0.08±0.37	0.38±0.43	−0.30 [−0.41, −0.18]	<0.001	0.11±0.32	0.63±0.42	−0.52 [−0.63, −0.42]	<0.001**
Loss index¶	0.07±0.40	0.29±0.36	−0.23 [−0.34, −0.11]	<0.001	0.08±0.28	0.42±0.27	−0.34 [−0.42, −0.25]	<0.001
Diameter stenosis (%)								
Pre-procedure†	59±11	59±10	−0.06 [−2.96, 2.85]	0.97				
Post-procedure†	21±9	21±9	0.03 [−2.39, 2.44]	0.98	12±5	11±5	0.72 [−0.76, 2.20]	0.34
At 9-months§	24±14	30±14	−5.60 [−9.72, −1.48]	0.008	16±12	28±14	−11.55 [−15.21, −7.89]	<0.001
Binary restenosis (%)								
At 9-months§	5.8% (8/138)	9.1% (6/66)	−3.3% [−11.3%, 4.7%]	0.39	1.4% (2/138)	7.6% (5/66)	−6.1% [−12.8%, 0.6%]	0.037

RVD: reference vessel diameter; MLD: minimal lumen diameter; LL: late loss, NL: number of lesions; *NES NL=152, ZES NL=75; †NES NL=154, ZES NL=75; ‡NES NL=137, ZES NL=66; #NES NL=152, ZES NL=74; ¶ NES NL=131, ZES NL=64; §NES NL=138, ZES NL=66; **P value for both non-inferiority (delta 0.20 mm) and superiority

Table 3. Intravascular ultrasound measurements post-procedure and at 9-months follow-up.

	Novolimus (n=24)			Zotarolimus (n=15)			P value
	Post	FUP	P value FUP vs. Post	Post	FUP	P value FUP vs. Post	NES vs. ZES at FUP
Volumetric analysis							
Vessel volume index, mm^3/mm	15.1±4.0	14.9±4.0	0.674	14.9±2.8	15.6±3.1	0.015	0.6
Lumen volume index, mm^3/mm	7.6±2.0	7.3±2.1	0.004	7.6±1.5	6.2±1.6	<0.001	0.09
Stent volume index, mm^3/mm	7.6±2.0	7.7±2.2	0.657	7.6±1.5	7.8±1.6	0.172	0.9
Cross-sectional analysis							
Minimum lumen area, mm^2	6.5±1.7	5.9±2.0	0.001	6.4±1.5	4.7±1.7	<0.001	0.08
Change in MLA from Post-FUP	0.6±0.8			1.6±1.5			0.007
Volumetric analysis	N=34			N=15			
Neointimal volume index, mm^3/mm	0.3±0.5			1.6±0.9			<0.001*
% Neointimal volume obstruction,%	4.5±5.1			20.9±11.3			<0.001*

Numbers are expressed as Mean±SD. All P values were calculated by paired T-test unless indicated. *P values were calculated by unpaired T-test; % Neointimal volume obstruction=100 x (neointimal volume index/stent volume index); usually this is equal to zero at post-stent, since the stent is newly implanted and no obstruction is expected. FUP: follow-up

commercially available DES, the absence of a primer coating, together with purification of the polymer, and lower doses of drug and polymer conceivably have advantages when considering that a hypersensitivity reaction to the presence of a polymer is thought, in part, to be responsible for precipitating ST.[14-18]

There are two notable differences between the performances of NES in the current study, and the previously reported FIM. Firstly, there is a marked reduction in the late loss from the 0.31±0.25 mm reported in the FIM study to the 0.11±0.32 mm seen in this study. These results, in the absence of any changes in stent specification, may relate to the small sample size in the FIM study. In addition late loss is widely recognised to have a rather large standard deviation when inter-observer variability is assessed; moreover the measure itself is made up of two individual measurements, each with their own inter-observer variability, which is due mainly to the process of calibration.[11,19] Finally both studies were performed in different angiographic core labs, using different analysis equipment possibly leading to inter-lab variability. The second notable difference between both studies is the rate of incomplete stent malapposition amongst lesions in the IVUS sub-group which was 43% in the FIM study and 22% in the current study. In the absence of any changes to the stent's radial strength, or any changes to the protocol for post-stent dilatation between the two studies, it is again likely that these differences are related to the small sample size of the FIM study, together with inter-observer variability.

Two important topical issues with respect to the evaluation of new DESs, namely the definition of clinical endpoints such as MI and the selection of an appropriate control stent, are highlighted by the present study. Firstly, the current report defines MI according to the historical definition from the WHO, which was primarily selected to enable comparability of the current results with those of previous DES studies. It is noteworthy that despite being published in 2007

Table 4. Hierarchical and non-hierarchical subject counts of adverse events through 9-months (intent-to-treat population).

0 to 270 days,% (n)	Novolimus (N=139)	Zotarolimus (N=71)	Difference [95% CI]	P-value*
Hierarchical events				
Device orientated composite‡	2.9% (4/139)	5.6% (4/71)	−2.8% [−8.8%, 3.3%]	0.45
Cardiac death	0.0% (0/139)	0.0% (0/71)	0.0% [—, —]	No p-value
Target vessel MI	2.2% (3/139)	1.4% (1/71)	0.7% [−2.9%, 4.4%]	1.00
Q-wave MI	1.4% (2/139)	0.0% (0/71)	1.4% [−0.5%, 3.4%]	0.55
Non-Q- wave MI	0.7% (1/139)	1.4% (1/71)	−0.7% [−3.8%, 2.4%]	1.00
CI-TLR	0.7% (1/139)	4.2% (3/71)	−3.5% [−8.4%, 1.4%]	0.11
CI-TLR CABG	0.0% (0/139)	0.0% (0/71)	0.0% [—, —]	No p-value
CI-TLR PCI	0.7% (1/139)	4.2% (3/71)	−3.5% [−8.4%, 1.4%]	0.11
Non-hierarchical events				
All death	0.0% (0/139)	0.0% (0/71)	0.0% [—, —]	No p-value
All MI	2.2% (3/139)	1.4% (1/71)	0.7% [−2.9%, 4.4%]	1.00
Q-wave	1.4% (2/139)	0.0% (0/71)	1.4% [−0.5%, 3.4%]	0.55
Non-Q Wave	0.7% (1/139)	1.4% (1/71)	−0.7% [−3.8%, 2.4%]	1.00
Target vessel MI	2.2% (3/139)	1.4% (1/71)	0.7% [−2.9%, 4.4%]	1.00
Q-wave	1.4% (2/139)	0.0% (0/71)	1.4% [−0.5%, 3.4%]	0.55
Non Q-wave	0.7% (1/139)	1.4% (1/71)	−0.7% [−3.8%, 2.4%]	1.00
Non-target vessel MI	0.0% (0/139)	0.0% (0/71)	0.0% [—, —]	No p-value
All revascularisation	10.1% (14/139)	9.9% (7/71)	0.2% [−8.3%, 8.8%]	1.00
Any TVR*	6.5% (9/139)	7.0% (5/71)	−0.6% [−7.8%, 6.7%]	1.00
CI – TVR*	4.3% (6/139)	4.2% (3/71)	0.1% [−5.7%, 5.9%]	1.00
Non CI- TVR*	2.2% (3/139)	2.8% (2/71)	−0.7% [−5.2%, 3.9%]	1.00
Any TLR*	2.9% (4/139)	5.6% (4/71)	−2.8% [−8.8%, 3.3%]	0.45
CI-TLR*	2.2% (3/139)	4.2% (3/71)	−2.1% [−7.3%, 3.2%]	0.41
Non-CI-TLR*	0.7% (1/139)	1.4% (1/71)	−0.7% [−3.8%, 2.4%]	1.00
Non-target lesion TVR*	3.6% (5/139)	1.4% (1/71)	2.2% [−1.9%, 6.3%]	0.67
Non-target lesion CI-TVR*	2.2% (3/139)	0.0% (0/71)	2.2% [−0.3%, 4.6%]	0.55
Non-target lesion non CI-TVR*	1.4% (2/139)	1.4% (1/71)	0.0% [−3.4%, 3.4%]	1.00
Non-TVR	3.6% (5/139)	2.8% (2/71)	0.8% [−4.2%, 5.7%]	1.00
CABG	0.7% (1/139)	0.0% (0/71)	0.7% [−0.7%, 2.1%]	1.00
PCI	2.9% (4/139)	2.8% (2/71)	0.1% [−4.7%, 4.8%]	1.00
Stent thrombosis				
Definite¶	0.7% (1/139)	0.0% (0/71)	0.7% [−0.7%, 2.1%]	1.00
Probable§	0.7% (1/139)	0.0% (0/71)	0.7% [−0.7%, 2.1%]	1.00
Possible	0.0% (0/139)	0.0% (0/71)	0.0% [—, —]	No p-value
Definite+Probable§	1.4% (2/139)	0.0% (0/71)	1.4% [−0.5%, 3.4%]	0.55
Definite+Probable+Possible§	1.4% (2/139)	0.0% (0/71)	1.4% [−0.5%, 3.4%]	0.55

NES: novolimus eluting stent; ZES: zotarolimus eluting stent; CI-TLR: clinically indicated target lesion indicated revascularisation; CI-TVR: clinically target vessel revascularisation; CABG: coronary artery bypass graft surgery; PCI: percutaneous coronary intervention; MI: myocardial infarction; CI: confidence interval; ‡Device orientated composite: Cardiac Death, MI not clearly attributable to a non-intervened vessel, CI-TLR; *No revascularisation via CABG; ¶Definite stent thrombosis at day 0; §Includes one patient with an MI at day 68, defined according to the ARC definition of MI, and therefore an ARC probable ST; however this MI does not satisfy the WHO definition of MI used in the determination of hierarchical clinical events, and therefore is not included in the table of clinical events

the ARC and the Universal definitions for MI[12,20] are still not utilised in recently published pivotal trials of first and second generation DESs such as Endeavor III (ZES vs. SES), Endeavor IV (ZES vs. PES) and COMPARE (EES vs. PES).[21-23] In fact, the RESOLUTE all-comers trial, which is due for publication later this year, will be the first study to report MI according to both historical and ARC definitions.[24] Conversely, interventional studies investigating new anti-coagulant agents such as ticagrelor have been quick to utilise the new Universal definitions.[25] This variation between device and pharmacological studies suggests that a definition of this important clinical endpoint, that is satisfactory to all parties, is yet to be established.

The selection of an appropriate control stent in the assessment of a new DES is an important aspect of trial design. Some may question the use of ZES as the control stent in the current study, when at present the market leader is considered to be the EES. Of note, authorities do not accept first-in-man studies for regulatory approval, instead they require randomised studies against a comparator DES, however this is not required to be the most efficacious or safest stent at the time of study. This subsequently allows non-inferiority trials to be designed without prohibitively large sample sizes.

At the time of the study design in 2007, in the aftermath of the "Barcelona firestorm" where first generation DES were reported as

causing an increased risk of very late ST,[7,26,27] ZES was considered the safest DES, although contemporary data now indicate that this may not now be the case.[28] Meta-analysis have confirmed a 1.4-3.5 times increased risk of very late ST with SES and PES compared to BMS out to 4-year follow-up.[6] On the other hand, in the randomised ENDEAVOR II study the rate of very late ST at 5-years follow-up was only 0.2% with ZES, compared to 0.3% for the BMS controls.[29] These differences in very late ST rates prompted the recently enrolled 8,800 patient PROTECT study which will be the only study adequately powered to report differences in ST between ZES and SES.[30]

We acknowledge that with respect to inhibition of neointimal proliferation, when ZES has been compared to SES and PES in the respective ENDEAVOR III, and ENDEAVOR IV studies, a significantly higher LLL of 0.60 mm and 0.67 mm respectively has been seen with ZES at 8-months follow-up. These values however are comparable to the 0.33 mm LLL seen with the NES in the Excella FIM study, thereby allowing a feasible non-inferiority study between NES and ZES to be performed.[9,22,31] Importantly, despite this higher LLL, no significant differences in TLR have been seen with ZES at 36- or 48-months compared to PES and SES, respectively.[29,32] Moreover, reductions in the absolute difference in TLR between short and long-term follow-up in favour of ZES indicate that ZES may not be susceptible to the delayed restenosis phenomenon observed with other mTOR inhibiting DES such as SES,[33] and EES.[34]

Limitations

This study is limited by its short duration of follow-up, lack of blinding of the operator, and lack of power to discriminate between clinical events.

Conclusions

This non-inferiority randomised study not only met its primary endpoint, but also demonstrated superiority of the novolimus eluting stent compared to the zotarolimus eluting stent in terms of in-stent late loss. In addition, rates of adverse cardiac events were low and comparable between both stents.

Appendix

Sponsor: Elixir Medical Corporation, Sunnyvale, CA, USA

Principal investigator: Patrick W. Serruys, Erasmus Medisch Centrum, Rotterdam, The Netherlands

Co-principal investigators: Stephan Windecker, University Hospital Bern, Bern, Switzerland; John Ormiston, Auckland City Hospital and Mercy Angiography, Auckland, New Zealand; Alexandre Abizaid, Instituto Dante Pazzanese, Sao Paulo, Brazil

Steering committee: Patrick W. Serruys, Principal Investigator and Chairman, Rotterdam, The Netherlands; Stephan Windecker, Bern Switzerland; John Ormiston, Auckland, New Zealand; Alexandre Abizaid, Sao Paulo, Brazil; Peter Fitzgerald, Cardiovascular Core Analysis Laboratory, Stanford University, Stanford, CA, USA; Elixir Medical Corporation, Sunnyvale, CA, USA

Data Safety Monitoring Board (DSMB): Prof. Dr. J.G.P. Tijssen, Chairman, Amsterdam, The Netherlands; Dr. B.J.W.M. Rensing, Nieuwegein, The Netherlands; Dr. M.J.B.M. van den Brand, Ouderkerk aan den Ijssel, The Netherlands

Clinical Events Committee (CEC): Dr. Pascal Vranckx, Luik, Belgium; Dr. Peter Smits, Rotterdam, The Netherlands; Dr. Anthony H. Gershlick, Glenfield, United Kingdom; Prof. Victor Legrand, Liège, Belgium

Data Management - Angiographic Core Laboratories: Cardialysis BV, Rotterdam, The Netherlands

Data Management - IVUS Core Laboratories: Cardiovascular Core Analysis Laboratory, Stanford University, Stanford, CA, USA

Data Coordination Centre and Site Monitoring: Cardialysis BV, Rotterdam, The Netherlands, Krakow Cardiovascular Research Institute (KCRI), Krakow, Poland, Medical Device Consultancy, Christchurch, New Zealand, Pacific Clinical Research Group (PCRG), Mosman, NSW, Australia, Kerstin Kupfer, Australasian Ltd, Bonn, Germany, Anton Maierl, München, Germany

The following investigators and institutions participated in the EXCELLA II Trial:

Patrick W. Serruys, Prof. MD, Erasmus Medisch Centrum, Rotterdam, The Netherlands; John Ormiston, MD, Auckland City Hospital and Mercy Angiography, Auckland, New Zealand; Stefan Verheye, MD, AZ Middelheim Hospital, Antwerp, Belgium; Christophe Dubois, MD, Universitair Ziekenhuis Gasthuisberg, Leuven, Belgium; Karl E. Hauptmann, MD, Krankenhaus der Barmherzigen Brüder, Trier, Germany; Jim Stewart, MD, Mercy Angiography, Auckland, New Zealand; Marcus Wiemer, MD, Herz- und Diabetes Zentrum, Bad Oeynhausen, Germany; Joachim Schofer, Prof. MD, Universitäres Herz- und Gefäßzentrum, Hamburg, Germany; Wolfgang Rutsch, Prof. MD, Charite Campus Charité Mitte, Berlin, Germany; Karl Stangl, Prof. MD, Charite Campus Charité Mitte, Berlin, Germany; Bernhard Witzenbichler, Prof. MD, Charite Benjamin Franklin Campus, Berlin, Germany; Emanuelle Barbato, MD, OLV Hospital Cardiovascular Center, Aalst, Belgium; Mark Webster, MD, Auckland City Hospital, Auckland New Zealand; Dariusz Dudek MD, PhD, Jagiellonian University, Krakow, Poland; Seif El-Jack, MD, North Shore Hospital, Auckland, New Zealand; Dougal McClean, MD, Christchurch Hospital, Christchurch, New Zealand; Patrick Kay, MD, Middlemore Hospital, Auckland, New Zealand; Sabine Genth-Zotz, MD, Klinikum der Johannes Gutenburg-Universität, Mainz, Germany; Pawel Buszman, Prof. MD, Upper-Silesian Heart Centre, Katowice, Poland; Ian Meredith, Prof. MD, Monash Medical Center, Melbourne, VIC, Australia; Thomas Ischinger, Prof. MD, Klinikum Bogenhausen der Stad Muenchen, Munich, Germany; Yves Taeymans, Prof. MD, University Hospital Gent, Gent, Belgium; Robert Whitbourn, Prof. MD, St. Vincent's Hospital, Melbourne, VIC, Australia

References

1. Garg S, Serruys PW. Coronary stents - Current Status. *J Am Coll Cardiol.* In Press.

2. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med.* 2002;346:1773-1780.

3. Colombo A, Drzewiecki J, Banning A, Grube E, Hauptmann K, Silber S, Dudek D, Fort S, Schiele F, Zmudka K, Guagliumi G, Russell ME.

Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. *Circulation.* 2003;108:788-794.

4. Serruys PW, Ong AT, Piek JJ, Neumann FJ, van der Giessen WJ, Wiemer M, Zeiher A, Grube E, Haase J, Thuesen L, Hamm C, Otto-Terlouw PC. A randomized comparison of a durable polymer Everolimus-eluting stent with a bare metal coronary stent: The SPIRIT first trial. *EuroIntervention.* 2005;1:58-65.

5. Fajadet J, Wijns W, Laarman GJ, Kuck KH, Ormiston J, Munzel T, Popma JJ, Fitzgerald PJ, Bonan R, Kuntz RE. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. *Circulation.* 2006;114:798-806.

6. Stettler C, Wandel S, Allemann S, Kastrati A, Morice MC, Schomig A, Pfisterer ME, Stone GW, Leon MB, de Lezo JS, Goy JJ, Park SJ, Sabate M, Suttorp MJ, Kelbaek H, Spaulding C, Menichelli M, Vermeersch P, Dirksen MT, Cervinka P, Petronio AS, Nordmann AJ, Diem P, Meier B, Zwahlen M, Reichenbach S, Trelle S, Windecker S, Juni P. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet.* 2007;370:937-948.

7. Lagerqvist B, James SK, Stenestrand U, Lindback J, Nilsson T, Wallentin L, the SSG. Long-Term Outcomes with Drug-Eluting Stents versus Bare-Metal Stents in Sweden. *N Engl J Med.* 2007;356:1009-1019.

8. Schomig A, Dibra A, Windecker S, Mehilli J, Suarez de Lezo J, Kaiser C, Park SJ, Goy JJ, Lee JH, Di Lorenzo E, Wu J, Juni P, Pfisterer ME, Meier B, Kastrati A. A meta-analysis of 16 randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary artery disease. *J Am Coll Cardiol.* 2007;50:1373-1380.

9. Costa JR, Jr., Abizaid A, Feres F, Costa R, Seixas AC, Maia F, Tanajura LF, Staico R, Siqueira D, Meredith L, Bhat V, Yan J, Ormiston J, Sousa AG, Fitzgerald P, Sousa JE. EXCELLA First-in-Man (FIM) study: safety and efficacy of novolimus-eluting stent in de novo coronary lesions. *EuroIntervention.* 2008;4:53-58.

10. Abizaid A, Costa JR Jr., Feres F, Costa R, Seixas A, Maia F, Staico R, Siqueira D, Ormiston J, Sousa AGMR, Fitzgerald P, Honda Y, Otake H, Sousa JE. TCT-429: Single Center, First-In-Man Study of the Elixir Novolimus Eluting Coronary Stent System with Durable Polymer 24-Month Clinical Safety and Efficacy Results. *Am J Cardiol.* 2009;104:158D-158D.

11. Serruys PW, Foley D, De Feyter PJ, eds. Quantitative coronary angiography in clinical practice. Dordrecht, The Netherlands, 1994.

12. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115:2344-2351.

13. Nomenclature and criteria for diagnosis of ischemic heart disease. Report of the Joint International Society and Federation of Cardiology/World Health Organization task force on standardization of clinical nomenclature. *Circulation.* 1979;59:607-609.

14. van der Giessen WJ, Lincoff AM, Schwartz RS, van Beusekom HM, Serruys PW, Holmes DR, Jr., Ellis SG, Topol EJ. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. *Circulation.* 1996;94:1690-1697.

15. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol.* 2006;48:193-202.

16. Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, Mihalcsik L, Tespili M, Valsecchi O, Kolodgie FD. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation.* 2004;109:701-705.

17. Nebeker JR, Virmani R, Bennett CL, Hoffman JM, Samore MH, Alvarez J, Davidson CJ, McKoy JM, Raisch DW, Whisenant BK, Yarnold PR, Belknap SM, West DP, Gage JE, Morse RE, Gligoric G, Davidson L, Feldman MD. Hypersensitivity Cases Associated With Drug-Eluting Coronary Stents: A Review of Available Cases From the Research on Adverse Drug Events and Reports (RADAR) Project. *J Am Coll Cardiol.* 2006;47:175-181.

18. Joner M, Nakazawa G, Finn AV, Quee SC, Coleman L, Acampado E, Wilson PS, Skorija K, Cheng Q, Xu X, Gold HK, Kolodgie FD, Virmani R. Endothelial cell recovery between comparator polymer-based drug-eluting stents. *J Am Coll Cardiol.* 2008;52:333-342.

19. Tsuchida K, Garcia-Garcia HM, Ong AT, Valgimigli M, Aoki J, Rademaker TA, Morel MA, van Es GA, Bruining N, Serruys PW. Revisiting late loss and neointimal volumetric measurements in a drug-eluting stent trial: analysis from the SPIRIT FIRST trial. *Catheter Cardiovasc Interv.* 2006;67:188-197.

20. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *Eur Heart J.* 2007;28:2525-2538.

21. Eisenstein EL, Leon MB, Kandzari DE, Mauri L, Edwards R, Kong DF, Cowper PA, Anstrom KJ, for the EIIII. Long-term clnical and economic analysis of the Endeavor Zotarolimus-eluting stent versus the Cypher Sirolimus-eluting stent: 3-year results from the ENDEAVOR III Trial (randomized controlled trial of the Medtronic Endeavor drug [ABT-578] eluting coronary stent system versus the Cypher Sirolimus-eluting coronary stent system in de novo native coronary artery lesions). *J Am Coll Cardiol* Intv. 2009;2:1199-1207.

22. Leon MB, Mauri L, Popma JJ, Cutlip DE, Nikolsky E, O'Shaughnessy C, Overlie PA, McLaurin BT, Solomon SL, Douglas Jr JS, Ball MW, Caputo RP, Jain A, Tolleson TR, Reen Iii BM, Kirtane AJ, Fitzgerald PJ, Thompson K, Kandzari DE. A randomised comparison of the Endeavor Zotarolimus-eluting stent versus the TAXUS Paclitaxel-eluting stent in de novo native coronary lesions: 12-Month outcomes from the ENDEAVOR IV Trial. *J Am Coll Cardiol.* 2010;55:543-554.

23. Kedhi E, Joesoef KS, McFadden E, Wassing J, van Mieghem C, Goedhart D, Smits PC. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. *Lancet.* 2010;375:201-209.

24. Vranckx P, Cutlip D, Mehran R, Kint P-P, Silber S, Windecker S, Serruys PW. Myocardial Infarction adjudication in Contemporary All-Comer Stent trials: Balancing sensitivity and specificity. *EuroIntervention.* 2010;5:871-874.

25. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, Freij A, Thorsen M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2009;361:1045-1057.

26. Nordmann AJ, Briel M, Bucher HC. Mortality in randomized controlled trials comparing drug-eluting vs. bare metal stents in coronary artery disease: a meta-analysis. *Eur Heart J.* 2006;27:2784-2814.

27. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. *Circulation.* 2007;115:1440-1455; discussion 1455.

28. Rasmussen K, Maeng M, Kaltoft A, Thayssen P, Kelbaek H, Tilsted HH, Abildgaard U, Christiansen EH, Engstrom T, Krusell LR, Ravkilde J,

Hansen PR, Hansen KN, Abildstrom SZ, Aaroe J, Jensen JS, Kristensen SD, Botker HE, Madsen M, Johnsen SP, Jensen LO, Sorensen HT, Theusen L, Lassen JF. Efficacy and safety of zotarolimus-eluting and sirolimus-eluting coronary stents in routine clinical care (SORT OUT III): a randomised controlled superiority trial. *Lancet.* 2010;375:1090-1099.

29. Hamm C. 5 years later and more than 20,000 patients studied: the ENDEAVOR clinical programme. EuroPCR 19th-22nd May 2009; Barcelona [online] Available: www.europcronline.com/fo/lecture/view_slide.php?idCongres=5&id=7617 [Accessed 20th June 2009].

30. Camenzind E, Wijns W, Mauri L, Boersma E, Parikh K, Kurowski V, Gao R, Bode C, Greenwood JP, Gershlick A, O'Neill W, Serruys PW, Jorissen B, Steg PG. Rationale and design of the Patient Related OuTcomes with Endeavor versus Cypher stenting Trial (PROTECT): randomized controlled trial comparing the incidence of stent thrombosis and clinical events after sirolimus or zotarolimus drug-eluting stent implantation. *Am Heart J.* 2009;158:902-909 e905.

31. Kandzari DE, Leon MB, Popma JJ, Fitzgerald PJ, O'Shaughnessy C, Ball MW, Turco M, Applegate RJ, Gurbel PA, Midei MG, Badre SS, Mauri L, Thompson KP, LeNarz LA, Kuntz RE. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease: a randomized controlled trial. *J Am Coll Cardiol.* 2006;48:2440-2447.

32. Leon M. The ENDEAVOR and ENDEAVOR Resolute Zotarolimus-Eluting Stent: Comprehensive Update of the Clinical Trial Program (Featuring the First Presentation of the ENDEAVOR IV 3-Year Results). Presentation at Transcatheter Cardiovascular Therapeutics, San Francisco, 21st September 2009. Available online: www.tctmd.com/txshow.aspx?tid=939082&id=84004&trid=938634. [Accessed October 28th 2009].

33. Raber L. SIRTAX-LATE: Five-Year Clinical and Angiographic Follow-up from a Prospective Randomized Trial of Sirolimus-Eluting and Paclitaxel-Eluting Stents. Presentation Transcatheter Cardiovascular Therapeutics, San Francisco, 22nd September 2009.

34. Claessen BE, Beijk MA, Legrand V, Ruzyllo W, Manari A, Varenne O, Suttorp MJ, Tijssen JGP, Miquel-Hebert K, Veldhof S, Henriques JPS, Serruys PW, Piek JJ. Two-Year Clinical, Angiographic, and Intravascular Ultrasound Follow-Up of the XIENCE V Everolimus-Eluting Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions: The SPIRIT II Trial. *Circ Cardiovasc Intervent.* 2009;2:339-347.

Chapter 7.5

The twelve month outcomes of a biolimus-eluting stent with a biodegradable polymer compared with a sirolimus-eluting stent with a durable polymer

EuroIntervention 2010; 6 (2):233-239

Scot Garg, Giovanna Sarno, Patrick W. Serruys, Ton de Vries, Pawel Buszman, Stan Trznadel, Axel Linke, Karsten Lenk, Thomas Ischinger, Volker Klauss, Franz Eberli, Roberto Corti, William Wijns, Marie-claude Morice, Carlo di Mario, Pawel Tyczynski, Robert-Jan van Geuns, Pedro Eerdmans, Gerrit-Anne van Es, Bernie Meier, Peter Juni, Stephan Windecker

EuroIntervention

The twelve-month outcomes of a biolimus eluting stent with a biodegradable polymer compared with a sirolimus eluting stent with a durable polymer

Scot Garg[1], MB ChB, MRCP; Giovanna Sarno[1], MD, PhD; Patrick W. Serruys[1]*, MD, PhD; Ton de Vries[2], MSc; Pawel Buszman[3], MD, PhD; Axel Linke[4], MD, PhD; Thomas Ischinger[5], MD, PhD; Volker Klauss[6], MD, PhD; Franz Eberli[7], MD; Roberto Corti[8], MD; William Wijns[9], MD, PhD; Marie-Claude Morice[10], MD; Carlo Di Mario[11], MD, PhD; Robert Jan van Geuns[1], MD, PhD; Pedro Eerdmans[12], MD, PhD; Gerrit-Anne van Es[2], PhD; Bernhard Meier[13], MD; Peter Jüni[14,15], MD; Stephan Windecker[13,14], MD, PhD

1. Department of Interventional Cardiology, Erasmus MC, Rotterdam, The Netherlands; 2. Cardialysis B.V, Rotterdam, The Netherlands; 3. Medical University of Silesia, Katowice, Poland; 4. Herzzentrum Leipzig, Leipzig, Germany; 5. Department of Cardiology, Hospital Bogenhausen, Munich, Germany; 6. Department of Cardiology, University Hospital Munich (Innenstadt), Munich, Germany; 7. Currently working at department of Cardiology, Triemli Spital, Zurich, Switzerland; 8. Department of Cardiology, University Hospital Zurich, Zurich, Switzerland; 9. Department of Cardiology, Onze Lieve Vrouw Ziekenhuis, Aalst, Belgium; 10. Institut Jacques Cartier Massy, France; 11. Department of Cardiology, Royal Brompton Hospital, London, United Kingdom; 12. Biosensors Europe SA, Morges, Switzerland; 13. Department of Cardiology, University Hospital Bern, Bern, Switzerland; 14. CTU Bern, Bern University Hospital, Bern, Switzerland; 15. Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

S. Windecker is a consultant for and receives fees from ABBOTT Vascular, Boston Scientific, Cordis, Medtronic, and Biosensors. F. Eberli is a speaker for Biosensors, and consultant for Cordis. P. Eerdmans is an employee of Biosensors, Europe. The remaining authors have no conflicts of interest to declare. Funding Source: The LEADERS trial was funded by Biosensors, Europe SA, Switzerland.

KEYWORDS
Biolimus eluting stent, sirolimus eluting stent, biodegradable polymer

Abstract

Aims: This study reports the 12-month clinical outcomes of the LEADERS clinical trial which compared a biolimus eluting stent with a biodegradable polymer (BES) to a sirolimus eluting stent with a durable polymer (SES).

Methods and results: The multicentre LEADERS trial employed an all-comers approach to recruit 1,707 patients who were randomised to treatment with either BES (n=857) or SES (n=850) in a non-inferiority design. The primary clinical endpoint of this study was a composite of cardiac death, myocardial infarction and clinical-indicated target vessel revascularisation. Follow-up was obtained in 97.6% of patients. At 12 months, BES remained non-inferior compared to SES for the primary endpoint (BES 10.6% vs. SES 12.0%, HR:0.88, 95% CI:0.66-1.17, p=0.37). Rates of cardiac death (2.1% vs. 2.7%, HR:0.77, 95% CI:0.42-1.44, p=0.42), MI (5.8% vs. 4.6%, HR:1.27, 95% CI:0.84-1.94, p=0.26) and clinically-indicated target vessel revascularisation (5.8% vs. 7.1%, HR:0.82, 95%CI:0.56-1.19, p=0.29) were similar for BES and SES. Similarly, there was no difference in the incidence of definite stent thrombosis at 12 months.

Conclusions: These findings support the safety and efficacy of the BES stent with a biodegradable polymer at 12-month clinical follow-up, and suggest it is a suitable alternative to the SES stent with a durable polymer.

** Corresponding author: Ba583a, Thoraxcentre, Erasmus MC,'s-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands*
E-mail: p.w.j.c.serruys@erasmusmc.nl

Introduction

Drug eluting stents (DES) revolutionised the field of percutaneous coronary intervention (PCI) after their introduction in 2002, by significantly reducing rates of restenosis compared to bare metal stents (BMS)[1]. In recent times there have been concerns that when compared to BMS, DES are associated with an increased risk of very late (>1 year) stent thrombosis (ST)[2-4]. The cause of this is likely to be multi-factorial, however delayed re-endothelialisation plays an important role, and this in turn may be the result of a hypersensitivity reaction induced by the presence of a permanent polymer[5,6].

The Biomatrix™ Flex biolimus eluting stent (BES) (Biosensors, Morges, Switzerland) elutes biolimus from a polylactic acid (PLA) biodegradable polymer applied to the stent's abluminal surface. The polymer is fully metabolised to water and carbon dioxide within six to nine months. Biolimus is a highly lipophilic sirolimus analogue[7] which inhibits the mammalian target of rapamycin, and inhibits smooth muscle cell proliferation by causing the arrest of the cell cycle at G_0 with similar potency to sirolimus. Grube et al were the first to demonstrate the feasibility of a BES with a biodegradable polymer, by reporting a significantly reduced late loss and neointimal volume with BES compared with a BMS. More recently, these findings have been confirmed by other studies of biolimus eluting stents which have enrolled more diverse patient populations[8-12].

The BioMatrix™ Flex has previously been shown to be non-inferior to the Cypher® sirolimus eluting stent (SES) (Cordis, Warren, NJ, USA) in terms of major adverse cardiovascular events (MACE) at nine months follow-up (9% vs. 11%, p for non-inferiority=0·003, p for superiority=0·39) in the randomised LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) clinical trial[10]. The current report presents the outcomes of the LEADERS trial at 12-month clinical follow-up, which represents a pre-specified secondary endpoint of the study.

Methods

Study population

The methods of the LEADERS trial have been published previously[10]. In brief the study applied an all-comers approach recruiting 1,707 patients with chronic stable coronary artery disease or acute coronary syndromes (ACS) including ST-elevation myocardial infarction (STEMI), who were eligible for enrolment if they had at ≥1 lesion with diameter stenosis (DS) ≥50% and a reference vessel diameter (RVD) 2.25-3.5 mm. The principle exclusion criteria were: known allergy to acetylsalicylic acid, clopidogrel, heparin, stainless steel, sirolimus, biolimus or contrast material that cannot be pre-medicated, planned surgery within six months of PCI unless the dual anti-platelet therapy (DAPT) could be maintained throughout the peri-operative period, pregnancy, participation in another trial before reaching the primary endpoint and lastly inability to give informed consent. The study complied with the Declaration of Helsinki and was approved by all institutional ethics committees. All patients provided written, informed consent for participation in the trial.

Randomisation and procedures

Patients were randomly allocated on a 1:1 basis to treatment with either a BES or SES, and to active angiographic follow-up at nine months or clinical follow-up only on a 1:3 basis with a factorial design. BES were available in diameters of 2.25-3.5 mm and in lengths of 8-28 mm, whilst SES were available in diameters of 2.25-3.5 mm and in lengths of 8-33 mm. Balloon angioplasty and stent implantation were performed according to standard technique, and direct stenting was allowed. The aim was to obtain full lesion coverage with one or several stents. No mixture of DES was permitted within a given patient, unless the operator was unable to insert the study stent, in which case crossover to another device of the operator's choice was possible. Procedural anticoagulation was achieved with unfractionated heparin 5,000 IU or 70-100 IU/kg, whilst the use of glycoprotein IIb/IIIa inhibitors was left to the operator's discretion. Pre-procedure all patients enrolled into the study received ≥75 mg of acetylsalicylic acid, and at least 300 mg of clopidogrel. All patients were discharged on ≥75 mg of acetylsalicylic acid indefinitely, and clopidogrel 75 mg for a minimum of 12 months following the index procedure. In the case of inter-current revascularisation procedures needing stent implantation, treating cardiologists were encouraged to use study stents.

Follow-up

Adverse events were assessed in hospital, and clinical follow-up was performed at 1, 6, 9, and 12 months. Additional clinical follow-up is planned at yearly intervals to five years. One in four patients was asked to return for angiographic follow-up at nine months.

Study endpoints

The clinical primary endpoint of this study was MACE, defined as the composite of cardiac death, myocardial infarction (MI), and clinically-indicated target vessel revascularisation (TVR) at 12 months. Secondary endpoints were death from any cause, cardiac death, MI, any target lesion revascularisation (TLR) (both clinically and non-clinically indicated); any TVR, and ST.

A blinded independent clinical events committee adjudicated all endpoints, and independent study monitors verified all case reports from data on-site. The operators were by necessity aware of the assigned study stent during PCI and angiographic follow-up, but patients and staff involved in follow-up assessment were blinded to the allocated stent type. Angiography films were centrally assessed at one angiographic core laboratory (Cardialysis, Rotterdam, Netherlands) with assessors unaware of the allocated stent.

Definitions

Definitions of all endpoints are provided in full elsewhere[10]. MI was defined using the electrocardiographic criteria of the Minnesota code, or by a measured level of creatinine kinase (CK) two times the upper limit of normal (ULN), with either a positive concentration of CK-myoglobin fraction, or troponin I or T. Revascularisation was regarded as clinically indicated if on quantitative coronary angiography (QCA) the lumen DS of the treated lesion was ≥50% in the presence of ischaemic signs or symptoms, or ≥70% in the absence of ischaemia. TVR was defined as any repeat PCI or

surgical bypass of any segment within the entire major coronary vessel proximal and distal to a target lesion, including upstream and downstream branches and the target lesion itself. TLR was defined as a repeat revascularisation due to a stenosis within the stent or within a 5 mm border proximal or distal to the stent. ST was defined according to the Academic Research Consortium definitions[13].

Statistics

This trial was powered for non-inferiority on the primary clinical endpoint at nine months. The rationale behind this and for the sample size is reported elsewhere[10]. In this paper continuous variables are expressed as mean ±standard deviation; and categorical data is presented as frequency (percentages). Patient demographic data was compared using the Student t-test, whilst χ^2 was used for categorical data. Survival curves were constructed for time-to-event variables using Kaplan-Meier estimates, and compared by the log-rank test. The Mantel-Cox model was used for the rate ratios of clinical outcome. All analyses were performed using SAS 8.02 by a dedicated statistician. All p-values and confidence intervals were two-sided; p<0.05 was considered statistically significant.

Results

Follow-up

Figure 1 shows the clinical follow-up of patients from enrolment to 12 months, on an intention to treat basis. Overall clinical follow-up was available in 1,666 patients (97.6%) made up of 837 of the original 857 BES patients, (97.7%) and 829 of the original 850 SES patients (97.5%). The reasons for incomplete follow up are shown in Figure 1.

Patient population and lesion characteristics

The baseline demographic, clinical and angiographic characteristics, have been published previously[10] and are summarised in Table 1. Procedural results and outcomes of nine month clinical and angiographic follow-up have all been presented elsewhere[10]. There was no significant difference in procedural characteristics between both groups. Similarly clinical outcomes at nine months in terms of death, cardiac death, MI, clinically-indicated TLR and TVR, any TLR and TVR were also comparable for both stents. Overall the primary endpoint at nine months met the pre-specified criteria for non-inferiority (BES 9% vs. SES 11%, p for non-inferiority=0.003, p for superiority=0.39).

Nine-month angiographic follow-up results were available in 335 patients (168 BES, and 167 SES), representing 78.5% of those allocated to angiographic follow-up. BES was non-inferior to SES for

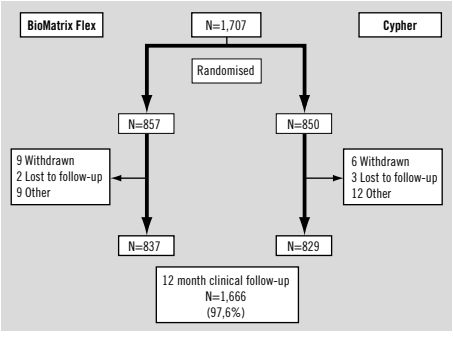


Figure 1. Flow chart of clinical follow-up of patient population.

Table 1. Baseline data.

Variables, n(%) unless stated	BES (n=857)	SES (n=850)
Patient demographics		
Age, years (SD)	64.6 (10.8)	64.5 (10.7)
Male	643 (75.0%)	634 (74.6%)
Body mass index, kg/m^2	27.6	27.5
Diabetes mellitus	223 (26.0%)	191 (22.5%)
Hypertension	630 (73.5%)	618 (72.7%)
Hypercholesterolaemia	560 (65.3%)	580 (68.2%)
Current smoker	206 (24.0%)	214 (25.2%)
Family history of CAD	339 (39.6%)	374 (44.0%)
Previous MI	276 (32.2%)	277 (32.6%)
Previous PCI	312 (36.4%)	312 (36.7%)
Previous CABG	90 (10.5%)	107 (12.6%)
Previous stroke	40 (4.7%)	28 (3.3%)
Peripheral vascular disease	70 (8.2%)	63 (7.4%)
Multi-vessel disease	209 (24.4%)	176 (20.7%)
Left ventricular ejection fraction, % (SD)*	55.9% (11.3)	55.4% (12.4)
SYNTAX score#	13.2	13.3
Clinical presentation		
Acute coronary syndrome	470 (54.8%)	473 (55.7%)
ST-elevation MI	135 (15.8%)	140 (16.5%)
Non ST-elevation MI	145 (16.9%)	153 (18.0%)
Unstable angina	190 (22.2%)	180 (21.2%)
Stable angina	387 (45.2%)	377 (44.4%)
Silent ischaemia	89 (10.4%)	85 (10.0%)
Angiographic parameters		
Number of lesions >50%	1256	1213
De novo lesions	1181/1256 (94.0%)	1126/1213 (92.9%)
Off-label use	696 (81.2%)	665 (78.2%)
Small-vessel disease (RVD<2.75 mm)	585 (68.3%)	568 (66.8%)
Lesions >20 mm	262 (30.6%)	225 (26.5%)
Total occlusion	147/1228 (12.0%)	142/1194 (11.9%)
Bifurcation lesion	282/1256 (22.5%)	252/1213 (20.8%)
Severe calcification	158/1210 (13.1%)	166/1172 (14.2%)
Reference vessel diameter, mm(SD)±	2.60 (0.61)	2.60 (0.57)
Minimum lumen diameter, mm (SD)§	0.91 (0.50)	0.95 (0.52)
Diameter stenosis, %(SD)§	64.6% (17.9)	63.3% (18.2)

* Left ventricular ejection fraction is available for 601 BES, and 607 SES patients; # 678 patients in the BES group, and 673 in the SES group; ± 1,246 assessed in the BES group, and 1,199 in the SES group; § 1,209 assessed in the BES group, and 1,186 in the SES group; BES: biolimus eluting stent; SES: sirolimus eluting stent; RVD: reference vessel disease; CAD: coronary artery disease; MI: myocardial infarction; CABG: coronary artery bypass grafting

the angiographic outcome in-stent percentage stenosis (20.9% vs. 23.3%, p for non-inferiority=0.001). There were no significant differences in superiority testing in other angiographic parameters such as in-stent and in-segment percentage stenosis, late loss, and binary restenosis.

Symptom control and medication at 12 months

Symptomatically at 12 months 14.5% of patients (13.2% BES, 15.7% SES) still experienced angina pectoris, or had clinical evidence of on-going silent ischaemia. In the majority of these patients the angina was stable, and at Canadian Cardiovascular Society (CCS) angina class 1. Over 80% of patients were on a beta-blocker, a statin and either an angiotensin converting enzyme inhibitor or angiotension-II blocker.

Clinical outcomes at 12 months

The hierarchical and non-hierarchical events at one year clinical follow-up are shown in Table 2. At 12-month follow-up the use of BES was associated with similar rates of death and cardiac-death. Whilst patients treated with BES experienced a numerically greater number of MIs at 12-month follow-up (5.8% vs. 4.6%, p=0.26), which was largely driven by the 0.9% higher rate of periprocedural MI recorded with BES, they also experienced numerically lower rates of TLR and TVR. The absolute differences between event rates observed with BES and SES were similar at nine and 12 months as can be appreciated in the Kaplan Meier survival curves (Figure 2). The rates of ST as per ARC definitions are listed in Table 3. There was no significant difference in definite, probable or possible, early or late ST between both groups. Table 4 gives a detailed description of each late ST, and indicates that eight of the nine (88.9%) events occurred in patients still taking DAPT. Furthermore, the only ST event to occur after nine months, when the BES polymer is expected to have completely biodegraded, occurred in a patient treated with BES. This patient however was also the only patient who prematurely discontinued DAPT in view of an impending elective operation.

Table 2. Clinical outcomes.

12-month outcomes, n (%)	BES (n=857)	SES (n=850)	Relative risk [95% CI]	P Value
Hierarchical				
Cardiac death	18 (2.1%)	23 (2.7%)	0.77 [0.42-1.44]	0.42
MI without cardiac death	41 (4.8%)	35 (4.1%)		
Q-wave	4 (0.5%)	6 (0.7%)		
Non-Q wave	37 (4.3%)	29 (3.4%)		
Clinically indicated TVR without death or MI	32 (3.7%)	44 (5.2%)		
Surgical	5 (0.6%)	5 (0.6%)		
Percutaneous	27 (3.2%)	39 (4.6%)		
Any MACE	91 (10.6%)	102 (12.0%)	0.88 [0.66-1.17]	0.37
Non-hierarchical				
Death	27 (3.2%)	28 (3.3%)	0.95 [0.56-1.62]	0.86
Cardiac death	18 (2.1%)	23 (2.7%)	0.77 [0.42-1.44]	0.42
MI	50 (5.8%)	39 (4.6%)	1.27 [0.84-1.94]	0.26
Q-wave	4 (0.5%)	7 (0.8%)	0.56 [0.17-1.93]	0.36
Non-Q-wave	46 (5.4%)	33 (3.9%)	1.39 [0.89-2.17]	0.15
Clinically indicated TLR	44 (5.1%)	49 (5.8%)	0.88 [0.59-1.33]	0.55
Percutaneous	42 (4.9%)	46 (5.4%)	0.90 [0.59-1.37]	0.62
Surgical	5 (0.6%)	5 (0.6%)	0.99 [0.29-3.41]	0.98
All TLR	56 (6.5%)	63 (7.4%)	0.87 [0.61-1.25]	0.46
Percutaneous	52 (6.1%)	59 (6.9%)	0.87 [0.60-1.26]	0.46
Surgical	8 (0.9%)	8 (0.9%)	0.99 [0.37-2.63]	0.98
Clinically indicated TVR	50 (5.8%)	60 (7.1%)	0.82 [0.56-1.19]	0.29
Percutaneous	47 (5.5%)	56 (6.6%)	0.82 [0.56-1.21]	0.33
Surgical	6 (0.7%)	7 (0.8%)	0.85 [0.28-2.52]	0.76
All TVR	67 (7.8%)	84 (9.9%)	0.78 [0.56-1.07]	0.13
Percutaneous	60 (7.0%)	75 (8.8%)	0.78 [0.56-1.10]	0.16
Surgical	11 (1.3%)	13 (1.5%)	0.83 [0.37-1.86]	0.66

BES: biolimus eluting stent; SES: sirolimus eluting stent; CI: confidence interval; MI: myocardial infarction; TVR: target vessel revascularisation; MACE: major adverse cardiovascular events; TLR: target lesion revascularisation

Discussion

This randomised prospective study has confirmed the comparable clinical outcomes at one year follow-up, in an 'all-comers' population, of the BES with a biodegradable polymer when compared to the sirolimus eluting stent with a durable polymer.

Early trials of new DES recruited patients with simple, *de novo* lesions, and although important, their results are not applicable to the 60-70% of today's PCI patients who receive DES for 'off-label' indications.[14] Compared to 'on-label' use, the use of DES for 'off-label' indications is associated with poorer outcomes and a higher risk of ST[14,15]. The current study had an 'all-comers' design, such that over half of the patients enrolled had an acute coronary syndrome (unstable angina, Non-ST elevation MI, ST-elevation MI), and over three-quarters of patients had stenting for an 'off-label' indication. Therefore, it comes as no surprise that the overall event rates reported in this study are somewhat higher than those observed in earlier trials of new DESs[16]. Notwithstanding this, these results can be regarded as being more applicable to routine clinical practice.

The formal comparison of outcomes in patients treated for 'on-label' versus 'off-label' indications is not yet available. However *post hoc* sub-group analysis of diabetic patients indicates significantly reduced in-stent restenosis with the use of BES compared to SES at nine months angiographic follow-up (21.79%±19.42 vs. 33.57%±25.42, p=0.01), whilst at 12-month clinical follow-up, insulin treated diabetics treated with BES had a significantly reduced rate of mortality (p<0.01)[17]. Overall no significant difference in clinical outcomes were observed between patients with ACS treated with either stent, however, in patients with STEMI, the use of BES was associated with a significantly lower rate of 12 month cardiac death (p=0.04) and MACE (p=0.02) compared with SES. This was largely driven by reduction in sub-acute ST and TVR within the first 30 days[18]. Other available analyses indicates similar performance between both stents in the management of patients with bifurcation lesions[19], lesions in vessels less than 2.75 mm in diameter[20], and lesions longer than 20 mm[21]. The higher rate of MI noted with BES was largely driven by periprocedural events, as opposed to spontaneous MIs. *Post hoc* analysis has demonstrated over half of these periprocedural events

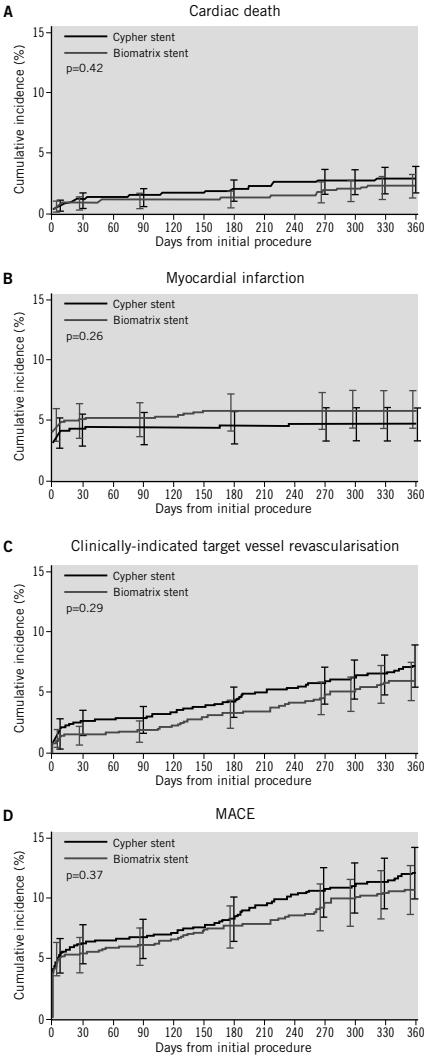


Figure 2. Kaplan Meier event curves at 12 months for (A) cardiac death, (B) myocardial infarction, (C) clinically-indicated target vessel revascularisation and (D) major adverse cardiovascular events.

occurred in patients who had at least one bifurcation lesion, with procedural factors, i.e., more frequent pre-dilatation suggested as a possible cause[19]. Furthermore these periprocedural MIs did not have any effect on cardiac death. At 30 days, 42 patients experienced an MI, and only three patients experienced a cardiac death. Currently the significance of a periprocedural MI has not been clearly established;

Table 3. Stent thrombosis events by ARC definitions.

	BES (n=857)	SES (n=850)	P Value
Definite stent thrombosis			
Early stent thrombosis [0-30 days]	14 (1.6%)	14 (1.6%)	0.98
Late stent thrombosis [30-360 days]	3 (0.4%)	4 (0.5%)	0.69
Total stent thrombosis [0-360 days]	17 (2.0%)	17 (2.0%)*	0.98
Probable stent thrombosis			
Early stent thrombosis [0-30 days]	5 (0.6%)	2 (0.2%)	0.26
Late stent thrombosis [30-360 days]	2 (0.2%)	0 (0.0%)	0.16
Total stent thrombosis [0-360 days]	7 (0.8%)	2 (0.2%)	0.10
Possible stent thrombosis			
Early stent thrombosis [0-30 days]	0 (0.0%)	0 (0.0%)	-
Late stent thrombosis [30-360 days]	7 (0.8%)	9 (1.1%)	0.60
Total stent thrombosis [0-360 days]	7 (0.8%)	9 (1.1%)	0.60
Definite or probable stent thrombosis			
Early stent thrombosis [0-30 days]	18 (2.1%)	16 (1.9%)	0.75
Late stent thrombosis [30-360 days]	5 (0.6%)	4 (0.5%)	0.75
Total stent thrombosis [0-360 days]	23 (2.7%)	19 (2.2%)	0.55

* Excludes one definite secondary stent thrombosis, which occurred in a patient at 60 days, who had already experienced a stent thrombosis at three days; BES: biolimus eluting stent; SES: sirolimus eluting stent; CI: confidence interval

recent studies demonstrate that rises in cardiac enzymes post-PCI are common and may predict short-term prognosis[22], but do not influence long-term prognosis[22], especially if the procedure is successful[23].

ST is one of the most prominent concerns with the widespread use of DES in daily clinically practice[1-4]. The occurrence of ST remains largely unpredictable and no specific causative factor has been identified. One area where concern has been focused is the potential of durable, or permanent polymers to precipitate very late ST. This may be the result of inducing a hypersensitivity reaction[5,6], however recent histopathological studies have also shown that durable polymers can also cause localised vascular inflammation, hyper-eosinophilia, thrombogenic reactions, and apoptosis of smooth muscle cells, all of which may precipitate ST[24-26]. Specifically the non-erodible polymers poly (ethylene co-vinyl acetate) and poly (n-butyl methacrylate) found on the first generation Cypher® SES have been shown to induce hypersensitivity reactions in animal models and humans[27,28]. One recent advance in polymer technology has been the development of PLA biodegradable polymers, as found on the BioMatrix BES stent used in this study. This polymer is located only on the abluminal surface of the stent, which not only allows for better targeted drug release, but also reduces systemic exposure to both the polymer and biolimus. Furthermore, the polymer is co-released with biolimus, and biodegrades to carbon dioxide and water, such that only a stainless steel stent, which is free of any primer polymer, remains after 6-9 months of stent deployment. In theory this should potentially reduce the risk of precipitating late and very late ST.

The similar rates of ST observed in the current study however should not be considered to indicate the lack of benefit of a biodegradable polymer. This is primarily because the current study is underpowered to detect differences in ST. In reality a considerably larger study population, followed long term will be required to enable definitive conclusions to be drawn about whether a biodegradable polymer will impact significantly on rates of late/very late ST.

Table 4. Detailed description of late stent thrombosis events.

Days post index PCI	Stent	Type of stent thrombosis	Presentation	Location	Outcome	DAPT at time of ST
34	BES	Probable	Target vessel related Q-wave MI	LAD#	No intervention performed Stable on discharge	Yes
60	SES	Definite	Unstable angina	LAD	Target lesion CABG (day 99)	Yes*
63	SES	Definite	Unstable angina	SVG	Unable to open occluded SVG Stable on discharge	Yes
89	BES	Definite	Stable angina	Circumflex	Unable to open occluded vessel Stable on discharge	Yes
99	SES	Definite	Target vessel related Q-wave MI	RCA	Clinically driven TLR (day 99)	Yes
107	BES	Definite	Stable angina	1st diagonal	Clinically driven TLR (day 107)	Yes
166	BES	Probable	Target vessel related MI	SVG#	Cardiac death (day 167)	Yes
237	SES	Definite	Non-Q-wave target vessel	RCA	Unable to open occluded vessel Stable on discharge	Yes
350	BES	Definite	Post-operative angina pectoris	LAD	Clinically driven TLR (day 350)	No (stopped 11 days prior for operation)

* Patient experienced an early definite ST as well; # Location suspected, but not confirmed, as no angiography performed; BES: biolimus eluting stent; SES: sirolimus eluting stent; PCI: percutaneous coronary intervention; DAPT: dual anti-platelet therapy; MI: myocardial infarction; TLR: target lesion revascularisation; RCA: right coronary artery; LAD: left anterior descending artery; SVG: saphenous vein graft; CABG: coronary artery bypass grafting

The limited long-term data that is available on metallic stents with biodegradable polymers show promising results, and suggests, as indicated in this study, the absence of significant repeat revascularisations or clinical events following the complete biodegradation of the polymer. The Excel stent (JW Medical Systems, China) is a stainless steel stent, coated with sirolimus and a PLA biodegradable polymer, which completes degradation in 6-9 months. A registry of over 2,000 patients has recently shown at 18-month follow-up, a rate of MACE of 3.1%, and despite 80.5% of patients discontinuing clopidogrel at six months, a rate of ST of 0.87%[29]. The longest follow-up data is available from the Nobori phase I trial which randomised the Nobori™ (Terumo, Japan) BES with a PLA biodegradable polymer to the TAXUS® Express[2] (Boston Scientific, Natick, MA, USA) paclitaxel eluting stent in 120 patients. After biodegradation of the polymer at 6-9 months there were no ST events, TVR or target vessel failures (cardiac death, MI-target vessel related, clinically driven TVR) in those treated with the Nobori stent, however the population enrolled was considerably less complex than the current study[30].

This limited data set indicates the importance of the long term follow-up results of the present study, which should help in establishing whether biodegradable polymers will be vital components of future DES.

Limitations

One limitation with the results of the current study are their reproducibility when considering that the PCI procedures were performed by experienced operators, in high volume centres throughout Europe.

Conclusions

The present report demonstrates the safety and efficacy during 12-month clinical follow-up of a biolimus eluting stent with a biodegradable polymer, and indicates that this stent is a suitable alternative to a sirolimus eluting stent with a durable polymer, in patients with simple and complex coronary artery disease.

References

1. Stettler C, Wandel S, Allemann S, Kastrati A, Morice MC, Schomig A, Pfisterer ME, Stone GW, Leon MB, de Lezo JS, Goy JJ, Park SJ, Sabate M, Suttorp MJ, Kelbaek H, Spaulding C, Menichelli M, Vermeersch P, Dirksen MT, Cervinka P, Petronio AS, Nordmann AJ, Diem P, Meier B, Zwahlen M, Reichenbach S, Trelle S, Windecker S, Juni P. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet.* 2007;370:937-48.

2. Lagerqvist B, James SK, Stenestrand U, Lindback J, Nilsson T, Wallentin L, the SSG. Long-Term Outcomes with Drug-Eluting Stents versus Bare-Metal Stents in Sweden. *N Engl J Med.* 2007;356:1009-1019.

3. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. *Circulation.* 2007;115:1440-55; discussion 1455.

4. Nordmann AJ, Briel M, Bucher HC. Mortality in randomized controlled trials comparing drug-eluting vs. bare metal stents in coronary artery disease: a meta-analysis. *Eur Heart J.* 2006;27:2784-814.

5. van der Giessen WJ, Lincoff AM, Schwartz RS, van Beusekom HM, Serruys PW, Holmes DR, Jr., Ellis SG, Topol EJ. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. *Circulation.* 1996;94:1690-7.

6. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol.* 2006;48:193-202.

7. Grube E, Buellesfeld L. BioMatrix Biolimus A9-eluting coronary stent: a next-generation drug-eluting stent for coronary artery disease. *Expert Rev Med Devices.* 2006;3:731-41.

8. Chevalier B, Serruys PW, Silber S, Garcia E, Suryapranata H, Hauptmann K, Wijns W, Schuler G, Fath-Ordoubadi F, Worthley S. Randomised comparison of Nobori™, biolimus A 9-eluting coronary stent with a Taxus®, paclitaxel-eluting coronary stent in patients with stenosis in native coronary arteries: the Nobori 1 trial. *EuroIntervention.* 2007;2:426-434.

9. Chevalier B, Silber S, Park S-J, Garcia E, Schuler G, Suryapranata H, Koolen J, Hauptmann KE, Wijns W, Morice M-C, Carrie D, van Es G-A, Nagai H, Detiege D, Paunovic D, Serruys PW, for the

NCI. Randomized Comparison of the Nobori Biolimus A9-Eluting Coronary Stent With the Taxus Liberte Paclitaxel-Eluting Coronary Stent in Patients With Stenosis in Native Coronary Arteries: The NOBORI 1 Trial--Phase 2. *Circ Cardiovasc Intervent.* 2009;2:188-195.

10. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Juni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet.* 2008;372:1163-73.

11. Verheye S, Agostoni P, Dubois CL, Dens J, Ormiston J, Worthley S, Trauthen B, Hasegawa T, Koo B-K, Fitzgerald PJ, Mehran R, Lansky AJ. 9-month clinical, angiographic, and intravascular ultrasound results of a prospective evaluation of the Axxess self-expanding biolimus A9-eluting stent in coronary bifurcation lesions: the DIVERGE (Drug-Eluting Stent Intervention for Treating Side Branches Effectively) study. *J Am Coll Cardiol.* 2009;53:1031-9.

12. Grube E. Custom clinical programme. EuroPCR May 19th-22nd 2008; Barcelona. [online] Available www.europcronline.com/fo/lecture/view_slide.php?idCongres=4&id=5514 [Accessed June 18th 2009].

13. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115:2344-51.

14. Kirtane AJ, Gupta A, Iyengar S, Moses JW, Leon MB, Applegate R, Brodie B, Hannan E, Harjai K, Jensen LO, Park SJ, Perry R, Racz M, Saia F, Tu JV, Waksman R, Lansky AJ, Mehran R, Stone GW. Safety and efficacy of drug-eluting and bare metal stents: comprehensive meta-analysis of randomized trials and observational studies. *Circulation.* 2009;119:3198-206.

15. Lasala JM, Cox DA, Dobies D, Baran K, Bachinsky WB, Rogers EW, Breall JA, Lewis DH, Song A, Starzyk RM, Mascioli SR, Dawkins KD, Baim DS, for the AaAPP. Drug-Eluting Stent Thrombosis in Routine Clinical Practice: Two-Year Outcomes and Predictors From the TAXUS ARRIVE Registries. *Circ Cardiovasc Intervent.* 2009;2:285-293.

16. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med.* 2002;346:1773-80.

17. Linke A, Lenk K, Serruys P, van Es GA, Buszman P, Ischinger T, Klauss V, Eberli F, Wijns W, Morice MC, di Mario C, Juni P, Schuler G, Windecker S. Impact of diabetes on angiographic and clinical outcomes of revascularization with biolimus-eluting stent with biodegradable polymer and sirolimus-eluting stent with durable polymer. LEADERS trial substudy. Poster presentation Transcatheter Therapeutics, San Francisco, September 20th 2009.

18. Buszman P. Outcomes with drug-eluting stents in acute coronary syndromes. A substudy from the LEADERS trial. Presentation EuroPCR, Barcelona, 20th May 2009.

19. Garg S. The outcome of bifurcation lesion stenting using a biolimus eluting stent with a biodegradable polymer compared to a sirolimus eluting stent with a durable polymer. Presentation EuroPCR, 20th May 2009. Online www.europcronline.com/fo/lecture/view_slide.php?idCongres=5&id=7856. Accessed July 14th 2009.

20. Wykrzykowska J, Serruys P, Onuma Y, De Vries T, van Es GA, Buszman P, Linke A, Ischinger T, Klauss V, Corti R, Eberli F, Wijns W, Morice MC, Dimario C, van Geuns RJ, Juni P, Windecker S. Impact of vessel size on angiographic and clinical outcomes of revascularization with biolimus-eluting stent with biodegradable polymer and sirolimus-eluting stent with durable polymer. LEADERS trial substudy. *JACC Cardiovasc Interv.* 2009;2:861-870.

21. Wykrzykowska JJ, Raber L, de Vries T, Bressers M, Buszman P, Linke A, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Regar E, Juni P, Windecker S, Serruys PW. Biolimus-eluting biodegradable polymer versus sirolimus-eluting permanent polymer stent performance in long lesions: results from the LEADERS multicentre trial substudy. *EuroIntervention.* 2009;5:310-7.

22. Prasad A, Rihal CS, Lennon RJ, Singh M, Jaffe AS, Holmes Jr DR. Significance of periprocedural myonecrosis on outcomes after percutaneous coronary intervention: an analysis of preintervention and postintervention troponin T levels in 5487 patients. *Circulation: Cardiovascular Interventions.* 2008;1:10.

23. Jeremias A, Baim DS, Ho KK, Chauhan M, Carrozza JP, Jr., Cohen DJ, Popma JJ, Kuntz RE, Cutlip DE. Differential mortality risk of postprocedural creatine kinase-MB elevation following successful versus unsuccessful stent procedures. *J Am Coll Cardiol.* 2004;44:1210-4.

24. Virmani R, Liistro F, Stankovic G, Di Mario C, Montorfano M, Farb A, Kolodgie FD, Colombo A. Mechanism of Late In-Stent Restenosis After Implantation of a Paclitaxel Derivate-Eluting Polymer Stent System in Humans. *Circulation.* 2002;106:2649-2651.

25. Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, Mihalcsik L, Tespili M, Valsecchi O, Kolodgie FD. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation.* 2004;109:701-5.

26. Nebeker JR, Virmani R, Bennett CL, Hoffman JM, Samore MH, Alvarez J, Davidson CJ, McKoy JM, Raisch DW, Whisenant BK, Yarnold PR, Belknap SM, West DP, Gage JE, Morse RE, Gligoric G, Davidson L, Feldman MD. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *J Am Coll Cardiol.* 2006;47:175-81.

27. Cook S, Ladich E, Nakazawa G, Eshtehardi P, Neidhart M, Vogel R, Togni M, Wenaweser P, Billinger M, Seiler C, Gay S, Meier B, Pichler WJ, Juni P, Virmani R, Windecker S. Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. *Circulation.* 2009;120:391-9.

28. Nakazawa G, Ladich E, Finn AV, Virmani R. Pathophysiology of vascular healing and stent mediated arterial injury. *Eurointervention.* 2008;4 Suppl C:C7-10.

29. Han Y, Jing Q, Xu B, Yang L, Liu H, Shang X, Jiang T, Li Z, Zhang H, Li H, Qiu J, Liu Y, Li Y, Chen X, Gao R, for the CI. Safety and Efficacy of Biodegradable Polymer-Coated Sirolimus-Eluting Stents in "Real-World" Practice: 18-Month Clinical and 9-Month Angiographic Outcomes. *J Am Coll Cardiol Intv.* 2009;2:303-309.

30. Chevalier B. Nobori I - Long term results. Two years Phase 1, One year Phase 2. EuroPCR, Barcelona 2008. [Online] Available: www.europcronline.com/fo/lecture/view_slide.php?idCongres=4&id=4540. Accessed August 1st 2009.

Chapter 7.6

The outcome of bifurcation lesion stenting using a biolimus-eluting stent with a biodegradable polymer compared to a sirolimus-eluting stent with a durable polymer

EuroIntervention 2011;6(8):928-35

Scot Garg, Joanna Wykrzykowska, Patrick W. Serruys, Ton de Vries, Pawel Buszman, Stan Trznadel, Axel Linke, Karsten Lenk, Thomas Ischinger, Volker Klauss, Franz Eberli, Roberto Corti, William Wijns, Marie-claude Morice, Carlo di Mario, Pawel Tyczynski, Robert-Jan van Geuns, Pedro Eerdmans, Gerrit-Anne van Es, Bernie Meier, Peter Juni, Stephan Windecker

EuroIntervention

The outcome of bifurcation lesion stenting using a biolimus-eluting stent with a bio-degradable polymer compared to a sirolimus-eluting stent with a durable polymer

Scot Garg[1], MB, ChB, MRCP; Joanna Wykrzykowska[1], MD; Patrick W. Serruys[1]*, MD, PhD; Ton de Vries[2], MSc; Pawel Buszman[3], MD, PhD; Stanislaw Trznadel[3], MD; Axel Linke[4], MD, PhD; Karsten Lenk[4], MD; Thomas Ischinger[5], MD, PhD; Volker Klauss[6], MD, PhD; Franz Eberli[7], MD; Roberto Corti[8], MD; William Wijns[9], MD, PhD; Marie-Claude Morice[10], MD; Carlo di Mario[11], MD, PhD; Pawel Tyczynski[11], MD; Robert Jan van Geuns[1], MD, PhD; Pedro Eerdmans[12], MD, PhD; Gerrit-Anne van Es[2], PhD; Bernhard Meier[13], MD; Peter Jüni[14,15], MD; Stephan Windecker[13,14], MD

1. Department of Interventional Cardiology, Erasmus MC, Rotterdam, The Netherlands; 2. Cardialysis B.V, Rotterdam, The Netherlands; 3. Medical University of Silesia, Katowice, Poland; 4. Herzzentrum Leipzig, Leipzig, Germany; 5. Department of Cardiology, Hospital Bogenhausen, Munich, Germany; 6. Department of Cardiology, University Hospital Munich (Innenstadt), Munich, Germany; 7. Currently working at department of Cardiology, Triemli Spital, Zurich, Switzerland; 8. Department of Cardiology, University Hospital Zurich, Zurich, Switzerland; 9. Department of Cardiology, Onze Lieve Vrouw Ziekenhuis, Aalst, Belgium; 10. Institut Jacques Cartier Massy, France; 11. Department of Cardiology, Royal Brompton Hospital, London, United Kingdom; 12. Biosensors Europe SA, Morges, Switzerland; 13. Department of Cardiology, Bern University Hospital, Bern, Switzerland; 14. CTU Bern, Bern University Hospital, Bern, Switzerland; 15. Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

Windecker is a consultant for and receives fees from ABBOTT Vascular, Boston Scientific, Cordis, Medtronic and Biosensors. Eberli is a speaker for Biosensors, and consultant for Cordis. Eerdmans is an employee of Biosensors Europe. The remaining authors declare they have no conflict of interest to declare. Funding source: The LEADERS trial was funded by Biosensors, Europe SA, Switzerland.

KEYWORDS

Biolimus-eluting stent, sirolimus-eluting stent, bifurcation lesions, biodegradable polymer

Abstract

Aims: This study investigated the differences in clinical outcomes between patients with bifurcation lesions (BL) treated with a biolimus-eluting stent (BES) with a biodegradable polymer, and a sirolimus-eluting stent (SES) with a durable polymer.

Methods and results: The clinical outcomes were assessed in the 497 patients (BES 258, SES 239) enrolled in the multicentre, randomised LEADERS trial who underwent treatment of ≥1 BL (total=534 BL). At 12-months follow-up there was no significant difference in the primary endpoint of MACE, a composite of cardiac death, myocardial infarction and clinically indicated target vessel revascularisation (BES 12.8% vs. SES 16.3%, p=0.31). Patients treated with BES had comparable rates of cardiac death (BES 2.7% vs. SES 2.9%, p=1.00), numerically higher rates of myocardial infarction (BES 8.9% vs. SES 5.4%, p=0.17), and significantly lower rates of clinically indicated target vessel revascularisation (4.3% vs. 11.3%, p=0.004) when compared to those treated with SES. The rate of stent thrombosis at 12-months was 4.3% and 3.8% for BES and SES, respectively (p=0.82).

Conclusions: In the treatment of BL the use of BES lead to superior efficacy and comparable safety compared to SES.

** Corresponding author: Ba583a, Thoraxcentre, Erasmus MC,'s-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands*
E-mail: p.w.j.c.serruys@erasmusmc.nl

Abbreviations

ACS	Acute coronary syndrome
BES	Biolimus-eluting stent
BL	Bifurcation lesion
CABG	Coronary artery bypass graft surgery
DES	Drug-eluting stent
MACE	Major adverse cardiovascular events
MB	Main branch
MI	Myocardial infarction
MLD	Minimum luminal diameter
NSTEMI	Non-ST-elevation myocardial infarction
PCI	Percutaneous coronary intervention
RVD	Reference vessel diameter
SB	Side branch
SES	Sirolimus-eluting stent
ST	Stent thrombosis
TIMI	Thrombolysis in Myocardial Infarction
TLR	Target lesion revascularisation
TVR	Target vessel revascularisation

Introduction

Bifurcation lesions (BL) account for up to one third of coronary lesions and are associated with lower procedural success, and poorer clinical outcomes.[1] The previously high rates of target lesion revascularisation (TLR) and major adverse cardiovascular events (MACE) observed after the treatment of BL with the use of bare metal stents[1,2] have improved significantly following the introduction of drug eluting stents (DES),[3,4] however safety concerns with respect to stent thrombosis (ST) have emerged.[5] One of the potential causes of ST is delayed re-endothelialisation which may occur as a consequence of a hypersensitivity reaction induced by the presence of a permanent polymer.[6,7] The concerns of ST have been greater with first generation DES with durable polymers, and recent studies have demonstrated numerically lower rates of ST with newer generation DES that have polymers which are more biocompatible,[8,9] or completely biodegradable.[10]

The Biomatrix™ Flex biolimus eluting stent (BES) (Biosensors, Morges, Switzerland) elutes biolimus from a polylactic acid (PLA) biodegradable polymer applied to the stent's abluminal surface. The polymer is fully metabolised to water and carbon dioxide within 6-9 months, and therefore has the potential to cause less long-term inflammatory sequelae. In the randomised LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial, BES was found to be non-inferior to the Cypher® sirolimus eluting stent (SES) (Cordis, NJ, USA) in terms of MACE at nine months follow-up (9% vs. 11%, p for non-inferiority=0.003, p for superiority= 0.39).[11]

The objective of the present study was to investigate whether there were any differences in clinical outcomes between patients with BL treated with a DES with a biodegradable polymer (BES) compared to a DES with a durable polymer (SES).

Method

Study population

The methods of the LEADERS trial have been published previously.[11] The study applied an all-comers approach recruiting 1,707 patients with chronic stable coronary artery disease or acute coronary syndromes (ACS) including ST-elevation myocardial infarction (STEMI), who were eligible for enrolment if they had at ≥1 lesion with diameter stenosis (DS) ≥50% and a reference vessel diameter (RVD) 2.25-3.5 mm. The principle exclusion criteria are described elsewhere.[11] The study complied with the Declaration of Helsinki and was approved by all institutional ethics committees. All patients provided written, informed consent for participation in the trial.

In this analysis, patients with ≥1 BL were identified using the electronic clinical record form (eCRF), and results from the core laboratory angiographic analysis which identified and classified all BL according to the SYNTAX bifurcation score.[12] The angiograms of 497 patients (258 BES, 239 SES) who had a total of 534 BL (282 BES, 252 SES) identified using either source were reviewed by two investigators (SG and JW), who were blinded to outcomes and stent type. During review of the digital angiogram films, the presence of a BL was confirmed if a lesion of ≥50% DS on visual estimation was present in a main branch (MB) and/or a contiguous side branch (SB) of ≥1.5 mm in diameter. Other information pertinent to the BL recorded during angiographic review was the number of guidewires used; stenting technique; use and site (MB, SB or both) of pre- and post-stenting dilatation; pre- and post-stenting TIMI flow and total number of stents used. Clinical outcomes were compared according to stent type, whilst procedural technique was compared between stents after dividing BL into "true" or "partial" BL. Those BL with a Medina classification[13] of 1,1,1; 1,0,1; 0,1,1 (i.e., those with lesions involving both the MB and SB) were defined as "true" BL, whilst those with a Medina classification of 1,0,0; 0,1,0; 1,1,0; 0,0,1 (i.e., those where either the MB or SB was involved) were defined as "partial" BL.

Randomisation and procedures

Patients were randomly allocated on a 1:1 basis to treatment with either a BES or SES, and to active angiographic follow-up at nine months or clinical follow-up only on a 1:3 basis with a factorial design. Percutaneous coronary intervention (PCI) was performed according to standard technique, and direct stenting was allowed. The choice of bifurcation stenting strategy and use of post stenting dilatation was left to the operator's discretion. No mixture of DES was permitted within a given patient, unless the operator was unable to insert the study stent, in which case crossover to another device of the operator's choice was possible. Procedural anticoagulation was achieved with unfractionated heparin 5000 IU or 70-100 IU/kg, whilst the use of glycoprotein IIb/IIIa inhibitors was left to the operator's discretion. Pre-procedure all patients enrolled into the study received ≥75 mg of acetylsalicylic acid, and ≥300 mg of clopidogrel. All patients were discharged on ≥75 mg of acetylsalicylic acid indefinitely, and clopidogrel 75 mg for ≥12 months following the index procedure.

Follow-up

Adverse events were assessed in-hospital, and clinical follow-up was performed at 1, 6, 9, and 12 months. One in four patients was asked to return for angiographic follow-up at nine months.

Study endpoints

The primary endpoint of this sub-study was MACE, defined as the composite of cardiac death, myocardial infarction (MI), and clinically-indicated target vessel revascularisation (TVR) within 12-months. Secondary endpoints were death from any cause, cardiac death, MI, any TLR (both clinically and non-clinically indicated); any TVR, and ST.

A blinded independent clinical events committee adjudicated all endpoints, and independent study monitors verified all case reports from data on-site. The operators were by necessity aware of the assigned study stent during PCI and angiographic follow-up, but patients and staff involved in follow-up assessment were blinded to the allocated stent type. Angiography films were centrally assessed at one angiographic core laboratory (Cardialysis, Rotterdam, The Netherlands) with assessors unaware of the allocated stent.

Definitions

Definitions of all endpoints are provided in full elsewhere.[11] MI was defined using the electrocardiographic criteria of the Minnesota code, or by a measured level of creatinine kinase (CK) two times the upper limit of normal (ULN), with either a positive concentration of CK-myoglobin fraction, or troponin I or T. Periprocedural MI was defined as any MI ≤48 hours of the index procedure. Revascularisation was regarded as clinically indicated if on quantitative coronary angiography (QCA) the lumen DS of the treated lesion was ≥50% in the presence of ischaemic signs or symptoms, or ≥70% in the absence of ischaemia. TVR was defined as any repeat PCI or surgical bypass of any segment within the entire major coronary vessel proximal and distal to a target lesion, including upstream and downstream branches and the target lesion itself. TLR was defined as a repeat revascularisation due to a stenosis within the stent or within a 5 mm border proximal or distal to the stent. ST was defined according to the Academic Research Consortium definitions.[14]

Statistical analysis

Continuous variables are expressed as mean±standard deviation; categorical data is presented as frequency (percentages). Patient demographic data was compared using the Student *t*-test, whilst χ^2 was used for categorical data. Angiographic outcomes were analysed using SAS v8 Proc Mixed for continuous, and Proc Genmod for binominal outcomes, taking into account the within-patient correlation structure of these data. Survival curves were constructed for time-to-event variables using Kaplan-Meier estimates, and compared by the log-rank test. The piecewise Cox proportional hazards model was used to compare clinical outcomes between the groups. All analyses were performed using SAS 8.02 by a dedicated statistician. All p-values and confidence intervals were two-sided; p<0.05 was considered statistically significant.

Results

Baseline characteristics (Tables 1 and 2)

A total of 1,707 patients were enrolled in the LEADERS study of which 29.1% (497 patients, 534 BL) had ≥1 treated BL (Figure 1). The baseline clinical and lesion characteristics were well matched between those patients with BL treated with BES (258 patients) and SES (239 patients) as indicated in Tables 1 and 2.

Procedural technique (Table 3)

The procedural technique employed to treat the 534 BL is summarised in Table 3. There were no significant differences in technique when comparing BES to SES for patients with a true or a partial BL. Differences in technique did exist however when comparing true BL to partial BL; those patients with a true bifurcation were significantly more likely to be treated with a two-stent strategy (27.5% vs. 12.3%, p<0.0001) and receive post-stenting dilatation (52.4% vs. 36.5%, p=0.0003).

Clinical endpoints (Table 4)

The hierarchical and non-hierarchical clinical outcomes at 1-year follow-up are shown in Table 4, and the Kaplan Meier survival curves are shown in Figure 2. There was no significant difference in

Table 1. Patient demographics and clinical presentation amongst patients with ≥1 treated bifurcation lesion.

Variables, n(%) unless stated	BES N=258	SES N=239	*p* value¶
Patient demographics			
Age, years	65.1±10.3	64.2±10.9	0.36
Male	183(70.9)	178(74.5)	0.38
Body mass index, kg/m²	27.2±4.0	27.3±4.2	0.63
Diabetes mellitus	64(24.8)	44(18.4)	0.08
Hypertension	187(72.5)	175(73.2)	0.85
Hypercholesterolaemia	170(65.9)	168(70.3)	0.29
Current smoker	45(17.4)	57(23.8)	0.08
Family history of CAD	98(38.0)	102(42.7)	0.29
Previous MI	92(35.7)	93(38.9)	0.45
Previous PCI	98(38.0)	93(38.9)	0.83
Previous CABG	19(7.4)	28(11.7)	0.10
Previous stroke	17(6.6)	8(3.3)	0.10
Peripheral vascular disease	17(6.6)	17(7.1)	0.82
Multivessel disease	98(38.0)	81(33.9)	0.34
LVEF (%)	55.7±11.2	53.8±12.9	0.20
Clinical presentation			
ACS	135(52.3)	133(55.6)	0.46
STEMI	29(11.2)	32(13.4)	0.47
NSTEMI	36(14.0)	49(20.5)	0.053
Unstable angina	70(27.1)	52(21.8)	0.16
Stable angina	85(32.9)	89(37.2)	0.32
Silent ischaemia	38(14.7)	17(7.1)	0.007

¶All p-values: Chi-square test; ACS: acute coronary syndrome; BES: biolimus-eluting stent; CABG: coronary artery bypass graft surgery; CAD: coronary artery disease; MI: myocardial infarctionv NSTEMI: non-ST elevation MI; PCI: percutaneous coronary intervention; SES: sirolimus-eluting stents

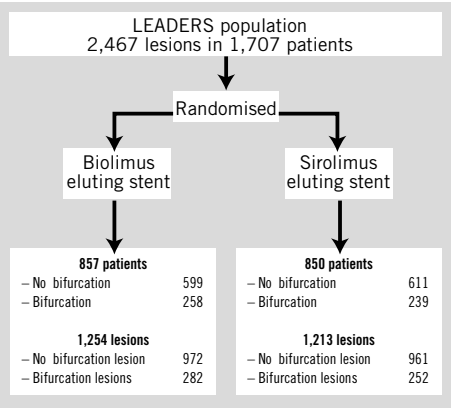


Figure 1. Flow chart indicating the number and type of bifurcation lesions, categorised according to make of stent.

the primary endpoint of MACE between BES and SES at 12-month follow-up (BES 12.8% vs. SES 16.3%, p=0.31). The rate of death was comparable between stents, whilst the rate of clinically-indicated TVR was significantly lower in those treated with BES (11.3% vs. 4.3%, p=0.004). MI occurred more frequently in those treated with BES (8.5% vs. 4.6%, p=0.10), and this was driven by the significantly higher incidence of periprocedural MI (MI 0-2 days: HR 2.53, 95% CI 1.1-6.0, p=0.03; MI 3-360 days: HR 0.64, 95% CI: 0.18-2.27, p=0.49, Figure 2B).

Table 2. Baseline lesions and procedural characteristics.

Variables, n(%) unless stated	BES (n=282 lesions)	SES (n=252 lesions)	P value
Angiographic characteristics			
Vessels with a lesion >50%	1.25±0.55	1.19±0.61	0.22
Lesions >50%	1.43±0.70	1.40±0.79	0.64
Vessel territory (per lesion)			
LAD	222/452(49.1)	208/417(49.9)	0.82
RCA	74/452(16.4)	75/417(18.0)	0.68
LCx	138/452(30.5)	123/417(29.5)	0.78
Left main stem	18/452(4.0)	8/417(1.9)	0.08
CABG	0/452(0.0)	3/417(0.7)	n.d.*
SYNTAX score¶	16.8±8.4 (n=198)	16.7±8.9 (n=182)	0.93
Postprocedure			
Number of stents	2.4±1.5	2.2±1.3	0.33
Number of stented lesions	1.75±0.80	1.74±0.77	0.92
Mean stent diameter, mm	2.88±0.33	2.89±0.32	0.89
Mean stent length, mm	17.6±14.7	17.8±4.9	0.72
Total stent length, mm	40.9±25.8	39.8±26.1	0.64
Use of glycoprotein 2b/3a	65(25.2)	46(19.2)	0.11
Hospital stay, days	3.2±3.1	3.2±3.1	0.88

*At least one observation required in both groups; ¶only calculated if both left and right angiograms were available; patients with previous CABG excluded; CABG, SES and BES as before; LVEF: left ventricular ejection fraction; LAD: left anterior descending artery; RCA: right coronary artery; LCx: left circumflex artery

Table 3. Summary of stenting technique.

Variables, n(%)	True bifurcations BES (n=131)	True bifurcations SES (n=102)	Partial bifurcation BES (n=151)	Partial bifurcation SES (n=150)	P value True vs. Partial
Number of wires					0.76
One	32(24.4)	27(26.5)	30(19.8)	42(28.0)	
Two	99(75.6)	75(73.5)	121(80.2)	108(72.0)	
Stenting technique					p<0.0001
One stent	94(71.8)	75(73.5)	129(85.4)	135(90.0)	
1 wire	32(24.4)	27(26.5)	30(19.9)	42(28.0)	
2 wires (Provisional T-stent)	55(42.0)	41(40.2)	57(37.7)	59(39.3)	
2 wires (2nd wire post MB stenting)	7(5.3)	7(6.9)	42(27.8)	34(22.7)	
Two stents	37(28.2)	27(26.5)	22(14.6)	15(10.0)	
Cross-over from 1-stent technique	7(5.3)	8(7.8)	6(4.0)	3(2.0)	
Classic T	7(5.3)	8(7.8)	9(6.0)	7(4.7)	
Crush	16(12.2)	7(6.9)	3(2.0)	4(2.7)	
Culotte	7(5.3)	0(0.0)	1(0.7)	0(0.0)	
Modified T	0(0.0)	1(1.0)	2(1.3)	0(0.0)	
V stenting	0(0.0)	3(2.9)	1(0.7)	1(0.7)	
Post dilatation	73(55.7)	49(48.0)	58(38.4)	52(34.7)	p=0.003
MB only	5(3.8)	3(2.9)	8(5.3)	14(9.3)	
MB-SB ostium	16(12.2)	14(13.7)	19(12.6)	16(10.7)	
Kissing balloon	52(39.7)	32(31.4)	31(20.5)	22(14.7)	

BES: biolimus-eluting stent; SES: sirolimus-eluting stent; MB: main branch; SB: side branch; No significant difference in technique between BES and SES for true or partial bifurcation

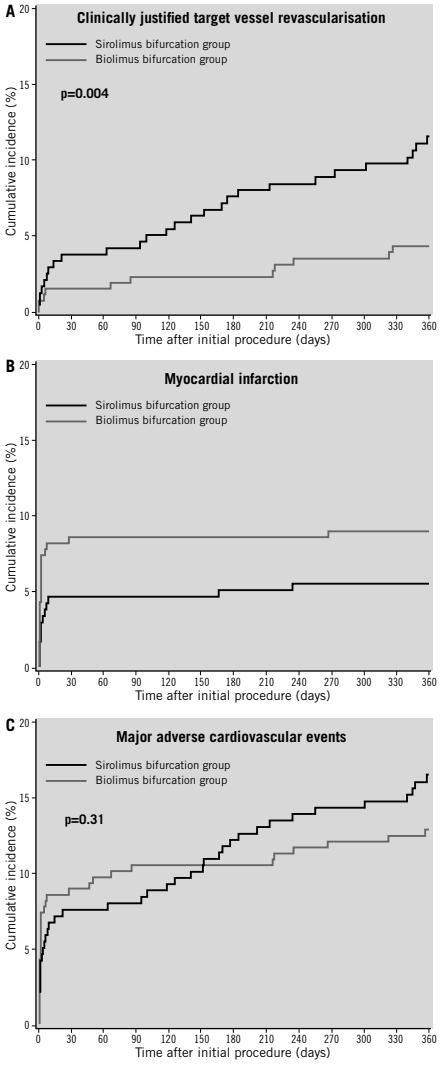


Figure 2. Kaplan Meier survival curves for (A) clinically indicated target vessel revascularisation, (B) myocardial infarction, and (C) MACE.

The primary endpoint at 12-months was not influenced by the type of BL treated (true or partial), or the stenting technique used (one or two-stent strategy); however compared to SES, the use of BES was associated with significantly lower rates of percutaneous revascularisation (TLR and TVR) amongst those patients with a true BL, and those treated with one-stent (p<0.05 for all).

Table 4. Clinical outcomes at 1-year follow-up.

Outcome n(%)	BES (n=258)	SES (n=239)	P Value
Hierarchical outcomes (1-year)			
Cardiac death	7(2.7)	7(2.9)	1.00
MI	21(8.1)	12(5.0)	
Q-wave	3(1.2)	2(0.8)	
Non-Q wave	18(7.0)	10(4.2)	
Clinically justified TVR	5(1.9)	20(8.4)	
Percutaneous	4(1.6)	18(7.5)	
Surgical	1(0.4)	2(0.8)	
Any MACE	33(12.8)	39(16.3)	0.31
Non-hierarchical outcomes (1-year)			
Death	9(3.5)	7(2.9)	0.80
Cardiac death	7(2.7)	7(2.9)	1.00
MI	23(8.9)	13(5.4)	0.17
All TLR	12(4.7)	29(12.1)	0.003
Percutaneous	12(4.7)	28(11.7)	0.005
Surgical	1(0.4)	4(1.7)	0.20
Clinically justified TLR	9(3.5)	23(9.6)	0.006
Percutaneous	9(3.5)	22(9.2)	0.009
Surgical	1(0.4)	2(0.8)	0.61
All TVR	16(6.2)	34(14.2)	0.004
Percutaneous	14(5.4)	32(13.4)	0.003
Surgical	3(1.2)	5(2.1)	0.49
Clinically justified TVR	11(4.3)	27(11.3)	0.004
Percutaneous	11(4.3)	26(10.9)	0.006
Surgical	1(0.4)	3(1.3)	0.36

TLR: target lesion revascularisation; TVR: target vessel revascularisation; MACE: major adverse cardiovascular events; MI, BES, SES as previously described

Stent thrombosis (Table 5)

The overall rates of early and late ST were similar between all patients treated with BES or SES, which was irrespective of the type of BL treated (True BL: BES 5.6% vs. SES 4.0%, p=0.76; Partial BL: BES 3.0% vs. SES 3.6%, p=1.00); or the number of stents used (one stent strategy: BES 4.9% vs. SES 3.6%, p=0.62; two stent strategy: BES 1.9% vs. SES 4.8%, p=0.48).

Table 5. Stent thrombosis events at 30-days and 1-year.

	BES (n=258)	SES (n=239)	*p* value
30-days			
Stent thrombosis	7(2.7)	7(2.9)	1.00
Definite	5(1.9)	6(2.5)	0.76
Possible	0(0.0)	0(0.0)	n.d.*
Probable	2(0.8)	1(0.4)	1.00
1-year			
Stent thrombosis	11(4.3)	9(3.8)	0.82
Definite	5(1.9)	6(2.5)	0.77
Possible	4(1.6)	2(0.8)	0.69
Probable	2(0.8)	1(0.4)	1.00

BES, SES as previously described; n.d*; not done (≥1 observation required in both groups)

Discussion

This is the first analysis comparing the management of patients with BL using a DES with a biodegradable polymer to a DES with a durable polymer, and demonstrates similar overall clinical outcomes between both patient groups, irrespective of the type of BL treated or the stenting strategy used.

Clinical outcomes

The use of DES have improved outcomes in patients with complex coronary artery disease, with significant reductions in restenosis, however "off-label" use of DES, such as in BL, is still associated with higher rates of restenosis and ST compared to "on-label" use.[15,16] Encouraging evidence from this study suggests newer DES, such as BES, may have the potential to improve some of these adverse clinical outcomes. In this study the significantly lower rate of repeat revascularisation in those patients treated with BES was achieved despite any significant differences between stent groups in baseline clinical, angiographic and lesion characteristics, or in procedural technique. This suggests other factors such as differences in stent design, strut thickness, cell size and the drug polymer may have had an influential role on restenosis, as indicated by previous studies comparing different DES in patients with BL treated with the same stenting technique. For example Pan et al reported a significantly lower rate of TLR with Cypher (Cordis, Johnson & Johnson, Warren, NJ, USA) compared to the TAXUS (Boston Scientific, Natick, MA, USA) stent (4% vs. 13%, $p<0.05$) in 205 patients undergoing provisional T stenting,[17] whilst more recently, in patients undergoing culotte stenting, Adriaenssens et al reported restenosis rates of 18%, 29% and 35% with Cypher, Endeavor (Medtronic, Minneapolis, MN, USA) and TAXUS stents, respectively ($p=0.12$).[18] These repeated observations warrant formal assessment in dedicated randomised trials.

In contrast to this reduction in repeat revascularisation, those patients treated with BES had a numerically higher incidence of MI, which was irrespective of the type of BL treated or the stenting strategy employed. Additional analysis indicates that these events were driven by a significantly higher rate of periprocedural MI with BES, which in the vast majority was triggered by the detection of a rise in cardiac enzymes.

Although these periprocedural MIs are a concern, their overall significance is questionable when considering that the rate of death amongst patients who sustained an MI was 0.0% at 30-days. However, setting this, and the on-going discussion regarding the significance of periprocedural MIs aside for a moment,[19] there is no disputing that these events did occur, and with a greater frequency in those patients treated with BES. Enzyme rises may be secondary to procedural factors[20] however in this study amongst those patients experiencing a periprocedural MI there were no significant differences between stent groups in TIMI flow (MB or SB) either pre- or post-PCI, or plaque shift. Notably however lesion pre-dilatation was significantly higher in the group of patients with periprocedural MIs who were treated with BES (88% vs. 43%, $p=0.03$).

The physical properties of the stent may also influence enzyme release. For example a smaller cell size can increase the chances of side branch occlusion; however bench studies indicate that the maximum cell circumference of a 3 mm BES is 10.8 mm compared to 9.5 mm in a similarly sized SES. Another physical stent property which merits discussion is the integrity of the polymer coating. Basalus et al recently evaluated the biodegradable coating on BES *in vitro* using electron microscopy, and observed cracks in the polymer after high pressure balloon inflation, which could potentially lead to the formation of free polymer fragments, capable of embolising and causing subsequent enzyme release.[21] These observations however must be interpreted with caution because these assessments were performed *in vitro* which may have affected the polymer's stability, and without the use of vascular phantoms which may have stabilised the polymer. In addition, the significant reductions in TLR and TVR with BES are unlikely to have been observed in the presence of polymer fragmentation which ultimately would have reduced the dose of biolimus that could be eluted.

Stent thrombosis

A DES with a biodegradable polymer offers the potential to reduce the risk of late/very-late ST, which is pertinent in patients with BL, as these lesions represent an independent risk factor for ST, and have higher rates of ST when compared with non-BL treated with the same DES (p=not significant).[5,22] The cause of this increased risk of ST is likely to be multi-factorial, but stent malapposition, and incomplete stent expansion, particularly in angulated bifurcation lesions, are likely to be two major contributing factors.[23] Reassuringly recent studies have dispelled the initial concerns that rates of ST are higher with the use of complex as opposed to simple stenting strategies, or between different complex strategies.[24-28] Following on from this, the rates of ST in this study were similar irrespective of stent type (BES vs. SES), type of BL (partial vs. true) or stenting strategy used (one vs. two). Encouragingly provisional results from 2-year follow-up of all patients enrolled in the LEADERS trial does suggest a reduction in very late ST events in patients treated with a stent with a biodegradable polymer;[29] however the current study is not powered in isolation to draw any definitive conclusions regarding ST.

Stenting technique for bifurcation lesions

Despite the frequent occurrence of BL, the optimal procedural strategy remains to be established. In the current study a single-stent strategy was preferred for BL, being used to treat over 80% of cases, with a respectable cross over rate from a one to a two stent strategy of 5.3%, and comparable MACE rates of 14.0% and 16.7% for one and two stent strategies, respectively. Historically a two stent strategy was considered the ideal method of dealing with a BL as this produced the best angiographic result, however data from multiple randomised studies[3,24,30-33] and three recent meta-analyses indicate that a provisional stenting strategy is as efficacious as a two stent strategy.[25,26,34] The current study supports this data, and demonstrates that these results are achievable in an unselected population where ≥50% of patients were treated for ACS.

Limitations

This sub-group analysis is limited by its *post-hoc* nature. The initial study was not a dedicated bifurcation study, and therefore angiographic analysis of BL was only available using conventional QCA. It is widely recognised that this is limited in its ability to accurately assess a BL, and as a consequence no QCA data is presented here.[35] In view of the results obtained a more detailed assessment of BL is warranted using dedicated bifurcation software; however the number of patients with BL returning for follow-up angiography is also a potential limiting factor of the analysis.

Conclusion

In the treatment of BLs, the use of BES lead to superior efficacy and comparable safety compared to SES.

References

1. Al Suwaidi J, Yeh W, Cohen HA, Detre KM, Williams DO, Holmes DR, Jr. Immediate and one-year outcome in patients with coronary bifurcation lesions in the modern era (NHLBI dynamic registry). *Am J Cardiol.* 2001;87:1139-1144.

2. Yamashita T, Nishida T, Adamian MG, Briguori C, Vaghetti M, Corvaja N, Albiero R, Finci L, Di Mario C, Tobis JM, Colombo A. Bifurcation lesions: two stents versus one stent—immediate and follow-up results. *J Am Coll Cardiol.* 2000;35:1145-1151.

3. Colombo A, Moses JW, Morice MC, Ludwig J, Holmes DR, Jr., Spanos V, Louvard Y, Desmedt B, Di Mario C, Leon MB. Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. *Circulation.* 2004;109:1244-1249.

4. Tanabe K, Hoye A, Lemos PA, Aoki J, Arampatzis CA, Saia F, Lee CH, Degertekin M, Hofma SH, Sianos G, McFadden E, Smits PC, van der Giessen WJ, de Feyter P, van Domburg RT, Serruys PW. Restenosis rates following bifurcation stenting with sirolimus-eluting stents for de novo narrowings. *Am J Cardiol.* 2004;94:115-118.

5. van Werkum JW, Heestermans AA, Zomer AC, Kelder JC, Suttorp MJ, Rensing BJ, Koolen JJ, Brueren BR, Dambrink JH, Hautvast RW, Verheugt FW, ten Berg JM. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. *J Am Coll Cardiol.* 2009;53:1399-1409.

6. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol.* 2006;48:193-202.

7. van der Giessen WJ, Lincoff AM, Schwartz RS, van Beusekom HM, Serruys PW, Holmes DR, Jr., Ellis SG, Topol EJ. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. *Circulation.* 1996;94:1690-1697.

8. Garg S, Serruys PW, Onuma Y, Dorange C, Veldhof S, Miquel-Hebert K, Sudhir K, Boland J, Huber KC, Garcia E, Riele te JAM. Three year clinical follow up of the XIENCE V Everolimus eluting coronary stent system in the treatment of patients with de novo coronary artery lesions. The SPIRIT II Trial. J *Am Coll Cardiol Intv.* 2009;2:1190-1198.

9. Hamm C. 5 years later and more than 20,000 patients studied: the ENDEAVOR clinical programme. EuroPCR 19th-22nd May 2009; Barcelona [online] Available: www.europcronline.com/fo/lecture/view_slide.php?idCongres= 5&id=7617 [Accessed 20th June 2009].

10. Chevalier B, Silber S, Park S-J, Garcia E, Schuler G, Suryapranata H, Koolen J, Hauptmann KE, Wijns W, Morice M-C, Carrie D, van Es G-A, Nagai H, Detiege D, Paunovic D, Serruys PW, for the NCI. Randomized Comparison of the Nobori Biolimus A9-Eluting Coronary Stent With the Taxus Liberte Paclitaxel-Eluting Coronary Stent in Patients With Stenosis in Native Coronary Arteries: The NOBORI 1 Trial–Phase 2. *Circ Cardiovasc Intervent.* 2009;2:188-195.

11. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Juni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet.* 2008;372:1163-1173.

12. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Van Dyck N, Russell ME, Serruys P. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention.* 2005;1:219-227.

13. Medina A, Suarez de Lezo J, Pan M. [A new classification of coronary bifurcation lesions]. *Rev Esp Cardiol.* 2006;59:183.

14. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115:2344-2351.

15. Kirtane AJ, Gupta A, Iyengar S, Moses JW, Leon MB, Applegate R, Brodie B, Hannan E, Harjai K, Jensen LO, Park SJ, Perry R, Racz M, Saia F, Tu JV, Waksman R, Lansky AJ, Mehran R, Stone GW. Safety and efficacy of drug-eluting and bare metal stents: comprehensive meta-analysis of randomized trials and observational studies. *Circulation.* 2009;119:3198-3206.

16. Lasala JM, Cox DA, Lewis SJ, Tadros PN, Haas RC, Schweiger MJ, Chhabra A, Untereker WJ, Starzyk RM, Mascioli SR, Dawkins KD, Baim DS. Expanded use of the TAXUS Express Stent: two-year safety insights from the 7,500 patient ARRIVE Registry programme. *EuroIntervention.* 2009;5:67-77.

17. Pan M, Suarez de Lezo J, Medina A, Romero M, Delgado A, Segura J, Ojeda S, Mazuelos F, Hernandez E, Melian F, Pavlovic D, Esteban F, Herrador J. Drug-eluting stents for the treatment of bifurcation lesions: a randomized comparison between paclitaxel and sirolimus stents. *Am Heart J.* 2007;153:15 e11-17.

18. Adriaenssens T, Byrne RA, Dibra A, Iijima R, Mehilli J, Bruskina O, Schomig A, Kastrati A. Culotte stenting technique in coronary bifurcation disease: angiographic follow-up using dedicated quantitative coronary angiographic analysis and 12-month clinical outcomes. *Eur Heart J.* 2008;29:2868-2876.

19. Vranckx P, Cutlip D, Mehran R, Kint P-P, Silber S, Windecker S, Serruys PW. Myocardial Infarction adjudication in Contemporary All-Comer Stent trials: Balancing sensitivity and specificity. *EuroIntervention.* 2010;5:871-4.

20. Nageh T, Sherwood RA, Harris BM, Byrne JA, Thomas MR. Cardiac troponin T and I and creatine kinase-MB as markers of myocardial injury and predictors of outcome following percutaneous coronary intervention. *Int J Cardiol.* 2003;92:285-293.

21. Basalus MW, van Houwelingen KG, Ankone M, de Man FH, von Birgelen C. Scanning electron microscopic assessment of the biodegradable coating on expanded biolimus-eluting stents. *EuroIntervention.* 2009;5:505-510.

22. Tsuchida K, Colombo A, Lefevre T, Oldroyd KG, Guetta V, Guagliumi G, von Scheidt W, Ruzyllo W, Hamm CW, Bressers M, Stoll HP, Wittebols K, Donohoe DJ, Serruys PW. The clinical outcome of percutaneous treatment of bifurcation lesions in multivessel coronary artery disease with the sirolimus-eluting stent: insights from the Arterial Revascularization Therapies Study part II (ARTS II). *Eur Heart J.* 2007;28:433-442.

23. Garg S, Serruys P. A Review of the Benefits of and Safety Concerns Associated with Drug Eluting Coronary Stents. *Expert Rev Cardiovasc Ther*. 2010;8:449-70.

24. Colombo A, Bramucci E, Sacca S, Violini R, Lettieri C, Zanini R, Sheiban I, Paloscia L, Grube E, Schofer J, Bolognese L, Orlandi M, Niccoli G, Latib A, Airoldi F. Randomized Study of the Crush Technique Versus Provisional Side-Branch Stenting in True Coronary Bifurcations: The CACTUS (Coronary Bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents) Study. *Circulation*. 2009;119:71-78.

25. Brar S, Gray W, Dangas G, Leon M, Aharonian V, Brar S, Moses J. Bifurcation Stenting with Drug-Eluting Stents: A Meta-Analysis *EuroIntervention*. 2009;5:475-484.

26. Zhang F, Dong L, Ge J. Simple versus Complex Stenting Strategy for Coronary Artery Bifurcation Lesions in the Drug-Eluting Stent Era: a Meta-Analysis of Randomized Trials. *Heart*. 2009;95:1676-81.

27. Erglis A, Kumsars I, Niemela M, Kervinen K, Maeng M, Lassen JF, Gunnes P, Stavnes S, Jensen JS, Galloe A, Narbute I, Sondore D, Makikallio T, Ylitalo K, Christiansen EH, Ravkilde J, Steigen TK, Mannsverk J, Thayssen P, Hansen KN, Syvanne M, Helqvist S, Kjell N, Wiseth R, Aaroe J, Puhakka M, Thuesen L, for the Nordic PCISG. Randomized Comparison of Coronary Bifurcation Stenting With the Crush Versus the Culotte Technique Using Sirolimus Eluting Stents: The Nordic Stent Technique Study. *Circ Cardiovasc Intervent*. 2009;2:27-34.

28. Ferenc M, Gick M, Kienzle RP, Bestehorn HP, Werner KD, Comberg T, Kuebler P, Buttner HJ, Neumann FJ. Randomized trial on routine vs. provisional T-stenting in the treatment of de novo coronary bifurcation lesions. *Eur Heart J*. 2008;29:2859-2867.

29. Klauss V. LEADERS: Two-Year Follow-up from a Prospective Randomized Trial of Biolimus A9-Eluting Stents with a Bioabsorbable Polymer vs. Sirolimus-Eluting Stents with a Durable Polymer. Presentation Transcatheter Cardiovascular Therapeutics, San Francisco, 22nd September 2009.

30. Latib A, Colombo A, Sangiorgi GM. Bifurcation stenting: current strategies and new devices. *Heart*. 2009;95:495-504.

31. Pan M, de Lezo JS, Medina A, Romero M, Segura J, Pavlovic D, Delgado A, Ojeda S, Melian F, Herrador J, Urena I, Burgos L. Rapamycin-eluting stents for the treatment of bifurcated coronary lesions: a randomized comparison of a simple versus complex strategy. *Am Heart J*. 2004;148:857-864.

32. Jensen JS, Galløe A, Lassen JF, Erglis A, Kumsars I, Steigen TK, Wiseth R, Narbute I, Gunnes P, Mannsverk J. Safety in simple versus complex stenting of coronary artery bifurcation lesions. The nordic bifurcation study 14-month follow-up results. *EuroIntervention*. 2008;4:229.

33. Hildick-Smith D, de Belder AJ, Cooter N, Curzen NP, Clayton TC, Oldroyd KG, Bennett L, Holmberg S, Cotton JM, Glennon PE, Thomas MR, Maccarthy PA, Baumbach A, Mulvihill NT, Henderson RA, Redwood SR, Starkey IR, Stables RH. Randomized trial of simple versus complex drug-eluting stenting for bifurcation lesions: the British Bifurcation Coronary Study: old, new, and evolving strategies. *Circulation* 2010;121:1235-43.

34. Katritsis DG, Siontis GCM, Ioannidis JPA. Double Versus Single Stenting for Coronary Bifurcation Lesions: A Meta-Analysis. *Circ Cardiovasc Intervent*. 2009;2:409-415.

35. Lansky A, Tuinenburg J, Costa M, Maeng M, Koning G, Popma J, Cristea E, Gavit L, Costa R, Rares A, Van Es GA, Lefevre T, Reiber H, Louvard Y, Morice MC. Quantitative angiographic methods for bifurcation lesions: a consensus statement from the European Bifurcation Group. *Catheter Cardiovasc Interv*. 2009;73:258-266.

PART VIII

Long-Term Outcomes of Drug-Eluting Stents in Complex Disease

Chapter 8.1

Five-year clinical outcomes of the Arterial Revascularization Therapies (ARTS-II) study of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions

J Am Coll Cardiol 2010; 55(11):1093-101

Patrick W. Serruys, Yoshi Onuma, Scot Garg, Pascal Vranckx, Bernard De Bruyne, Marie-Claude Morice, Antonio Colombo, Carlos Macaya, Gert Richardt, Jean Fajadet, Christian Hamm, Monique Schuijer, Tessa Rademaker, Kristen Wittebols, Hans-Peter Stoll, on behalf of the ARTS-II investigators.

5-Year Clinical Outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the Sirolimus-Eluting Stent in the Treatment of Patients With Multivessel De Novo Coronary Artery Lesions

Patrick W. Serruys, MD, PHD,* Yoshinobu Onuma, MD,* Scot Garg, MBCHB,* Pascal Vranckx, MD,† Bernard De Bruyne, MD, PHD,‡ Marie-Claude Morice, MD,§ Antonio Colombo, MD,‖ Carlos Macaya, MD,¶ Gert Richardt, MD,# Jean Fajadet, MD,** Christian Hamm, MD,†† Monique Schuijer, PHD,‡‡ Tessa Rademaker, MSC,‡‡ Kristel Wittebols, MSC,§§ Hans Peter Stoll, MD,§§ on behalf of the ARTS II Investigators

Rotterdam, the Netherlands, Hasselt, Aalst, and Waterloo, Belgium; Paris and Toulouse, France; Milan, Italy; Madrid, Spain; and Bad Segeberg and Bad Nauheim, Germany

Objectives The purpose of this study is to compare the 5-year clinical outcomes, safety, and efficacy of sirolimus-eluting stents (SES) in the ARTS II (Arterial Revascularization Therapies Study II) with the outcomes of coronary artery bypass graft (CABG) and bare-metal stenting (BMS) from the ARTS I.

Background The long-term outcomes after SES implantation in patients with multivessel disease remains to be established.

Methods The ARTS I was a randomized trial of 1,205 patients with multivessel disease comparing CABG and BMS. The ARTS II study was a nonrandomized trial with the Cypher sirolimus-eluting stent (Cordis, a Johnson & Johnson Company, Warren, New Jersey), applying the same inclusion and exclusion criteria, end points, and protocol definitions. The ARTS II trial enrolled 607 patients, with an attempt to enroll at least one-third of patients with 3-vessel disease.

Results At 5-year, the death/stroke/myocardial infarction event-free survival rate was 87.1% in ARTS II SES, versus 86.0% ($p = 0.1$) and 81.9% ($p = 0.007$) in ARTS I CABG and BMS cohorts, respectively. The 5-year major adverse cardiac and cerebrovascular event (MACCE) rate in ARTS II (27.5%) was significantly higher than ARTS I CABG (21.1%, $p = 0.02$), and lower than in ARTS I BMS (41.5%, $p < 0.001$). The cumulative incidence of definite stent thrombosis was 3.8%. Thirty-two percent (56 of 176) of major adverse cardiac events (MACE) at 5 years were related to possible, probable, or definite stent thrombosis.

Conclusions At 5 years, SES had a safety record comparable to CABG and superior to BMS, and a MACCE rate that was higher than in patients treated with CABG, and lower than in those treated with BMS. Approximately one-third of the events seen with SES could be prevented through the elimination of early, late, and very late stent thrombosis. (J Am Coll Cardiol 2010;55:1093–101) © 2010 by the American College of Cardiology Foundation

The randomized RAVEL (Randomized Comparison of a Sirolimus-Eluting Stent With a Standard Stent for Coronary Revascularization), SIRIUS (Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions), and TAXUS VI studies have all demonstrated the efficacy and safety of drug-eluting stents (DES) compared with bare-metal stent (BMS) at 5-year follow-up (1–3). These studies, however, enrolled patients with simple de novo lesions, and although important, their results are not applicable to the 60% to 70% of today's percutaneous coronary intervention (PCI) patients who receive DES for "off-label" indications (4). Compared with "on-label" use, the use of DES for off-label indications is

From the *Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands; †Hartcentrum, Hasselt, Belgium; ‡Onze Lieve Vrouw Ziekenhuis, Aalst, Belgium; §Cardiovascular Institute, Paris, France; ‖San Raffaele Hospital, Milan, Italy; ¶Hospital Clinico San Carlos, Madrid, Spain; #Segeberger Kliniken GmbH, Bad Segeberg, Germany; **Clinique Pasteur, Toulouse, France; ††Kerckhof-Klinik, Bad Nauheim, Germany; ‡‡Cardialysis BV, Rotterdam, the Netherlands; and §§Cordis Clinical Research EMEA, a Johnson and Johnson Company, Waterloo, Belgium. Ms. Wittebols and Dr. Stoll are employees of Cordis Clinical Research. Dr. Hamm is a consultant for Cordis and Medtronic, and has received research support from Boston Scientific.

Manuscript received September 2, 2009; revised manuscript received November 11, 2009, accepted November 30, 2009.

Abbreviations and Acronyms

ARC = Academic Research Consortium

BMS = bare-metal stent(s)

CABG = coronary artery bypass graft

CVA = cerebrovascular accident

DES = drug-eluting stent(s)

MACCE = major adverse cardiac and cerebrovascular event(s)

MACE = major adverse cardiac event(s)

MI = myocardial infarction

OR = odds ratio

PCI = percutaneous coronary intervention

SES = sirolimus-eluting stent(s)

ST = stent thrombosis

associated with poorer outcomes and a higher risk of stent thrombosis (ST); conversely, for off-label lesions, DES are associated with superior outcomes when compared with BMS (4–8). These data are limited to only short- and medium-term follow-up, and the outcomes at 5 years in this complex patient group remain to be fully established. The ARTS II (Arterial Revascularization Therapies Study II) population clearly represents off-label use of sirolimus-eluting stents (SES), with a mean of 3.7 stents implanted per patient, and a mean total stent length of 72.5 mm per patient. Therefore, although a nonrandomized trial, ARTS II can address important issues regarding the safety of DES implantation in patients with complex multivessel disease.

The present analysis is the final report on the 5-year safety and effectiveness of the SES in patients with multivessel disease: it compares the outcomes of ARTS II with the outcomes of the 2 historical arms of ARTS I, and assesses the impact on long-term outcome of ST, which has been readjudicated according to the new Academic Research Consortium (ARC) definitions (9).

Methods

Study design. ARTS II was a multicenter, nonrandomized, open-label trial designed to compare the safety and efficacy of the SES in patients with de novo multivessel coronary artery disease, with the surgical group of ARTS I acting as a historical control (10–16). In order to obtain a population comparable to ARTS I, patients were stratified by clinical site in order to ensure the inclusion of at least one-third of patients with 3-vessel disease. The details of patient selection and end point definitions are described elsewhere (16–21). In the current analysis, the ARTS II population, the PCI arm, and CABG arm from the ARTS I trials are labeled as SES, BMS, and coronary artery bypass graft (CABG) groups, respectively.

Study objectives. The primary objective of ARTS II was to compare the safety and effectiveness of coronary stent implantation using the SES with the surgical arm of ARTS I. End points are measured in terms of major adverse cardiac and cerebrovascular events (MACCE) comprising all-cause death, any cerebrovascular accident (CVA), nonfatal myocardial infarction (MI), or any repeat revascularization, which is equivalent to the patient-oriented clinical end points of ARC definition (9).

The secondary objectives of this study were to compare the ARTS II patients with both arms of ARTS I with respect to: MACCE at 30 days and 1, 3, and 5 years; the composite end point of death, CVA, and MI; the itemized outcomes of death, CVA, MI, and repeat revascularization; resource utilization at 30 days and 1 year; cost effectiveness at 1 year; and quality of life at 6 months and 1, 3, and 5 years. Finally, the study aimed at describing the prognostic value of the SYNTAX score (22,23) on the MACCE rates in the ARTS II population.

The tertiary objectives of the current study were to report the rate of ST and major cardiac adverse events (MACE; defined as a composite of all-cause death, nonfatal MI, or repeat revascularization) with post hoc readjudication of events according to the ARC definition, which was first described during the follow-up of this trial (9).

End point measurement. In ARTS II, the interventional procedure was performed within 48 h of inclusion, whereas in ARTS I, patients were randomized after informed consent had been obtained, after which, patients were placed on a waiting list; there were 3 deaths in the ARTS I CABG arm while patients were awaiting revascularization. To compensate for the temporal difference in allocation between groups, events for the present report were counted from the time of the procedure for all 3 arms and not from the time of allocation as previously published.

In ARTS I and II, only data on subacute thrombotic occlusion (<30 days) were collected in the case record form. In ARTS II, ST was readjudicated according to the ARC definitions. In this process, all coronary angiograms, both procedure-related (n = 104) and nonprocedure-related (n = 165), were reviewed by an independent core laboratory and adjudicated by an independent critical event committee. Thus far, no attempt has been made to assess data on ST in ARTS I in a similar fashion.

In addition, a detailed coronary risk score that has been previously published and tested in a subgroup of ARTS II patients with 3-vessel disease (the SYNTAX score) was used to characterise the complexity of the coronary anatomy (19). In brief, each coronary lesion producing ≥50% luminal obstruction, in vessels ≥1.5 mm, was separately scored and added to provide the overall SYNTAX score. The SYNTAX score was calculated using dedicated software that integrates the number of lesions with their specific weighting factors based on the amount of myocardium distal to the lesion according to the score of Leaman et al. (24), and the morphologic features of each single lesion, as previously reported (23). This SYNTAX score is now available for the entire ARTS II population and its implications in terms of prognosis at 5 years are reported in the current paper.

Statistical analysis. Binary variables are reported as percentages, and the difference between groups was presented with 95% confidence intervals. Time-to-event variables are

presented as Kaplan-Meier curves, and incidences were compared using the log-rank test.

A separate multivariate regression analysis was performed to determine independent predictors of MACE and ST (according to ARC definition) within the ARTS II population only. The following variables were tested on a per patient basis by univariate analysis to determine suitability for inclusion in the multivariate model: sex, previous history of MI, current smoking habit, left ventricular ejection fraction, presence of diabetes, hypertension, 3-vessel disease, family history of MI or sudden death at age <55 years, presentation with unstable angina, use of glycoprotein IIb/IIIa inhibitors, logistic euroSCORE, and SYNTAX score. Finally, a logistic regression model was built using the significant univariate predictors ($p < 0.1$).

Results

Baseline and procedural characteristics. Between April 1997 and June 1998, a total of 1,205 patients were randomly assigned to PCI with BMS (n = 600) or CABG (n = 605) in 67 participating centers in the ARTS I trial. Between February 2003 and November 2003, 607 patients at 45 participating centers were treated by PCI using SES and entered into the ARTS II study. Table 1 presents their baseline demographic and angiographic characteristics. Patients treated in ARTS II were significantly older than those in ARTS I. ARTS II had a significantly higher incidence of diabetes mellitus, hypertension, hypercholesterolemia, and silent ischemia, and a lower percentage of current smokers or patients with a history of prior MI as compared with the CABG groups. Seven patients did not receive any stents during the index procedure (4 underwent elective CABG, 1 required emergent CABG, 1 underwent PCI 35 days later, and 1 remained on medical therapy).

The percentage of percutaneous 3-vessel treatment was 46.6% in SES versus 18.0% in BMS ($p < 0.001$). The mean number of significant lesions per patient was 3.6 ± 1.3 in SES versus 2.8 ± 1.0 in CABG ($p < 0.001$) and 2.8 ± 1.0 in BMS. SES patients received 3.7 ± 1.5 stents with an average total stented length of 72 ± 32 mm compared with 2.8 ± 1.3 stents and 48 ± 22 mm in BMS patients ($p < 0.001$). In the SES population, SYNTAX score and logistic euroSCORE were 20.8 ± 9.51 and 2.16 ± 15.2, respectively.

5-year follow-up. MACCE. Clinical follow-up at 5 years was available in 97.6% of ARTS II population (Fig. 1). The 5-year event rates are depicted in Table 2 and Figure 2. The survival rate in ARTS II was comparable to the historical, surgical, and PCI groups from ARTS I (SES: 94.5%, CABG: 92.6%, BMS: 92.0%). The death/CVA/MI event-free survival was 87.1% in ARTS II, versus 86.0% (log-rank p = 0.42) and the 81.9% (log-rank p = 0.008) in the CABG and BMS cohorts, respectively. At 5-years follow-up, the MACCE-free survival rate in ARTS II (72.5%), which had been comparable to the surgical cohort of ARTS I at 3 years, was significantly lower than CABG (78.9%, p = 0.02), and significantly higher than BMS (58.5%, log-rank $p < 0.001$).

ST ACCORDING TO THE ARC DEFINITIONS. In ARTS II, a total of 57 patients (Table 3) experienced at least 1 stent thrombotic event (definite, probable, or possible) at 5 years. The rate of ST (definite or probable or possible) in ARTS II was 1.5% at 30 days, 3.1% at 1 year, 4.4% at 2 years, 6.4% at 3 years, and 9.4% at 5 years, respectively. The rate of definite ST was 1.0% at 30 days, 1.6% at 1 year, 2.1% at 2 years, 3.5% at 3 years, and 3.8% at 5 years. Among the 23 patients with definite ST, the numbers experiencing acute (<30 days), late (>30 days, <1 year), and very late (>1 year) ST were 6, 4, and 13, respectively. Four of the acute thrombotic events occurred within the first 4 days post-procedure.

Although clopidogrel was only recommended for 3 months, a total of 266 patients were still using thienopyridines at 1 year. The impact of ST on the ARC-defined patient-oriented composite end point is presented in Figure 3A. If none of these ST events (definite, probable, and possible) had occurred, the event-free rate from mortality, the composite of mortality or any MI, and the patient-oriented composite end point would have increased from 94.5%, 84.3%, 70.7% to 96.8%, 92.7%, 78.0%, respectively (absolute difference: 2.3%, 8.4%, and 7.3%).

IMPACT OF SYNTAX SCORE ON CLINICAL OUTCOME. A significant separation of MACCE-free survival was observed when patients were stratified according to SYNTAX score tertiles, with low, intermediate, and high groups defined by SYNTAX scores of <16 (n = 209), 16 to 24 (n = 199) (Fig. 4). When compared with the lowest tertile group (SYNTAX score: <16, 5-year MACE-free rate: 80.1%), both the intermediate (SYNTAX score: 16 to 24) and high (SYNTAX score: >24) tertile groups demonstrated a lower MACE-free survival rate (intermediate: 70.1%, log-rank p = 0.02; high: 67.1%, p = 0.001).

Multivariate analysis. Univariable and multivariable independent predictors for 5-year MACE and ST were presented in Table 4. In univariate analysis, diabetes, logistic euroSCORE, and SYNTAX score were significant predictors of MACE. In multivariate analysis, diabetes (odds ratio [OR]: 1.68 [95% CI: 1.24 to 2.28]), logistic euroSCORE (OR 1.09 [95% CI: 1.003 to 1.14]), and SYNTAX score (OR: 1.68 [95% CI: 1.24 to 2.28]) remained significant, although history of carotid surgery was not. With respect to ST (definite, probable, or possible), SYNTAX score, use of glycoprotein IIb/IIIa inhibitors, and logistic euroSCORE were significant predictors in the univariate analysis, whereas multivariate analysis demonstrated that only SYNTAX score (OR: 1.03 [95% CI: 1.00 to 1.05]) and the use of glycoprotein IIb/IIIa inhibitors (OR: 1.71 [95% CI: 0.99 to 1.32]) were independent predictors of ST at 5 years.

Table 1 Baseline and Procedural Characteristics of ARTS II and I Population

	SES (n = 607)	CABG (n = 605)	BMS (n = 600)	SES/CABG Difference (95% CI)	SES/BMS Difference (95% CI)
Baseline characteristics					
Male sex	77	76	77	0.6% (−4.2% to 5.4%)	−0.4% (−5.2% to 4.4%)
Age (yrs)	63 ± 10	61 ± 9	61 ± 10	1.5 (0.4 to 2.6)	2.1 (1.0 to 3.2)
Body mass index (kg/m^2)	27.5 ± 4.1	27.4 ± 3.7	27.2 ± 3.7	0.2 (−0.3 to 0.6)	0.3 (−0.1 to 0.8)
Risk factors					
Myocardial infarction	34	42	44	−7.6% (−13.0% to −2.1%)	−9.9% (−15.4% to −4.4%)
Diabetes	26	16	19	10.3% (5.8% to 14.9%)	7.5% (2.8% to 12.2%)
Hypertension	67	45	45	22.3% (16.8% to 27.7%)	22.5% (17.1% to 28.0%)
Hypercholesterolemia	74	58	58	16.4% (11.2% to 21.7%)	16.1% (10.8% to 21.4%)
Family history of MI or sudden death at age <55 yrs	36	42	39	−6.0% (−11.5% to −0.5%)	−3.2% (−8.7% to 2.2%)
Current smoker	19	26	28	−6.5% (−11.2% to −1.8%)	−8.7% (−13.4% to −3.9%)
Peripheral vascular disease	7	5	6	1.8% (−0.9% to 4.5%)	1.4% (−1.3% to 4.2%)
Indication for treatment					
Stable angina	53	58	56	−4.8% (−10.4% to −0.8%)	−3.1% (−8.7% to 2.5%)
Unstable angina	36	37	38	−0.8% (−6.2% to 4.6%)	−1.3% (−6.7% to 4.2%)
Silent ischemia	10	5	6	5.6% (2.6% to 8.5%)	4.4% (1.3% to 7.5%)
Angiographic characteristics					
Ejection fraction	60 ± 12	60 ± 13	61 ± 12	−0.2 (−1.6 to 1.3)	−0.8 (−2.2 to 0.7)
No. of lesions with stenosis >50%	3.6 ± 1.3	2.8 ± 1.0	2.8 ± 1.0	0.8 (0.6 to 0.9)	0.8 (0.6 to 0.9)
No. of diseased vessels					
1	0	4	4	−3.4% (−5.0% to −1.8%)	−3.6% (−5.3% to −2.0%)
2	46	66	69	−20.1% (−25.6% to −14.6%)	−22.4% (−27.9% to −17.0%)
3	54	30	27	23.5% (18.1% to 28.9%)	26.1% (20.7% to 31.4%)
Vessel territory with stenosis (% of lesions)					
Right coronary artery	29	29	31	−0.4% (−3.3% to 2.5%)	−2.1% (−5.0% to 0.9%)
Left main	0	0	0	−0.1% (−0.2% to 0.1%)	−0.1% (−0.2% to 0.1%)
Left anterior descending	42	41	39	0.4% (−2.7% to 3.6%)	2.1% (−1.1% to 5.3%)
Left circumflex artery	29	29	29	0.0% (−2.9% to 3.0%)	0.0% (−2.9% to 3.0%)
Lesion length (visual) (% of lesions)					
Discreet (<10 mm)	61	68	66	−7.3% (−10.4% to −4.2%)	−4.7% (−7.9% to −1.5%)
Tubular (10–20 mm)	27	25	27	2.0% (−0.9% to 4.9%)	−0.1% (−3.0% to 2.8%)
Diffuse (>20 mm)	12	7	7	5.3% (3.4% to 7.2%)	4.8% (2.9% to 6.7%)
Lesion classification (% of lesions)					
Type A	7	7	6	0.0% (−1.6% to 1.6%)	0.9% (−0.7% to 2.5%)
Type B1	23	31	26	−7.9% (−10.8% to −5.1%)	−3.0% (−5.8% to −0.2%)
Type B2	56	54	60	1.9% (−1.3% to 5.1%)	−3.7% (−6.9% to −0.5%)
Type C	14	8	8	6.0% (4.0% to 8.0%)	5.9% (3.9% to 7.8%)
Procedural characteristics					
Bifurcation requiring double wiring	34	32	35	2.2% (−0.9% to 5.3%)	−0.6% (−3.7% to 2.6%)
Number of stents implanted	3.7 ± 1.5	—	2.8 ± 1.3	—	0.9 (0.7 to 1.0)
Total stent length (mm)	72.5 ± 32.1	—	47.6 ± 21.7	—	24.9 (21.8 to 28.1)
Maximum dilatation pressure (atm)	16.4 ± 2.9	—	14.6 ± 2.8	—	1.7 (1.4 to 2.1)
Direct stenting (% of lesions)	34.6	—	3.3	—	31.3% (29.1% to 33.6%)
Duration of procedure (min)	85 ± 43	193 ± 67	99 ± 50	−108.2 (−114.6 to −101.8)	−13.6 (−18.9 to −8.3)
Post-procedural hospital stay (days)	3.4 ± 2.7	9.6 ± 4.9	3.9 ± 3.7	−6.2 (−6.6 to −5.8)	−0.5 (−0.9 to −0.2)

Values are % or mean ± SD. Data are expressed per patient unless stated otherwise.
BMS = bare-metal stent(s); CABG = coronary artery bypass graft; CI = confidence interval; MI = myocardial infarction; PCI = percutaneous coronary intervention; SES = sirolimus-eluting stent(s).

Discussion

The current analysis reports the 5-year outcomes of patients with multivessel disease treated with SES, and historical cohorts treated with CABG and BMS. The main findings of the study are the following: 1) 5-year mortality was similar between SES, CABG, and BMS groups; 2) the 5-year composite safety end point of death, stroke, and MI in the SES group was comparable to the CABG group, and lower than the BMS group; 3) at 5 years, the MACCE rate in the SES group was higher than the CABG group, which was mainly driven by a higher rate of repeat revascularization in the SES group; however, the MACCE rate of the SES group remained lower than that of the BMS group; 4) at 5-year follow-up, ST events (early, late, and very late) were potentially involved in approximately one-third of

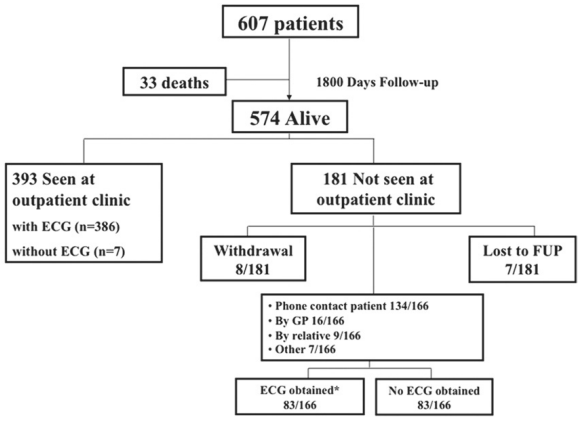


Figure 1 Flow Chart of 5-Year Follow-Up

*Electrocardiogram (ECG) obtained by center. FUP = follow-up; GP = general practitioner.

MACE events; and 5) baseline SYNTAX score has a role in the prediction of 5-year MACCE events.

Long-term safety. Despite the more complex angiographic profile and clinical risk factors in the SES cohort, there was no difference in 5-year mortality between the ARTS II and I cohorts. Although the present study might have been underpowered to demonstrate any significant difference in mortality, the findings concur with the meta-analyses of randomized trials of CABG versus BMS and more specifically, CABG versus multivessel stenting with BMS (25,26). In the current study, the composite end point of mortality, stroke, and MI was lowest in the SES group and was significantly better than in the BMS cohort.

Long-term efficacy. The significantly higher MACCE rate in the SES group compared with the CABG cohort (21.1% vs. 17.5%, p = 0.02) at 5-years was not observed consistently through the study. At 1 year, the MACCE rate was slightly lower in the SES cohort compared with the CABG group, whereas at 2 and 3 years, following a

Table 2 Clinical End Points at 5 Years (Hierarchical and Nonhierarchical MACCE Up to 1,800 Days, Per Patient) Counted Since Date of Procedure

	SES (n = 607)	CABG (n = 602)*	BMS (n = 600)	SES/CABG Difference (95% CI)	SES/BMS Difference (95% CI)
Hierarchical					
Death	33 (5.4)	43 (7.1)	47 (7.8)	−1.7 (−4.4 to 1.0)	−2.4 (−5.2 to 0.4)
CVA	17 (2.8)	16 (2.7)	19 (3.2)		
MI	27 (4.4)	24 (4.0)	41 (6.8)		
Death/CVA/MI	77 (12.7)	83 (13.8)	107 (17.8)	−1.1 (−4.9 to 2.7)	−5.1 (−9.2 to −1.1)
Revascularization	88 (14.5)	42 (7.0)	140 (23.3)		
(re) CABG	15 (2.5)	5 (0.8)	47 (7.8)		
(re) PTCA	73 (12)	37 (6.1)	93 (15.5)		
Any MACCE	165 (27.2)	125 (20.8)	247 (41.2)	6.4 (1.6 to 11.2)	−14 (−19.3 to −8.7)
Nonhierarchical					
CVA	22 (3.6)	20 (3.3)	23 (3.8)	0.3 (−1.8 to 2.4)	−0.2 (−2.3 to 1.9)
MI	35 (5.8)	34 (5.6)	49 (8.2)	0.1 (−2.5 to 2.7)	−2.4 (−5.3 to 0.5)
Revascularization	123 (20.3)	52 (8.6)	181 (30.2)	11.6 (7.7 to 15.5)	−9.9 (−14.8 to −5.0)
(re) CABG	17 (2.8)	7 (1.2)	63 (10.5)	1.6 (0.1 to 3.2)	−7.7 (−10.5 to −4.9)
(re) PTCA	108 (17.8)	49 (8.1)	138 (23.0)	9.7 (5.9 to 13.4)	−5.2 (−9.7 to −0.7)

Values are n (%). *3 patients on the waiting list died.
CVA = cardiovascular accident; MACCE = major adverse cardiac and cerebrovascular event; PTCA = percutaneous transluminal coronary angioplasty; other abbreviations as in Table 1.

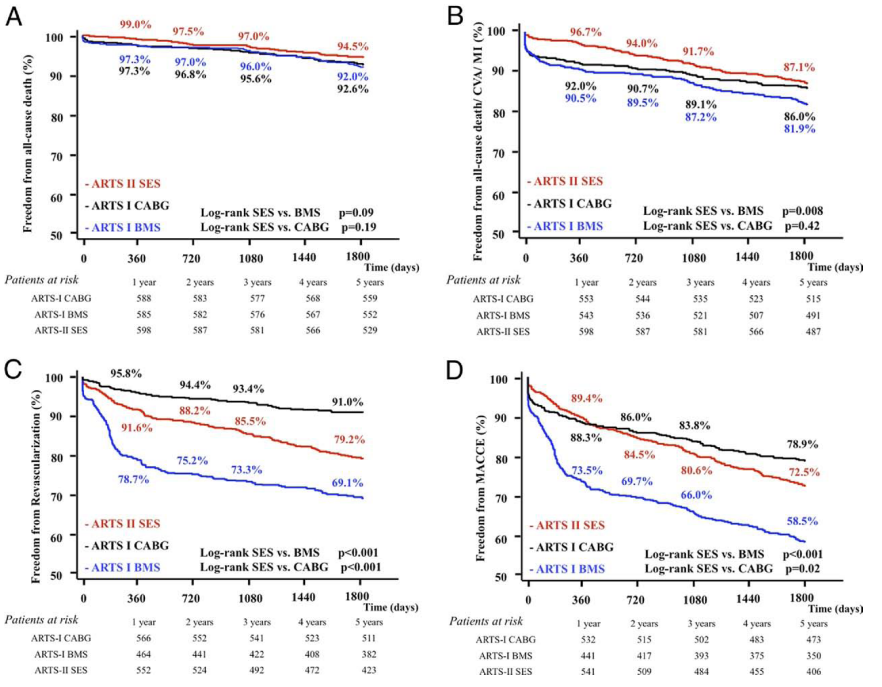


Figure 2 Kaplan-Meier Curves of Freedom From Clinical Events

Kaplan-Meier estimates up to 1,800 days of: **(A)** freedom from all-cause mortality; **(B)** freedom from a composite of death, cerebrovascular accident (CVA), or myocardial infarction (MI); **(C)** freedom from revascularization; and **(D)** freedom from major adverse cardiac and cardiovascular events (MACCE) (all-cause mortality, any MI, CVA, or any reintervention). ARTS = Arterial Revascularization Therapy Study; BMS = bare-metal stent(s); CABG = coronary artery bypass graft; SES = sirolimus-eluting stent(s).

comparatively greater number of additional MACCE events in the SES group, the overall MACCE rate was insignificantly higher in the SES group compared with CABG (17,27). This reversal was mainly driven by the relatively higher rates of reintervention in patients in SES compared with CABG, such that the absolute difference in repeat revascularization between the 2 groups increased progressively from 4.2 % at 1 year to 6.2%, 7.9%, and 11.6% at 2, 3, and 5 years, respectively. Therefore, the current trial confirms that surgical revascularization is more durable than percutaneous revascularization. It is noteworthy, however, that the freedom from surgical or percutaneous reintervention at 5 years increased from 69.1% in the BMS to 79.2% in SES. Furthermore, at 5 years, only 2.8% of patients from the SES cohort required CABG compared with 10.5% from the BMS cohort.

Table 3 ST According to the ARC Definitions

	ARTS II	Death Up to 1,800 Days	MI Up to 1,800 Days*
Acute/subacute (<30 days)	9 (1.4%)	1/9 (11%)	9/9 (100%)
Late (<1 yr)	9 (1.4%)	3/9 (30.0%)	4/9 (40.0%)
Very late (>1 yr)	39 (6%)	10/39 (26%)	29/39 (74%)
Definite	23 (4%)	2/23 (9%)	19/23 (83%)
Definite or probable	46 (8%)	3/46 (7%)	42/46 (91%)
Definite, probable or possible	57 (9%)	14/57 (25%)	42/57 (74%)

*MI according to ARC definition.
ARC = Academic research consortium; MI=myocardial infarction; ST = stent thrombosis.

ST. Occurrence of late and very late ST has been recognized as a long-term safety concern with drug-eluting stents (28,29). Recent studies have suggested that in patients with 2- and 3-vessel disease, ST negatively impacts long-term outcomes (30). There was a gradual rise in the rate of ST during follow-up, but overall rates of definite ST were similar to those reported in all-comer

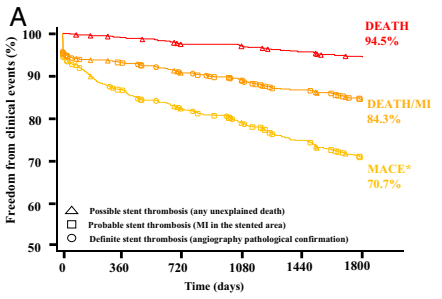


Figure 3 Kaplan-Meier Curves of Freedom From ARC-Defined MACE, With or Without ST

Kaplan-Meier estimates of freedom from death **(red lines)**, death or myocardial infarction (MI) **(orange lines)**, and major adverse cardiac events (MACE) (all-cause mortality, MI, or revascularization) **(yellow lines)** according to Academic Research Consortium (ARC) definition **(A)**. Possible stent thrombosis (ST) is superimposed on the Kaplan-Meier curves as a **triangle**, probable stent thrombosis as a **square**, and definite stent thrombosis as a **circle**. If all these ST-related events had been eliminated **(B)**, freedom from death at 5 years would have increased from 94.5% to 96.8%, freedom from death or death/MI from 84.3% to 92.7%, and freedom from MACE from 70.5% to 78.0%. Please note MI and MACE were readjudicated according to ARC definition. *All-cause death, MI, or any revascularization according to ARC definition. Troponin was not collected in the ARTS II.

populations treated with DES (28,29). When analyzing the impact of ST on safety outcomes, reassurance can be obtained by considering the rate of all-cause mortality (5-year mortality, SES: 5.4% vs. BMS: 7.8%) and MI (5-year MI, SES: 5.8% vs. BMS: 8.2%), because despite the fact that two-thirds of the patients with definite ST sustained an MI or underwent a repeat revascularization, only 2 of these 23 patients died at 5-year follow-up. The ST events from ARTS I PCI have not been reported because of the absence of any adjudication of late and very late stent thrombotic events.

Figure 3 illustrates the fact that early, late, and very late, as well as definite, probable, or possible ST all contributed to a deterioration in the treatment effect expressed as freedom from death, death/MI, and death/MI/repeat revascularization. Of the 176 patients who had a major adverse cardiac event (ARC definitions), 22 had definite ST, 45 definite or probable ST, and 56 definite, probable, or possible ST (32% of adverse events). Thus, one-third of adverse events occurring during 5-year follow-up could be explained, and potentially prevented, by eliminating ST. These results emphasize the importance of optimal stent implantation, development of less thrombogenic devices such as DES with biocompatible or bioabsorbable coatings, or fully bioabsorbable DES, and in addition, more effective antithrombotic therapies (31–35).

Impact of SYNTAX score on long-term clinical outcome. The recently reported SYNTAX trial compared surgery with percutaneous treatment in patients with left main or 3-vessel disease (36). Of interest, when patients with 3-vessel disease from the SYNTAX trial were subdivided into tertiles of SYNTAX score (cutoff of 23 and 33), the lowest tertile group showed similar 1-year MACCE rates

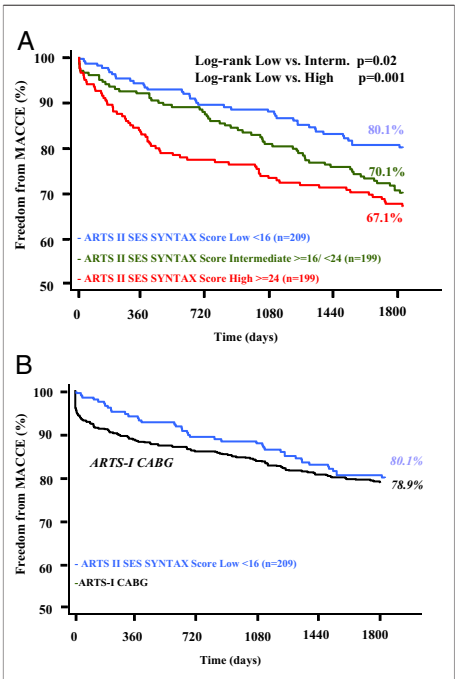


Figure 4 Kaplan-Meier Curves of Freedom From MACCE According to Tertiles of SYNTAX Score

Freedom from protocol-defined major adverse cardiac and cerebrovascular event (MACCE) rate according to SYNTAX score tertiles **(A)**. When the coronary artery bypass graft (CABG) MACCE rate is superimposed, the lowest SYNTAX score tertile shows a similar event rate at 5 years **(B)**.

Table 4 Independent Predictors of MACE and ST in the ARTS II Group

	Univariable Predictors at 5 Yrs			Multivariable Predictors at 5 Yrs		
Variables	Odds Ratio	95% CI	p Value	Odds Ratio	95% CI	p Value
MACE						
Diabetes	1.82	1.35–2.47	<0.001	1.68	1.24–2.28	<0.001
Logistic euroSCORE	1.11	1.03–1.21	0.01	1.09	1.003–1.14	0.04
SYNTAX score	1.04	1.02–1.05	<0.001	1.68	1.24–2.28	0.001
Any ST						
SYNTAX score	1.03	1.00–1.06	0.02	1.03	1.00–1.05	0.04
Use of glycoprotein IIb/IIIa inhibitor	1.68	0.99–2.83	0.05	1.71	1.01–2.89	0.045
Logistic euroSCORE	1.14	0.99–1.31	0.05	1.15	0.99–1.32	0.06

Major adverse cardiac events (MACE) are according to ARC definition (all-cause death, myocardial infarction, or revascularization).
Abbreviations as in Tables 1 through 3.

between PCI and CABG. On the other hand, for the highest tertile groups, the 1-year MACCE rate was significantly higher in the PCI group (36).

After applying the tertile division of the SYNTAX score to the ARTS II study (cutoffs 16 and 24), patients with a score of <16 had a MACCE-free survival rate that was greater than patients in the middle or highest tertiles. In addition, the SYNTAX score was identified as an independent predictor of 5-year ST and MACE, indicating that it has a role in the risk stratification of patients with multivessel disease. Furthermore, the MACE rate was similar between the lowest tertiles of the ARTS II group and the entire surgical cohort from ARTS I (Fig. 4). These results further support the notion that patients with multivessel disease and a low SYNTAX score may be adequately treated with PCI, whereas those patients with high SYNTAX scores benefit more from CABG.

Of note, the cutoff values for the tertile division of the SYNTAX score in the SYNTAX trial (23 and 33) are for obvious reasons different from those in the ARTS II trial (16 and 24). Further assessment of the distribution and clinical impact of the SYNTAX score in various populations is warranted; however, only a propensity-matched analysis based on SYNTAX score will allow a definitive comparison of outcomes between the SYNTAX randomized controlled trial and the ARTS II registry.

Study limitations. First, it was nonrandomized, and thus the groups are not directly comparable, precluding a formal noninferiority comparison. In view of the higher risks anticipated as a result of the greater severity of disease in the ARTS II population compared with the ARTS I population, the clinical outcomes may be biased against ARTS II; however, this may be partially offset by other advances in interventional technology. Statistical adjustment therefore might be required to correct for the differences. This is currently being conducted and will be presented in a separate report. Second, there was a 5-year time lag between the enrollment periods of the ARTS I and II cohorts. With recent improvements in surgical techniques and concomitant medication (statins), it is more than likely that the clinical results of a true randomized trial would have come out more in favor of surgical treatment. Third, the incidence and impact of ST was not readjudicated according to the ARC definitions in the ARTS I study, which was primarily because pieces of clinical information required for readjudication were missing and not obtainable retrospectively. Finally, the baseline SYNTAX scores in the historical cohorts have not been calculated because the baseline cineangiograms are no longer available.

Reprint requests and correspondence: Dr. Patrick W. Serruys, Thoraxcenter, Ba-583, 's Gravendijkwal 230, 3015 CE Rotterdam, the Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl.

REFERENCES

1. Weisz G, Leon MB, Holmes DR Jr., et al. Five-year follow-up after sirolimus-eluting stent implantation results of the SIRIUS (Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions) trial. J Am Coll Cardiol 2009;53:1488–97.
2. Morice MC, Serruys PW, Barragan P, et al. Long-term clinical outcomes with sirolimus-eluting coronary stents: five-year results of the RAVEL trial. J Am Coll Cardiol 2007;50:1299–304.
3. Grube E, Dawkins K, Guagliumi G, et al. TAXUS VI final 5-year results: a multicentre, randomised trial comparing polymer-based moderate-release paclitaxel-eluting stent with a bare metal stent for treatment of long, complex coronary artery lesions. EuroIntervention 2009;4:572–7.
4. Kirtane AJ, Gupta A, Iyengar S, et al. Safety and efficacy of drug-eluting and bare metal stents: comprehensive meta-analysis of randomized trials and observational studies. Circulation 2009;119:3198–206.
5. Lasala JM, Cox DA, Lewis SJ, et al. Expanded use of the TAXUS Express Stent: two-year safety insights from the 7,500 patient ARRIVE Registry programme. EuroIntervention 2009;5:67–77.
6. Win HK, Caldera AE, Maresh K, et al. Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. JAMA 2007;297:2001–9.
7. Farb A, Boam AB. Stent thrombosis redux—the FDA perspective. N Engl J Med 2007;356:984–7.
8. Brodie BR, Stuckey T, Downey W, et al. Outcomes and complications with off-label use of drug-eluting stents: results from the STENT (Strategic Transcatheter Evaluation of New Therapies) group. JACC Cardiovasc Interv 2008;1:405–14.
9. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
10. Serruys PW, Ong AT, van Herwerden LA, et al. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of

multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. J Am Coll Cardiol 2005;46:575–81.
11. Ix JH, Mercado N, Shlipak MG, et al. Association of chronic kidney disease with clinical outcomes after coronary revascularization: the Arterial Revascularization Therapies Study (ARTS). Am Heart J 2005;149:512–9.
12. Gruberg L, Mercado N, Milo S, et al. Impact of body mass index on the outcome of patients with multivessel disease randomized to either coronary artery bypass grafting or stenting in the ARTS trial: the obesity paradox II? Am J Cardiol 2005;95:439–44.
13. Aoki J, Ong AT, Arampatzis CA, et al. Comparison of three-year outcomes after coronary stenting versus coronary artery bypass grafting in patients with multivessel coronary disease, including involvement of the left anterior descending coronary artery proximally (a subanalysis of the arterial revascularization therapies study trial). Am J Cardiol 2004;94:627–31.
14. Legrand VM, Serruys PW, Unger F, et al. Three-year outcome after coronary stenting versus bypass surgery for the treatment of multivessel disease. Circulation 2004;109:1114–20.
15. van den Brand MJ, Rensing BJ, Morel MA, et al. The effect of completeness of revascularization on event-free survival at one year in the ARTS trial. J Am Coll Cardiol 2002;39:559–64.
16. Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 2001;344:1117–24.
17. Serruys PW, Ong ATL, Morice M-C, et al. Arterial Revascularisation Therapies Study Part II: sirolimus-eluting stents for the treatment of patients with multivessel de novocoronary artery lesions. EuroIntervention 2005;1:147–56.
18. Tsuchida K, Colombo A, Lefevre T, et al. The clinical outcome of percutaneous treatment of bifurcation lesions in multivessel coronary artery disease with the sirolimus-eluting stent: insights from the Arterial Revascularization Therapies Study part II (ARTS II). Eur Heart J 2007;28:433–42.
19. Valgimigli M, Serruys PW, Tsuchida K, et al. Cyphering the complexity of coronary artery disease using the syntax score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. Am J Cardiol 2007; 99:1072–81.
20. Daemen J, Kuck KH, Macaya C, et al. Multivessel coronary revascularization in patients with and without diabetes mellitus: 3-year follow-up of the ARTS II (Arterial Revascularization Therapies Study-Part II) trial. J Am Coll Cardiol 2008;52:1957–67.
21. Vaina S, Voudris V, Morice MC, et al. Effect of gender differences on early and mid-term clinical outcome after percutaneous or surgical coronary revascularisation in patients with multivessel coronary artery disease: insights from ARTS I and ARTS II. EuroIntervention 2009;4:492–501.
22. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219–27.
23. Serruys P, Onuma Y, Garg S, et al. Assessment of the SYNTAX score in the Syntax study EuroIntervention 2009;5:50–6.
24. Leaman DM, Brower RW, Meester GT, Serruys P, van den Brand M. Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. Circulation 1981;63:285–99.
25. Daemen J, Boersma E, Flather M, et al. Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. Circulation 2008;118:1146–54.
26. Hlatky MA, Boothroyd DB, Bravata DM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. Lancet 2009;373:1190–7.
27. Serruys PW, Daemen J, Morice M-C, et al. Three-year follow-up of the ARTS II: sirolimus-eluting stents for the treatment of patients with multivessel coronary artery disease. EuroIntervention 2007;3: 450–9.
28. Wenaweser P, Daemen J, Zwahlen M, et al. Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice. 4-year results from a large 2-institutional cohort study. J Am Coll Cardiol 2008;52:1134–40.
29. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;369:667–78.
30. Kukreja N, Onuma Y, Garcia-Garcia HM, Daemen J, van Domburg R, Serruys PW. Three-year survival following multivessel percutaneous coronary intervention with bare-metal or drug-eluting stents in unselected patients. Am J Cardiol 2009;103:203–11.
31. Serruys PW, Ormiston JA, Onuma Y, et al. A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. Lancet 2009;373: 897–910.
32. Ormiston JA, Serruys PW, Regar E, et al. A bioabsorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions (ABSORB): a prospective open-label trial. Lancet 2008;371:899–907.
33. Kukreja N, Onuma Y, Daemen J, Serruys PW. The future of drug-eluting stents. Pharmacol Res 2008;57:171–80.
34. Wykrzykowska JJ, Onuma Y, Serruys PW. Advances in stent drug delivery: the future is in bioabsorbable stents. Expert Opin Drug Deliv 2009;6:113–26.
35. Wiviott SD, Braunwald E, McCabe CH, et al. Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomised trial. Lancet 2008;371: 1353–63.
36. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.

Key Words: multivessel disease ■ sirolimus-eluting stent ■ long-term outcomes.

Chapter 8.2

Five-year outcomes of percutaneous coronary intervention compared to bypass surgery in patients with multi-vessel disease involving the proximal left anterior descending artery: an ARTS-II sub-study

EuroIntervention. In press

Scot Garg, Giovanna Sarno, Juan-Luis Gutiérrez-Chico, Hector M. Garcia-Garcia, Josep Gomez-Lara, Patrick W. Serruys

EuroIntervention

Five-year outcomes of percutaneous coronary intervention compared to bypass surgery in patients with multivessel disease involving the proximal left anterior descending artery: an ARTS-II sub-study

Scot Garg[1], MB, ChB, MRCP; Giovanna Sarno[1], MD, PhD; Juan-Luis Gutiérrez-Chico[1], MD, PhD; Hector M Garcia-Garcia[2], MD, PhD; Josep Gomez-Lara[1], MD; Patrick W. Serruys[1]*, MD, PhD on behalf of the ARTS-II investigators

1. Department of Interventional Cardiology, Erasmus MC, Rotterdam, The Netherlands; 2. Cardialysis, Rotterdam, The Netherlands

The authors have no conflicts of interest to declare.

KEYWORDS

Drug eluting stents, bare metal stents, CABG, proximal LAD

Abstract

Aim: The aim of this study was to compare the 5-year outcomes of patients with multivessel disease (MVD) involving the proximal left anterior descending (LAD) artery who were treated with sirolimus drug eluting stents (SES), bare metal stents (BMS) and coronary artery bypass surgery (CABG).

Methods and results: Clinical outcomes were compared between the 682 patients enrolled in the ARTS-I and ARTS-II study who had MVD involving the proximal LAD, and were treated with BMS (27.4%), CABG (30.2%), and SES (42.4%). At 5-year follow-up the primary endpoint of major adverse cardiovascular and cerebrovascular events (MACCE) occurred in 33.7%, 18.0% and 24.9% of patients treated with BMS, CABG and SES, respectively (BMS vs. SES p=0.04, CABG vs. SES p=0.07). Unadjusted and adjusted rates of mortality and death/stroke/myocardial infarction (safety) were comparable between all three treatments. Repeat revascularisation was significantly lower following CABG irrespective of adjustment. The absolute difference in MACCE between patients with a logistic EuroSCORE above and below the mean (i.e., 2.09%) was 18.8% (p=0.001), and 1.9% (p=0.28) for CABG and SES, respectively. In patients with a high EuroSCORE, SES was a significantly safer treatment (p=0.04) whilst repeat revascularisation remained lower with CABG irrespective of the EuroSCORE.

Conclusions: At 5-year follow-up CABG has comparable safety, and superior efficacy in terms of reducing repeat revascularisation compared to BMS and SES in the treatment of patients with MVD involving the proximal LAD however, appropriate patient selection remains imperative.

** Corresponding author: Ba583a, Thoraxcentre, Erasmus MC,'s-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands*
E-mail: p.w.j.c.serruys@erasmusmc.nl

Introduction

The proximal segment of the left anterior descending (LAD) artery is the most important segment of the coronary tree after the left main stem (LMS). Its importance is highlighted by the poor prognosis if left untreated,[1] and the recent appropriateness guidelines for revascularisation from the American Heart Association/American College of Cardiology (AHA/ACC), which do not deem revascularisation of the proximal LAD inappropriate, even if it is present in isolation, or associated with no symptoms in patients on little, or no therapy.[2]

The optimal method of revascularisation in patients with multivessel disease (MVD) (with or without involvement of the proximal LAD) continues to remain a contentious issue.[3] Although patients with MVD have preferentially been treated with coronary artery bypass grafting (CABG), no survival advantage has ever been demonstrated in randomised trials comparing CABG to percutaneous coronary intervention (PCI) with either bare metal stents (BMS) or drug eluting stents (DES).[4-6] Moreover, recent evidence suggests that PCI with DESs offer a safe and suitable alternative to CABG in specific groups of patients with MVD.[6-7]

In patients with MVD with proximal LAD involvement previous observational studies have demonstrated a prognostic advantage following revascularisation with CABG compared to balloon angioplasty, or PCI with BMS.[8-10] This benefit however, has not been reproduced in the sub-group analyses of patients with proximal LAD lesions enrolled in randomised studies of MVD comparing BMS to CABG.[11,12] Moreover, in this group of patients the data on the use of DES, which offer the advantage of reduced rates of restenosis compared to BMS,[13] is limited by the availability of only medium term outcomes.[14-16]

The Arterial Revascularisation Therapies Part I (ARTS-I) and Part II (ARTS-II) studies both recruited patients with MVD using the same inclusion criteria.[17-18] In the ARTS-I study patients were randomised to treatment with a BMS or CABG, whilst in the single arm ARTS-II study all patients received a sirolimus eluting stent (SES). The 3-year outcomes of 682 patients with proximal LAD disease from the ARTS-I and ARTS-II study have been published previously.[14] The aim of this report was to describe the 5-year outcomes (i.e., major adverse cardiovascular and cerebrovascular events – [MACCE]) of this important pre-specified sub-group of patients, which consequently represents the longest reported follow-up of proximal LAD disease treated with DES.

Methods

Study population

The ARTS-I and ARTS-II studies have been published previously.[17,18] In brief, the multicentre ARTS-I study randomised 1,205 patients between April 1997 and June 1998 to treatment with PCI with a BMS or CABG. The ARTS-II study was a multicentre, non-randomised, open label trial which recruited 607 patients between February and November 2003 who were all treated with PCI using a SES.

Patient selection

The inclusion and exclusion criteria for both studies were the same. Patients with stable angina, unstable angina or silent ischaemia, who had ≥2 coronary lesions, located in different major epicardial vessels and/or their side-branches (not including the LMS) that were potentially amenable to stent implantation were eligible for inclusion. All patients were required to have a lesion with a diameter stenosis >50% in the LAD, and ≥1 other major epicardial coronary artery. The goal was to achieve complete anatomic revascularisation. There was no restriction on the total implanted stent length. Decisions to place stents in lesions with bifurcations, fresh thrombus, calcification, diffuse disease, complex anatomy or stenting of side branches were left to the discretion of the operators. By protocol surgical revascularisation was performed "on-pump", and where possible the left internal mammary artery graft was used for LAD revascularisation. The major exclusion criteria were: patients with previous PCI, LMS disease, overt congestive heart failure, left ventricular ejection fraction <30 percent, history of a cerebrovascular accident (CVA), transmural myocardial infarction (MI) in the preceding week, severe hepatic or renal disease, neutropenia or thrombocytopenia, an intolerance or contraindication to acetylsalicylic acid or thienopyridines, the need for concomitant major surgery and life-limiting major concomitant non-cardiac diseases. Written informed consent was obtained from each patient prior to enrolment, and the study was approved by the ethics committee of each participating site.

The five year outcomes of the ARTS-I and ARTS-II patient cohorts have already been published elsewhere.[19,20] This pre-specified sub-group analysis included only those patients with a >50% diameter stenosis lesion in the proximal LAD, defined as the coronary segment between the branching point of the LMS and the first major septal branch (segment 6 in the AHA classification).[21]

Endpoints

The primary endpoint of this study was MACCE, defined as a composite of death, stroke, MI and repeat revascularisation (percutaneous or surgical) at 5-year follow-up. Secondary endpoints included death, stroke, MI, safety (a composite of death, stroke and MI) and repeat revascularisation at 5-year follow-up.

Definitions

Deaths included mortality from any cause. Cerebrovascular accidents included transient ischaemic attacks, reversible neurological deficits, intracranial haemorrhage, and ischaemic stroke.[17] MI was defined in the first seven days after the intervention, if there was documentation of new abnormal Q-waves and either a ratio of serum creatinine kinase MB (CK-MB) isoenzyme to total creatinine kinase (CK) that was ≥0.1, or a CK-MB value that was five times the upper limit of normal. Serum CK and CK-MB isoenzyme concentrations were measured 6, 12, and 18 hours after the intervention. Commencing eight days after the intervention (the length of the hospital stay after surgery), either abnormal Q-waves or enzymatic changes were sufficient for a diagnosis of MI. An MI was only confirmed after the relevant electrocardiograms had been analysed by the core laboratory and adjudicated by the clinical-events committee. This two-part method of defining MI was developed for ARTS-I to address the difficulty in diagnosing an MI after cardiac surgery.[17] The incidence of stent thrombosis according to the Academic Research Consortium definitions was only available for patients in ARTS-II.[22]

Statistical methods

Continuous variables are expressed as mean±standard deviation (SD) and were compared using the unpaired Student's *t*-test. Categorical data are presented as percentages, and were compared using the χ^2 test or Fischer's exact test. Survival curves were constructed for time-to-event variables using Kaplan-Meier estimates, and compared by the log-rank test. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. The overall association between treatment type and MACCE was further examined using univariate and multivariate Cox proportional hazard models. In the multivariate model, to compensate for difference in baseline and procedural characteristics between patients enrolled in ARTS-I and ARTS-II adjustments were made for the potential confounders of gender, logistic EuroSCORE (EUROLOG), smoking status, diabetes, hypercholesterolaemia, hypertension, and previous myocardial infarction. Finally patient outcomes were also stratified into two groups according to the mean value of the EUROLOG. A p value of <0.05 was considered significant, and all tests were two-tailed. Data were analysed with SPSS version 17.0 software (SPSS Inc., Chicago, IL, USA).

Results

The ARTS-I study recruited 1,205 patients, of whom a total of 393 (32.6%) had involvement of the proximal LAD. The ARTS-II study enrolled 607 patients, of whom 289 (47.6%) had proximal LAD disease. In total there were 682 patients in this sub-group analysis of whom 187 (27.4%), 206 (30.2%), and 289 (42.4%) received treatment with BMS, CABG and SES, respectively.

Baseline angiographic characteristics (Table 1)

Baseline angiographic characteristics of the study population, stratified according to method of revascularisation, have been published previously, and are summarised in Table 1.[11,14] As expected considering the time lag between the two studies the incidence of risk factors was significantly higher in the cohort treated with SES. Despite this however, the overall risk as assessed using the EuroSCORE (additive or logistic) was similar for each treatment group.

Table 1. Baseline patient characteristics.

Variable (%) unless stated	ARTS-II SES (N=289)	ARTS-I BMS (N=187)	ARTS-I CABG (N=206)
Baseline characteristics			
Male gender	80.6	78.1	181.1
Age, years	63.0±10.2	60.1±9.5¶	62.0±9.0
Body mass index, kg/m^2	27.5±4.1	26.9±3.6	27.4±3.4
Risk factors			
Previous myocardial infarction	32.5	44.4¶	37.9
Diabetes	24.9	11.2¶	14.6¶
Hypertension	65.7	41.2¶	44.2
Hypercholesterolaemia	74.0	63.1¶	58.5
Current smoker	17.6	27.4¶	20.4
Peripheral vascular disease	8.0	5.3	5.3
Chronic obstructive airways disease	4.8	6.4	4.4
EuroSCORE			
Additive	2.49±2.02	2.22±1.87	2.28±1.78
Logistic (%)	2.23±1.67	1.99±1.40	1.98±1.31
Ejection fraction	59.2±11.5	60.8±12.2	60.5±13.3
Indication for treatment			
Stable angina	57.4	53.5	59.7
Unstable angina	32.9	41.7	34.5
Silent ischemia	9.7	4.8	5.8

¶ p<0.05 vs. ARTS-II SES group; SES: sirolimus eluting stent; BMS: bare metal stent; CABG: coronary artery bypass graft surgery

Angiographic and lesion characteristics (Table 2)

The characteristics of the proximal LAD lesions are shown in Table 2. Patients treated with SES had significantly more complex lesions as indicated by the longer lesion length, and greater proportion of Type C lesions, calcified lesions and bifurcations when compared with those treated with BMS or CABG. The characteristics of coronary lesions in segments other than in the proximal LAD are presented elsewhere.[14] Overall patients treated with SES had more extensive disease, and significantly lower rates of complete revascularisation compared to those treated with BMS or CABG. Patients receiving CABG had the longest hospital stay.

Table 2. Angiographic and procedural characteristics.

Variable (%) unless stated	ARTS-II SES (N=289)	ARTS-I BMS (N=187)	ARTS-I CABG (N=206)
Proximal LAD lesion characteristics			
Ostial LAD	17.4	26.2	21.4
Lesion Length(visual)			
Discreet (<10 mm)	49.8	64.2¶	69.9¶
Tubular (10-20 mm)	25.4	25.1	27.2
Diffuse (>20 mm)	22.0	6.4¶	1.0¶
Lesion classification			
Type A	3.1	1.1	7.3¶
Type B1	11.9	20.9¶	21.8¶
Type B2	61.9	68.9	70.6
Type C	23.1	7.5¶	1.9¶
Moderate/heavy calcification	59.9	36.7¶	27.7¶
Thrombus containing lesions	0.0	2.8	1.0
Eccentric lesion	86.8	86.1	80.6
Occlusion	0.0	3.2	1.0
Bifurcation requiring double wiring	51.2	42.8	39.3¶
Additional disease characteristics			
No. of diseased vessels	2.5±0.5	2.3±0.5¶	2.3±0.5¶
No. of diseased lesions with stenosis > 50%	3.7±1.3	3.0±1.0¶	3.0±1.1¶
Extent of other coronary disease			
Two-vessel disease	45.3	67.4¶	60.2¶
Three-vessel disease	54.0	29.4¶	36.9¶
Location of other lesions (% of all lesions)			
Circumflex artery	28.5	29.3	29.0
Right coronary artery	28.6	24.3	25.7
Procedural characteristics			
Total number of stents implanted	3.8±1.6	2.9±1.2¶	–
Total stent length, mm	73.9±33.4	48.3±21.5¶	–
Number of anastomoses	–	–	3.0±1.0
Left internal mammary graft use	–	–	94.5
Completeness of revascularisation	57.7	70.1¶	87.1¶
Length of hospital stay, days	3.56±2.68	3.80±3.60	9.76±4.74¶

¶ p<0.05 vs. ARTS-II SES group; No.: number; LAD: left anterior descending artery; SES: sirolimus eluting stent; BMS: bare metal stent; CABG: coronary artery bypass grafting

Outcomes at 5-years (Table 3, Figure 1)

The hierarchical and non-hierarchical outcomes at 5-years follow-up are shown in Table 3, whilst unadjusted Kaplan Meier survival curves are shown in Figure 1. Overall there was a significant reduction in the primary endpoint of 5-year MACCE following treatment with SES compared to BMS (Relative risk [RR] 1.35, 95% CI [1.02-1.80], p=0.04), whilst only a trend towards a lower incidence of MACCE was seen amongst those treated with CABG compared to SES (RR 0.72, 95% CI [0.51-1.03], p=0.07). In general, safety was comparable between all three treatments modalities.

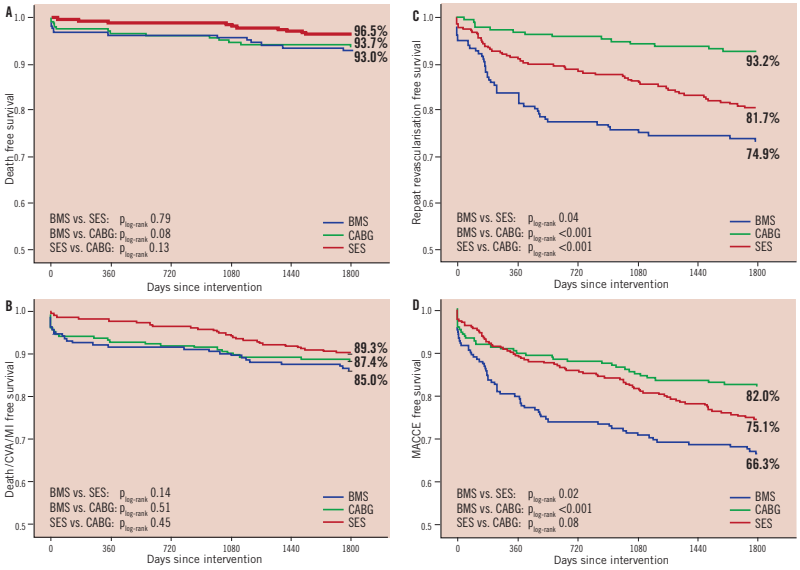


Figure 1. Kaplan Meier survival curves at 5-year follow-up for (A) death (B) death/stroke/myocardial infarction (C) any repeat revascularisation and (D) major adverse cardiovascular and cerebrovascular events (MACCE) for treatment with sirolimus eluting stents (SES), bare metal stents (BMS) and coronary artery bypass surgery (CABG).

Table 3. Unadjusted clinical outcomes at 5-year follow-up.

Variable (%) unless stated	ARTS-II SES (N=289)	ARTS-I BMS (N=187)	ARTS-I CABG (N=206)	SES vs. BMS	SES vs. CABG
Hierarchical events					
Death	3.5	7.0	6.3	2.00[0.90-4.49] p=0.08	1.82[0.82-4.08]p=0.14
Cerebrovascular accident	2.8	2.1	1.5		
Myocardial infarction	4.5	5.9	4.9		
Q wave	2.1	4.3	4.4		
Non-Q wave	2.4	1.6	0.5		
Death/CVA/MI	10.7	15.0	12.6	1.18[0.91-1.52] p=0.17	1.08[0.84-1.39] p=0.52
Repeat revascularisation	14.2	18.7	5.3		
PCI	11.1	12.8	4.9		
CABG	3.1	5.9	0.5		
Any MACCE	24.9	33.7	18.0	1.35[1.02-1.80] p=0.04	0.72[0.51-1.03] p=0.07
Non-hierarchical					
Cerebrovascular accident	3.1	2.7	1.9	0.86[0.29-2.52] p=0.78	0.62[0.20-2.00] p=0.42
Myocardial infarction	4.5	7.5	6.8	1.66[0.80-3.46] p=0.17	1.51[0.73-3.15] p=0.27
Q wave	2.1	5.3	6.3	2.58[0.95-6.97] p=0.053	3.04[1.18-7.87] p=0.02
Non-Q wave	2.4	2.1	0.5	0.88[0.26-2.98] p=0.84	0.40[0.08-1.91] p=0.23
Repeat revascularisation	18.3	25.1	6.8	1.37[0.97-1.94] p=0.08	0.37[0.21-0.65] p<0.001
PCI	15.2	20.9	6.3	1.37[0.93-2.02] p=0.11	0.41[0.23-0.75] p=0.002
CABG	3.5	7.0	0.5	2.00[0.90-4.49] p=0.08	0.14[0.02-1.00] p=0.03

PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; CVA: cerebrovascular accident; MI: myocardial infarction; MACCE: major adverse cardiovascular and cerebrovascular events; BMS: bare metal stent; DES: drug eluting stent

The 5-year outcomes between patients treated with CABG and SES stratified according to a EUROLOG above or below the mean of 2.09% is shown in Figure 2. The absolute difference in MACCE for patients treated with CABG, and SES between those with low and high EUROLOG was 18.8% (p=0.001), and 1.9% (p=0.28), respectively, which was primarily driven by the increased incidence of death/CVA/MI in those patients with high EUROLOG. Repeat revascularisation remained lower with CABG irrespective of EUROLOG; in addition, within each treatment group there was no significant difference in rates of repeat revascularisation between patients with high or low EUROLOG.

Figure 3 shows the univariate and multivariate Cox proportional hazard models for outcomes between SES and CABG at 5-year follow-up. After adjusting for confounding factors, rates of mortality, the composite of safety, and the composite of MACCE remained comparable between SES and CABG. Of note, even after adjustment CABG remained the most effective treatment in terms of reducing repeat revascularisations.

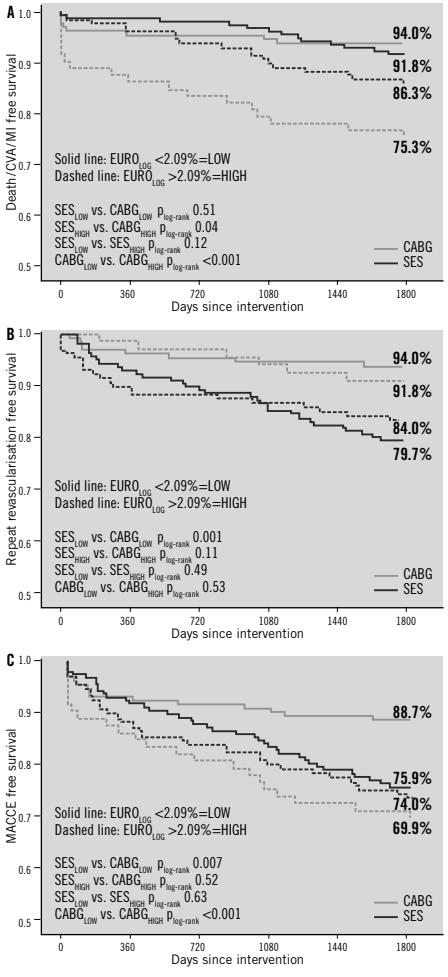


Figure 2. Kaplan Meier survival curves at 5-year follow-up up for (A) death/stroke/myocardial infarction (B) any repeat revascularisation and (C) major adverse cardiovascular and cerebrovascular events (MACCE) for treatment with sirolimus eluting stents (SES), and coronary artery bypass surgery (CABG) stratified according to patients with a logistic EuroSCORE above (dotted line) or below (solid line) 2.09%.

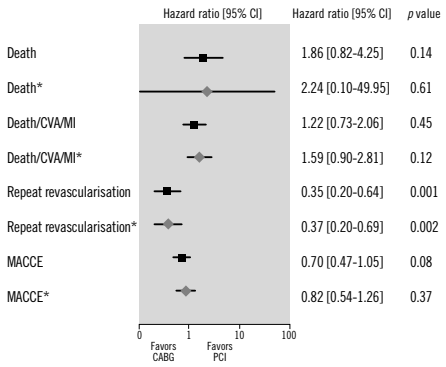


*Figure 3. Unadjusted (■) and adjusted (◆) Hazard ratios at 5-years follow-up between treatment with sirolimus eluting stents (SES) and coronary artery bypass surgery (CABG). Hazard ratios were adjusted for gender, logistic EuroSCORE, smoking status, diabetes, hypercholesterolaemia, hypertension, and previous myocardial infarction. *Adjusted for, gender, logistic EuroSCORE, smoking status, diabetes, hypercholesterolaemia, hypertension, and previous myocardial infarction.*

Stent thrombosis

Definite stent thrombosis according to ARC definitions occurred in 2.8% of the ARTS-II proximal LAD patients (early 0.7%; late 0.3%; very late 1.7%), while the composite of definite or probable stent thrombosis occurred in 6.6% (early 1.4%; late 0.7%; very late 4.5%).

Discussion

The main findings from this study are that in patients with MVD involving the proximal LAD, overall long-term safety outcomes are comparable following treatment with SES, BMS, or CABG. Moreover, this study also demonstrates that in this complex group of patients CABG remains the most effective treatment in terms of reducing repeat revascularisation out to 5-year follow-up.

The proximal LAD occupies an important location in the coronary arterial tree, and as such it is no surprise that untreated lesions in this location are associated with poor outcomes.[1] Its importance is

further reflected by recommendations that revascularisation of any significant proximal LAD lesions, even in the absence of symptoms, is not deemed inappropriate.[2]

Proximal LAD disease can occur in isolation or in association with MVD. The former has been the subject of numerous randomised controlled trials, which have compared PCI using BMS, to surgical revascularisation by standard CABG or minimally invasive direct CABG with a LIMA-to-LAD anatomosis.[23-25] Meta-analysis of these studies report similar survival between groups out to 5-year follow-up, and reduced repeat revascularisation with CABG.

In the setting of MVD, data is confined to retrospective studies, and long-term outcome (>3 years) data is limited.[9-12,14-16] In general there is little dispute over the superiority of DES over BMS in terms of reducing rates of target lesion revascularisation (TLR).[13] For lesions in the proximal LAD however, the issue is complicated by the proximal LAD having a normal mean minimum lumen diameter of approximately 3 mm,[26] the cut off above which DES have been shown to offer only limited clinical benefit.[27] Consistent with this, Bonello et al recently reported no significant difference in MACE or TLR at 1-year follow-up among 487 patients with MVD and non-ostial proximal LAD lesions, treated with BMS or DES (mean stent diameter 3.2 mm).[15] In contrast to these results, the current study demonstrates not only comparable safety, but also a significant reduction in repeat revascularisation (p(log-rank)=0.04) and overall MACCE (p(log-rank)=0.02) out to 5-years with the use of DES compared to BMS.

In this the sub-group of patients with MVD and proximal LAD lesions, treatment with CABG has shown a consistent benefit in terms of reduced repeat revascularisation compared to balloon angioplasty, and PCI with either BMS or DES.[9-12,14,16,28] With respect to safety, there have been conflicting results. The majority of the data comes from sub-group analyses of the New York State registry, and results demonstrate a consistent and significant improvement in adjusted survival out to 3-years follow-up after treatment with CABG compared to balloon angioplasty or stenting with BMS.[9,10] In contrast however, comparable safety was seen in this group of patients in the sub-group analysis of the randomised ARTS-I study.[11]

Similar inconsistent results have also been seen in the more recent observational studies which have included patients treated with DES. Yan et al recently reported comparable adjusted mortality at 2-year follow-up between DES and CABG,[16] whilst Hannan et al demonstrated no difference in unadjusted survival between groups, however following adjustment, outcomes were superior following CABG.[28] In addition, Kukreja et al reported the 3-year outcomes from the current cohort and showed significantly improved unadjusted survival following SES implantation. This benefit has not been maintained out to 5-years, and is likely to reflect the larger absolute increase in death (SES Δ2.4%, CABG Δ1.0%) and MI (SES Δ2.8%, CABG Δ1.0%) between 3- and 5-years follow-up observed in patients treated with SES compared to CABG. It is more than likely that these events were driven by definite/probable stent thrombosis which rose by 73% in this cohort between 3- and 5-year follow-up.

One of the limitations of these previous observational studies is the difficulty in effectively adjusting outcomes according to different baseline clinical and angiographic variables.[29] In daily practice, this heterogeneity reiterates the importance of appropriate patient selection when deciding individualised revascularisation strategy in patients with MVD.[6,7] Historically CABG has been the preferred method of revascularisation in these patients; however it is now apparent that in select patients, PCI is a safe and effective alternative.[6] In the current study the EUROLOG identified those patients who were at highest risk of adverse events following treatment with either CABG or PCI. Most importantly, in those patients with a high EUROLOG, PCI offered a significantly safer treatment, and an improved MACCE free survival compared to CABG. This is in keeping with previous published data which have indicated that the EuroSCORE has a role to play in risk stratification amongst patients undergoing revascularisation by either PCI or CABG.[30,31]

In contrast to this patient based risk assessment, assessment of coronary anatomy, using for example, the SYNTAX score, is also of vital importance.[32] Studies indicate that the SYNTAX score can help aid revascularisation decisions; however it also has an increasingly important role in patient risk stratification.[6,7,33,34] Importantly the calculation of the SYNTAX score requires a careful and through review of the coronary angiogram. This may identify those patients in whom completely revascularisation with PCI cannot be achieved, which can have significant implications on overall outcome.[35] In the current cohort complete revascularisation was accomplished in only 57.7% of patients in the SES group, compared to 87.1% (p<0.05) of those treated with CABG. In additional incomplete revascularisation was a univariate predictor of MACCE in patients treated with SES (HR:1.65, 95% CI:1.02-2.66, p=0.04). These results reiterate the importance of a comprehensive risk assessment to ensure that patients receive the most appropriate tailored revascularisation strategy, which takes into consideration their comorbidities and coronary anatomy.[36,37]

Limitations

The current study is limited by the long time lag between the enrolment of patients in ARTS-I and ARTS-II, which may have influenced outcomes. The development of new surgical techniques and increasing use of arterial conduits may of lead to improved surgical outcomes if the CABG patients had been enrolled at the same time as ARTS-II patients. Conversely the patients in ARTS-II had a worse baseline and procedural risk profile compared to those included in ARTS-I, however better stent design, improved PCI technique and equipment, as well as the advances in pharmacological therapy probably account for the overall improved outcomes. In addition ARTS-II was a registry, and as such suffers from the inherent limitation of this type of study. Moreover, this cohort represents a sub-group analysis and therefore endpoints were not adequately powered to provide definitive results. Leaving these study design limitations aside, the absence of SYNTAX scores in patients treated with CABG is a limitation which otherwise would have allowed a more effective comparison of anatomical complexity. Unfortunately the angiographic films for ARTS-I are unavailable.

Conclusion

At 5-years follow-up surgical revascularisation remains the most effective treatment in terms of reducing repeat revascularisation in patients with MVD involving the proximal LAD. Safety at 5-year follow-up is comparable overall; however in those patients with a high EUROLOG SES appears to provide a safer alternative to CABG. These results reiterate that appropriate patient selection, taking into account both anatomical and clinical variables is imperative when determining the optimal revascularisation strategy in these complex patients.

References

1. Emond M, Mock MB, Davis KB, Fisher LD, Holmes DR, Jr., Chaitman BR, Kaiser GC, Alderman E, Killip T, 3rd. Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) Registry. *Circulation.* 1994;90:2645-2657.

2. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization: a report by the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol.* 2009;53:530-553.

3. Serruys P, Garg S. Percutaneous Coronary Interventions for All Patients With Complex Coronary Artery Disease: Triple Vessel Disease or Left Main Coronary Artery Disease. Yes? No? Don't Know? *Rev Esp Cardiol.* 2009;62:719-725.

4. Daemen J, Boersma E, Flather M, Booth J, Stables R, Rodriguez A, Rodriguez-Granillo G, Hueb WA, Lemos PA, Serruys PW. Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. *Circulation.* 2008;118:1146-1154.

5. Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, Carrie D, Clayton TC, Danchin N, Flather M, Hamm CW, Hueb WA, Kahler J, Kelsey SF, King SB, Kosinski AS, Lopes N, McDonald KM, Rodriguez A, Serruys P, Sigwart U, Stables RH, Owens DK, Pocock SJ. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet.* 2009;373:1190-1197.

6. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med. 2009;360:961-972.

7. Capodanno D, Capranzano P, Di Salvo ME, Caggegi A, Tomasello D, Cincotta G, Miano M, Patane M, Tamburino C, Tolaro S, Patane L, Calafiore AM. Usefulness of SYNTAX score to select patients with left main coronary artery disease to be treated with coronary artery bypass graft. *JACC Cardiovasc Interv.* 2009;2:731-738.

8. Jones RH, Kesler K, Phillips HR, 3rd, Mark DB, Smith PK, Nelson CL, Newman MF, Reves JG, Anderson RW, Califf RM. Long-term survival benefits of coronary artery bypass grafting and percutaneous transluminal angioplasty in patients with coronary artery disease. *J Thorac Cardiovasc Surg.* 1996;111:1013-1025.

9. Hannan EL, Racz MJ, Walford G, Jones RH, Ryan TJ, Bennett E, Culliford AT, Isom OW, Gold JP, Rose EA. Long-term outcomes of coronary-artery bypass grafting versus stent implantation. *N Engl J Med.* 2005;352:2174-2183.

10. Hannan EL, Racz MJ, McCallister BD, Ryan TJ, Arani DT, Isom OW, Jones RH. A comparison of three-year survival after coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol.* 1999;33:63-72.

11. Aoki J, Ong AT, Arampatzis CA, Vijaykumar M, Rodriguez Granillo GA, Disco CM, Serruys PW. Comparison of three-year outcomes after coronary stenting versus coronary artery bypass grafting in patients with multivessel coronary disease, including involvement of the left anterior descending coronary artery proximally (a subanalysis of the arterial revascularization therapies study trial). *Am J Cardiol.* 2004;94:627-631.

12. Rodriguez A, Rodriguez Alemparte M, Baldi J, Navia J, Delacasa A, Vogel D, Oliveri R, Fernandez Pereira C, Bernardi V, O'Neill W, Palacios IF. Coronary stenting versus coronary bypass surgery in patients with multiple vessel disease and significant proximal LAD stenosis: results from the ERACI II study. *Heart.* 2003;89:184-188.

13. Stettler C, Wandel S, Allemann S, Kastrati A, Morice MC, Schomig A, Pfisterer ME, Stone GW, Leon MB, de Lezo JS, Goy JJ, Park SJ, Sabate M, Suttorp MJ, Kelbaek H, Spaulding C, Menichelli M, Vermeersch P, Dirksen MT, Cervinka P, Petronio AS, Nordmann AJ, Diem P, Meier B, Zwahlen M, Reichenbach S, Trelle S, Windecker S, Juni P. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet.* 2007;370:937-948.

14. Kukreja N, Serruys PW, De Bruyne B, Colombo A, Macaya C, Richardt G, Fajadet J, Hamm C, Goedhart D, Macours N, Stoll HP. Sirolimus-eluting stents, bare metal stents or coronary artery bypass grafting for patients with multivessel disease including involvement of the proximal left anterior descending artery: analysis of the Arterial Revascularization Therapies study part 2 (ARTS-II). *Heart.* 2009;95:1061-1066.

15. Bonello L, De Labriolle A, Lemesle G, Roy P, Steinberg DH, Slottow TL, Xue Z, Torguson R, Kaneshige K, Suddath WO, Satler LF, Kent KM, Lindsay J, Pichard AD, Waksman R. Comparison of outcomes of drug-eluting stents versus bare-metal stents in nonostial proximal left anterior descending coronary arteries. *Am J Cardiol.* 2009;103:496-500.

16. Yan Q, Changsheng M, Shaoping N, Xiaohui L, Junping K, Qiang L, Xin D, Rong H, Yin Z, Changqi J, Jiahui W, Xinmin L, Jianzeng D, Fang C, Yujie Z, Shuzheng L, Fangjiong H, Chengxiong G, Xuesi W. Percutaneous treatment with drug-eluting stent vs bypass surgery in patients suffering from chronic stable angina with multivessel disease involving significant proximal stenosis in left anterior descending artery. *Circ J.* 2009;73:1848-1855.

17. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schonberger JP, Buller N, Bonser R, van den Brand MJ, van Herwerden LA, Morel MA, van Hout BA. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med.* 2001;344:1117-1124.

18. Serruys PW, Ong ATL, Morice M-C, Bruyne BD, Colombo A, Macaya C, Richardt G, Fajadet J, Hamm C, Dawkins K, O'Malley AJ, Bressers M, Dennis D, on behalf of the ARTS II Investigators. Arterial Revascularisation Therapies Study Part II - Sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. *EuroIntervention.* 2005;1:147-156.

19. Serruys PW, Ong AT, van Herwerden LA, Sousa JE, Jatene A, Bonnier JJ, Schonberger JP, Buller N, Bonser R, Disco C, Backx B, Hugenholtz PG, Firth BG, Unger F. Five-year outcomes after coronary

stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. *J Am Coll Cardiol*. 2005;46:575-581.

20. Serruys PW, Onuma Y, Garg S, Vranckx P, De Bruyne B, Morice MC, Colombo A, Macaya C, Richardt G, Fajadet J, Hamm C, Schuijer M, Rademaker T, Wittebols K, Stoll HP. 5-Year Clinical Outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the Sirolimus-Eluting Stent in the Treatment of Patients With Multivessel De Novo Coronary Artery Lesions. *J Am Coll Cardiol*. 2010;55:1093-1101.

21. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, McGoon DC, Murphy ML, Roe BB. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation*. 1975;51:5-40.

22. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344-2351.

23. Aziz O, Rao C, Panesar SS, Jones C, Morris S, Darzi A, Athanasiou T. Meta-analysis of minimally invasive internal thoracic artery bypass versus percutaneous revascularisation for isolated lesions of the left anterior descending artery. *BMJ*. 2007;334:617.

24. Kapoor JR, Gienger AL, Ardehali R, Varghese R, Perez MV, Sundaram V, McDonald KM, Owens DK, Hlatky MA, Bravata DM. Isolated Disease of the Proximal Left Anterior Descending Artery: Comparing the Effectiveness of Percutaneous Coronary Interventions and Coronary Artery Bypass Surgery. *J Am Coll Cardiol Intv*. 2008;1:483-491.

25. Thiele H, Neumann-Schniedewind P, Jacobs S, Boudriot E, Walther T, Mohr FW, Schuler G, Falk V. Randomized comparison of minimally invasive direct coronary artery bypass surgery versus sirolimus-eluting stenting in isolated proximal left anterior descending coronary artery stenosis. *J Am Coll Cardiol*. 2009;53:2324-2331.

26. Ge J, Erbel R, Gerber T, Gorge G, Koch L, Haude M, Meyer J. Intravascular ultrasound imaging of angiographically normal coronary arteries: a prospective study in vivo. *Br Heart J*. 1994;71:572-578.

27. Pfisterer M, Brunner-La Rocca HP, Rickenbacher P, Hunziker P, Mueller C, Nietlispach F, Leibundgut G, Bader F, Kaiser C. Long-term benefit-risk balance of drug-eluting vs. bare-metal stents in daily practice: does stent diameter matter? Three-year follow-up of BASKET. *Eur Heart J*. 2009;30:16-24.

28. Hannan EL, Wu C, Walford G, Culliford AT, Gold JP, Smith CR, Higgins RS, Carlson RE, Jones RH. Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. *N Engl J Med*. 2008;358:331-341.

29. Daemen J, Kukreja N, Serruys PW. Drug-eluting stents vs. coronary-artery bypass grafting. *N Engl J Med*. 2008;358:2641-2642; author reply 2643-2644.

30. Romagnoli E, Burzotta F, Trani C, Siviglia M, Biondi-Zoccai GG, Niccoli G, Leone AM, Porto I, Mazzari MA, Mongiardo R, Rebuzzi AG, Schiavoni G, Crea F. EuroSCORE as predictor of in-hospital mortality after percutaneous coronary intervention. *Heart*. 2009;95:43-48.

31. Toumpoulis IK, Anagnostopoulos CE, DeRose JJ, Swistel DG. European system for cardiac operative risk evaluation predicts long-term survival in patients with coronary artery bypass grafting. *Eur J Cardiothorac Surg*. 2004;25:51-58.

32. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Van Dyck N, Russell ME, Mohr FW, Serruys PW. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention*. 2005;1:219-227.

33. Capodanno D, Di Salvo ME, Cincotta G, Miano M, Tamburino C, Tamburino C. Usefulness of the SYNTAX Score for Predicting Clinical Outcome After Percutaneous Coronary Intervention of Unprotected Left Main Coronary Artery Disease. *Circ Cardiovasc Intervent*. 2009;2:302-308.

34. Wykrzykowska J, Garg S, Girasis C, de Vries T, Morel MA, van Es GA, Buszman P, Linke A, Ischinger T, Klauss V, Corti R, Eberli F, Wijns W, Morice MC, di Mario C, van Geuns RJ, Juni P, Windecker S, Serruys PW. Value of the Syntax Score (SX) for Risk Assessment in the "All-comers" Population of the Randomized Multicenter Leaders Trial. *J Am Coll Cardiol*. 2010;56:272-277.

35. Ong AT, Serruys PW. Complete revascularization: coronary artery bypass graft surgery versus percutaneous coronary intervention. *Circulation*. 2006;114:249-255.

36. Capodanno D, Miano M, Cincotta G, Caggegi A, Ruperto C, Bucalo R, Sanfilippo A, Capranzano P, Tamburino C. EuroSCORE refines the predictive ability of SYNTAX score in patients undergoing left main percutaneous coronary intervention. *Am Heart J*. 2010;159:103-109.

37. Garg S, Sarno G, Garcia-Garcia HM, Girasis C, Wykrzykowska J, Dawkins KD, Serruys PW. A New Tool for the Risk Stratification of Patients With Complex Coronary Artery Disease: The Clinical SYNTAX Score. *Circ Cardiovasc Interv*. 2010;3:317-326.

Chapter 8.3

Five-year clinical outcomes of diabetic patients in the Arterial Revascularisation Therapies (ARTS-II) study of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions

J Am Coll Cardiol Intv. In press

Yoshi Onuma, Joanna Wykrzykowska, Scot Garg, Pascal Vranckx, Patrick W. Serruys

ABSTRACT

Objectives: This study compared the 5-year clinical outcomes of diabetic patients with multivessel disease who were treated with bare metal stents (BMS), sirolimus eluting stents (SES), and coronary artery bypass surgery (CABG) and enrolled in the Arterial Revascularization Therapies Studies (ARTS) Part I and II.

Background: Diabetes is an established risk factor for major adverse cardiac events after revascularization. Recent trials, however, suggest that revascularization with drug eluting stents has equivalent safety to by-pass surgery up to three-years.

Methods and Results: The ARTS I and II included 367 diabetic patients (BMS: 112, SES: 159 and CABG: 96) and 1445 non-diabetic patients (BMS: 509, SES 448 and CABG 488). The rate of major adverse cardiovascular and cerebrovascular events (MACCE), a composite of death, myocardial infarction, stroke and repeat revascularization was significantly higher in diabetic patients treated with BMS (BMS 53.6% vs. SES 40.5% vs. CABG 23.4%; log rank $p<0.01$for SES vs. BMS and SES vs. CABG). Overall there were no significant differences in either mortality (BMS 13.6%, SES 9.0%, CABG 8.6%, $p=0.23$ for SES vs. BMS and $p=0.91$ for SES vs. CABG) or MI (BMS 11.0%, SES 4.8% and CABG 5.2%, $p=0.04$ for SES vs. BMS and $p=0.76$ for SES vs. CABG) amongst all three treatment groups. The rate of repeat revascularization was significantly lower in patients treated with CABG compared to patients treated with SES (SES 33.2% vs. CABG 10.7%, $p<0.001$). The superior outcomes with CABG persisted even after adjustment of confounding factors. Revascularization rate of patients treated with SES at 5 years approached that of patients treated with BMS (43.7%), although it remained significantly lower. This "catch-up" phenomenon was not apparent in the non-diabetic population.

Conclusion At 5-year follow-up, CABG has comparable safety, and superior efficacy in terms of reducing repeat revascularization compared to BMS and SES in the treatment of diabetic patients with multivessel disease. MI rate was twofold higher in diabetic patients treated with BMS than in patients treated with either SES or CABG.

INTRODUCTION

Diabetes mellitus is an established risk factor for development and progression of coronary atherosclerosis, and is associated with an increased incidence of major adverse cardiac events (MACE) after revascularization.(1-2) The difference in MACE between diabetic and non-diabetic patients treated with percutaneous revascularization has consistently been driven by the higher rates of repeat revascularization in diabetic patients.(3-4) Similarly, among diabetic patients with multivessel (MVD) disease randomized to treatment with percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG), a correspondingly higher rate of repeat revascularization has been seen in those treated with PCI. With respect to mortality, other than the BARI trial which reported a lower mortality with CABG compared to balloon angioplasty,(5) more contemporary studies report equivalent mortality amongst diabetic patients with MVD treated with CABG or PCI with either bare metal or drug eluting stents (DES).(4,6-10)

At present there are limited data on the long-term follow-up of patients with diabetes and MVD treated with DES. The Arterial Revascularization Therapies Part I (ARTS-I) and Part II (ARTS-II) studies both recruited patients with MVD using the same inclusion criteria.(11-12) In the ARTS-I study patients were randomized to treatment with a bare metal stent (BMS) or CABG, while in the single arm ARTS-II study all patients received a sirolimus eluting stent (SES). The 3-year outcomes of 367 patients with diabetes from the ARTS-I and ARTS-II study have been published previously.(3) The aim of this report was to describe the 5-year outcomes of this important sub-group of patients, which consequently represents the longest reported follow-up of diabetic patients with MVD treated with DES. (3-4)

METHODS

ARTS-II study design

The ARTS-I and ARTS-II studies has been published previously.(11-12) In brief, the ARTS-II study was a multicenter non-randomized open label trial designed to assess the safety and efficacy of SES in patients with native MVD, and to compare the results with historical controls enrolled in the ARTS-I study.(3,13-14)

The inclusion and exclusion criteria for both studies were the same. Patients with stable or unstable angina, or silent ischemia who had ≥2 coronary lesions, located in different major epicardial vessels and/or their side-branches (not including the left main stem) that were potentially amenable to stent implantation were eligible for inclusion. All patients were required to have a lesion with a diameter stenosis>50% in the LAD, and ≥1 other major epicardial coronary artery. Stents with a diameter of 2.5 to 3.5mm and length up to 33mm were used. The goal was to achieve complete anatomic revascularization. There was no restriction on the total implanted stent length. Decisions to place stents in lesions with bifurcations, fresh thrombus, calcification, diffuse disease, complex anatomy or stenting of side branches were left to the discretion of the operators.

Patients with any prior coronary intervention, left main coronary disease, overt congestive heart failure or a left ventricular ejection fraction of less than 30% were excluded. Additional exclusion criteria included: history of a cerebrovascular accident, transmural myocardial infarction in the preceding week, severe hepatic or renal disease, neutropenia or thrombocytopenia, intolerance or contraindication to acetylsalicylic acid or thienopyridines, need for concomitant major surgery, and life-limiting major non-cardiac diseases. The study was approved by the ethical committees of each participation institution. All patients signed informed consent prior to study entry.

Patient population

In total 367 diabetic patients (20.4% of the overall ARTS I and II population) were studied in this analysis comprising of the 208 diabetic patients enrolled in the ARTS-I trial who were treated with BMS (n=112) or CABG (n=96), and the 159 diabetic patients enrolled in ARTS-II treated with SES. In addition, comparison is made with the non-diabetic patient cohort.

Study objectives and Endpoints

The primary objectives of the present analysis were to assess the long-term safety and efficacy of the SES compared to BMS and CABG in patients with diabetes and MVD. Comparison with the non-diabetic population is also provided.

The primary endpoint of this study was 5-year MACCE, a composite of death, stroke, myocardial infarction (MI), and repeat revascularization. Other secondary endpoints included: death, stroke, MI, repeat revascularization, and stent thrombosis at 5-year follow-up.

Endpoints and definitions

Deaths from all causes were reported. Cerebrovascular events (CVA) included: stroke, transient ischemic attacks, and reversible ischemic neurologic deficits. Within 7 days after the intervention, a diagnosis of myocardial infarction was made if new abnormal Q-waves (according to the Minnesota code) and either a ratio of serum creatine kinase MB (CK-MB) isoenzyme to total cardiac enzyme that was greater than 0.1 or a CK-MB value that was 5 times the upper limit of normal were present. Serum creatine kinase levels were measured 6 and 12 hours after the intervention and before discharge. Beginning 8 days after the intervention, either abnormal Q-waves or enzymatic changes were sufficient for a diagnosis of myocardial infarction. This two-part method of defining myocardial infarction was developed for ARTS I to address the difficulty of diagnosing a myocardial infarction after surgery. A myocardial infarction was confirmed only after the relevant electrocardiograms had been analyzed by the electrocardiographic core laboratory. All repeat revascularization procedures were recorded. Events were counted from the time of the start of the initial procedure. All clinical events were adjudicated by the clinical events committee. Five year clinical follow-up was required in all patients and was obtained via a telephone interview with the patient, and when needed also the patient's physician. The incidence of stent thrombosis according to the Academic Research Consortium definitions was only available for patients in ARTS-II.(15) Renal impairment was classified by estimated creatinine clearance (Ccr) calculated by use of the Cockcroft–Gault formula(16): Ccr (mL/min) = [(140 - age) x weight (kg)] / [serum creatinine (mg/dL) x 72]. The formula was multiplied by a factor of 0.85 for

female patients. Patients who had Ccr < 60 mL/min was regarded as renal impairment. Amongst 1205 patients in the ARTS I, 1062 patients (88%) had their Ccr level before the revascularization, while in the ARTS II, 580 patients (96%) had CCR level pre-procedure amongst 607 patients.

Statistical analysis

Baseline characteristics were compared for diabetic patients in both ARTS-I and ARTS-II trial. Continuous variables are reported as mean ± standard deviation. Binary variable are reported as percentages with 95% confidence intervals. Two group t-test and Fisher tests were used for continuous and discrete variables respectively. Time-to-event variables are presented as Kaplan-Meier curves generated using log-rank test. To compensate for differences in baseline and procedural characteristics between patients enrolled in ARTS-I and ARTS-II outcomes were adjusted using a Cox regression analysis with adjustments made for the potential confounding factors. Post hoc Bonferroni correction was performed for ANOVA analysis. All analyses were performed using SPSS.

Table 1. Baseline clinical and angiographic characteristics

	Diabetic patients				Non-Diabetic patients			
	SES (N=159)	BMS (N=112)	CABG (N=96)	P-value	SES (N=448)	BMS (N=509)	CABG (N=488)	P-value
Age in years, mean	65	63	63	0.12	62	60	61	0.01
Ejection Fraction, %	60	61	60	0.81	60	61	60	0.66
Male %	67	73	69	0.53	80	78	77	0.56
Diabetes insulin-treated %	18	21	17	0.78				
Hypertension %	80	64	56	**<0.01**	63	40	43	**<0.01**
Hypercholesterolemia %	74	55	49	**<0.01**	74	59	59	**<0.01**
Renal impairment, %*	5	15	15	**<0.01**	4	13	14	**<0.01**
Previous MI %	30	41	49	**<0.01**	36	41	41	**0.02**
Previous PCI %	0	2	2	0.17	1	1	2	0.1
Current Smoking, %	12	21	17	0.15	22	30	28	**0.02**
Unstable Angina %	32	38	33	0.64	38	38	38	1
Stable Angina %	54	59	63	0.35	53	56	57	0.45
Silent Ischaemia %	15	4	4	**<0.01**	9	7	5	**0.04**
2 Vessel Disease, %	49	65	64	**0.01**	45	69	67	**<0.01**
3 Vessel Disease, %	50	31	35	**<0.01**	55	27	29	**<0.01**
Total Number of implanted stent, mean±SD	3.6±1.5	3.0±1.5		**<0.01**	3.7±1.5	2.7±1.2		**<0.01**
Total Stented Length in mm, mean±SD	73.9±31.9	52.7±25.6		**<0.01**	72.0±32.1	46.4±20.6		**<0.01**
Max. Stent Pressure in atm, mean±SD	16.2±2.7	14.9±2.9		**<0.01**	16.4±2.9	14.6±2.8		**<0.01**

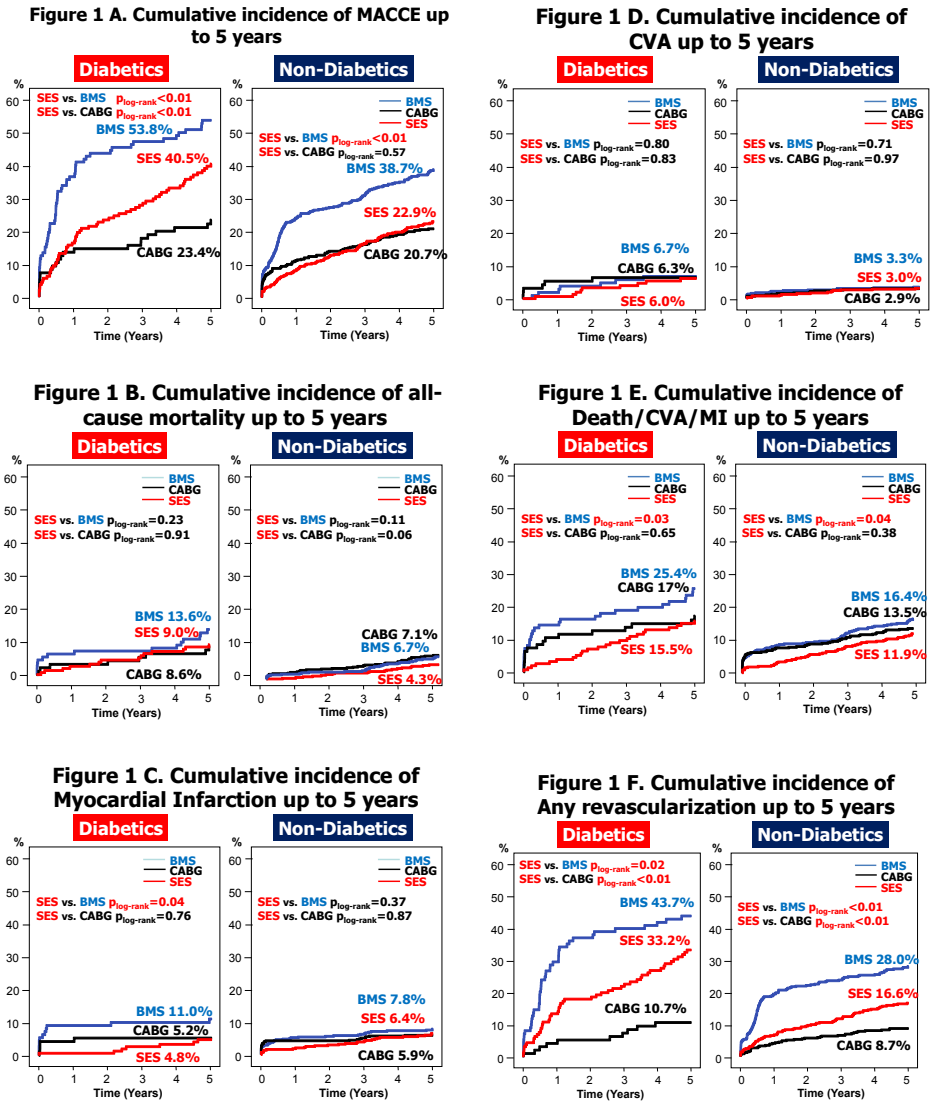
*Patients who had Ccr < 60 mL/min (calculated by Cockcroft-Gault formula) was regarded as renal impairment.

MI = myocardial infarction, PCI = percutaneous coronary intervention, SD = standard deviation, CABG = coronary artery bypass graft, SES = sirolimus-eluting stent, BMS = bare-metal stent

Table 2. Unadjusted Non-hierarchical event rates up to 1800 days and hazard ratios

	Diabetic patients							Non-Diabetic patients						
	SES	BMS	CABG	HR CABG vs. SES	p-value	HR BMS vs. SES	p-value	SES	BMS	CABG	HR CABG vs. SES	p-value	HR BMS vs. SES	p-value
MACCE	63 (39.6%)	60 (53.6%)	22 (22.9%)	**0.54 (0.34-0.88)**	**0.01**	**1.65 (1.16-2.35)**	**0.006**	102 (22.8%)	187 (38.3%)	103 (20.5%)	0.93 (0.70-1.22)	0.58	**1.94 (1.53-2.47)**	**<0.001**
Death	14 (8.8%)	15 (13.4%)	8 (8.3%)	0.95 (0.40-2.27)	0.91	1.56 (0.76-3.24)	0.23	19 (4.2%)	32 (6.6%)	35 (7.0%)	1.70 (0.97-2.97)	0.06	1.57 (0.89-2.78)	0.12
CVA	9 (5.7%)	7 (6.3%)	6 (6.3%)	1.24 (0.42-3.65)	0.7	1.33 (0.49-3.59)	0.58	13 (2.9%)	16 (3.3%)	14 (2.8%)	0.99 (0.45-2.18)	0.99	1.34 (0.81-2.23)	0.25
MI	7 (4.4%)	12 (10.7%)	5 (5.2%)	1.20 (0.38-3.78)	0.75	**2.65 (1.01-6.51)**	**0.048**	28 (6.3%)	37 (7.6%)	29 (5.8%)	0.96 (0.57-1.61)	0.87	1.25 (0.76-2.04)	0.38
Revasc.	50 (31.4%)	47 (42.0%)	10 (10.4%)	**0.29 (0.15-0.57)**	**<0.001**	**1.58 (1.06-2.35)**	**0.03**	73 (16.3%)	134 (27.5%)	42 (8.4%)	**0.51 (0.35-0.74)**	**<0.001**	**1.88 (1.41-2.50)**	**<0.001**

MACCE = Major adverse cardiac and cerebrovascular events (a composite of all-cause mortality, myocardial infarction, cardiovascular accident, or revascularization), CVA = cardiovascular accident, Revasc. = Revascularization, other abbreviations as in Table 1.



Figures 1. present cumulative Kaplan-Meier incidence estimates up to 5 years in diabetics and in non-diabetics,

(A) for MACCE (major adverse cardiac and cerebrovascular events [a composite of all-cause mortality, myocardial infarction, cardiovascular accident, or revascularization])

(B) for all-cause mortality

(C) for myocardial infarction

(D) cerebrovascular accidents

(E) for a composite endpoint of death, cerebrovascular accidents, or myocardial infarction (F) for any revascularization

SES = Sirolimus-eluting stents, BMS = Bare-metal stents, CABG = Coronary artery bypass graft

RESULTS

Baseline characteristics of diabetic patients

Baseline and procedural characteristics of the 367 diabetic patients enrolled in the ARTS-I and ARTS-II trials are summarized in **Table 1 and 2**. Patients treated with SES were significantly more likely to be hypertensive, have hypercholesterolemia, and complex coronary artery disease (type C lesions) compared to historical controls from the ARTS-I trial. Consequently, a greater number of stents and an overall longer total length was implanted in the ARTS-II cohort. In addition, reported completeness of revascularization was lower for patients treated with SES versus BMS (68.6% for BMS versus 59.9% for SES treated patients and 77.4% for CABG treated patients with diabetes; p=0.017).

Five-year clinical outcomes

Overall MACCE, death, MI, CVA and repeat revascularization rates at 5 years are reported in Kaplan-Meier curves (**Figure 1 A-F**). The event rates were higher than those reported for the overall ARTS-I and ARTS-II populations (17). MACCE rate was the highest in patients treated with BMS (BMS 53.8% versus SES 40.5% versus CABG 23.4%; log rank p-values for SES vs. BMS and SES vs. CABG p<0.001). Cumulative incidence of all-cause mortality was 13.6%, 9.0% and 8.6% for patients treated with BMS, SES and CABG, respectively (log rank for SES vs. BMS p=0.23; SES vs. CABG p=0.91). The rate of myocardial infarction was highest (11.0%) for BMS, versus 4.8% for SES-treated patients and 5.2% for CABG patients (log rank SES vs. BMS p=0.04; SES vs. CABG p=0.76); with a statistically significant difference between SES and BMS. There were no differences in the rates of cerebrovascular events between treatment groups at 5 years. Rates of repeat revascularization were the highest in the BMS revascularization group at 43.7% versus 33.2% in the SES treated group and 10.7% in the CABG group (log-rank SES vs. BMS p=0.02; SES vs. CABG p<0.01).

In SES group, clopidogrel use at 5 years was 13.2% in diabetic patients and 23.2% in non-diabetic patients (p=0.008). Aspirin use was 68.6% in the diabetic patients and 77.7% in the non-diabetic patients (p=0.03).

Cox regression analysis

The hazard ratios (adjusted for baseline characteristics) for CABG versus SES and BMS versus SES are shown in **Table 3**. Treatment with BMS conferred significantly higher risk of MACCE, death, MI and repeat revascularization than treatment with SES. CABG offered no advantage over treatment with SES in terms of mortality or risk of myocardial infarction. There was a reduced risk of repeat revascularization and overall (revascularization driven) MACCE with CABG compared to treatment with SES in diabetic patients. Similar analysis in the non-diabetic population (**Table 3**) showed equivalent hazard ratios for MACCE and MI between CABG and SES and higher mortality for CABG. Revascularization rates remained higher in the SES group when compared to CABG, although the HR was 0.54 in the non-diabetic population versus 0.31 in the diabetic population. The interaction, however, between treatment type and diabetic status was non-significant for all clinical end-points.

Table 3. Adjusted hazard ratios

	Diabetic patients				Non-diabetic patients			
	HR CABG vs. SES	p-value	HR BMS vs. SES	p-value	HR CABG vs. SES	p-value	HR BMS vs. SES	p-value
Death	1.11 (0.47-2.66)	0.81	1.77 (0.85-3.67)	0.13	1.99 (1.12-3.53)	0.02	1.88 (1.05-3.38)	0.04
CVA	1.24 (0.42-3.65)	0.70	1.33 (0.49-3.59)	0.58	0.99 (0.45-2.18)	0.99	1.15 (0.53-2.50)	0.72
MI	1.19 (0.38-3.76)	0.76	2.55 (1.00-6.47)	0.049	1.01 (0.60-1.73)	0.96	1.34 (0.81-2.23)	0.25
Death/CVA/ MI	1.33 (0.70-2.50)	0.38	2.09 (1.21-3.62)	<0.01	1.26 (0.83-1.72)	0.33	1.49 (1.05-2.11)	0.03
Any Revasc.	0.31 (0.16-0.62)	0.001	1.61 (1.08-2.41)	0.02	0.54 (0.37-0.80)	<0.01	2.01 (1.49-2.71)	<0.01
MACCE	0.58 (0.36-0.95)	0.03	1.80 (1.25-2.57)	0.001	0.97 (0.75-1.32)	0.97	2.10 (1.64-2.70)	<0.01

Hazard ratios are presented with 95% confidence interval in brackets. The cox regression models are constructed to adjust the following variables: age, gender, previous myocardial infarction, history of revascularization, CABG, insulin dependence (only for diabetic patients), current smoking, dyslipidemia and hypertension.
HR = hazard ratio, other abbreviations as in Table 1and Table2

Stent thrombosis

In diabetic patients treated with SES there were a total of 17 stent thrombosis events (10.7%) with 6 definite, 6 probable and 5 possible stent thrombosis events. This is higher than the overall stent thrombosis rate reported for the ARTS-II population of 9.4% and 8.7% for the non-diabetic subgroup. The rate of definite stent thrombosis in both the diabetic and non-diabetic patient population was 3.8%. Two late and two very late stent thrombosis cases occurred in the diabetic patient population. Two patients with diabetes receiving SES (1.3% of 159) and 12 patients without diabetes receiving SES suffered from very late stent thrombosis (2.7% of 448).

DISCUSSION

In this analysis we present 5 year outcomes of PCI with SES in diabetic patients with multivessel disease. At 3-year follow-up of the ARTS-II trial, patients treated with SES had lower MACCE rates than patients treated with BMS PCI and CABG in ARTS-I, although the differences did not reach statistical significance. (3) In contrast, at 5-year follow-up MACCE rates were lowest for diabetic patients treated with CABG in ARTS-I. Patients treated with SES had a MACCE rate lower than that of patients treated with BMS but considerably higher than that of patients treated with CABG. As illustrated by the Kaplan-Meier curves for MACCE (**Figure 1 A**), while the event rate for patients treated with BMS and CABG reach an asymptotic value at 1 year, events continue to accumulate for patients treated with SES. After two years this increase in events is partly explained by an increase in myocardial infarction rates (**Figure 1 B**). This "catch-up" phenomenon is much more apparent in the diabetic population compared to non-diabetic patients (**Table**

3). The rate of repeat revascularizations also continues to accumulate approaching closer to that of the BMS treated patients at 5 years (**Figure 1 F**). Cox regression model hazard ratios suggest an advantage of CABG over SES in reducing repeat revascularization procedures but equivalence of the two procedures in terms of mortality and myocardial infarction risk after adjusting for baseline covariates in patients with diabetes (**Table 3**). SES clearly reduced the risk of myocardial infarction, repeat revascularization and overall MACCE but had only a non-significant effect on mortality compared to treatment with BMS. Overall stent thrombosis rate in the diabetic population treated with DES is 10.7% at 5 years, which is somewhat higher than that observed in the overall ARTS-II population (9.4%). The rates of definite stent thrombosis in diabetic and non-diabetic patients are the same at 3.8% with two thirds of the cases classified as late or very late stent thrombosis.

Our analysis at 5 years follow-up is in agreement with other recent trials such as CARDIA and SYNTAX which also demonstrate equivalent mortality of PCI with drug eluting stents and CABG in patients with diabetes at one year follow-up.(4,9-10) Both of these studies also demonstrate consistently higher revascularization rates in the PCI arms versus CABG arm. The SYNTAX diabetic subgroup analysis may have, however, been underpowered to detect differences in mortality at 1 and 2 years. Our results are also consistent with the BARI-2D trial findings where survival rates were similar between PCI treated and CABG treated groups (86.4% for CABG vs. 89.2% for PCI) at 5 years. The differences in the MACE-free survival rate in patients with multivessel disease randomized to CABG versus medical therapy were statistically significant but no such difference was appreciated in patients randomized to PCI versus medical therapy. Effectiveness of PCI over medical therapy versus CABG will be assessed in the FREEDOM trial, the first properly powered prospective trial of revascularization strategies in diabetic patients.

LIMITATIONS

This study is a sub-analysis of the main ARTS-I and ARTS-II trials and hence suffers from inherent limitations, such as the lack of sufficient power because of the limited number of patients in the subgroups to provide definite answers. While the protocol required that the lesions in ARTS-II be potentially treatable by CABG, the absence of dialogue with the surgeons prior to the intervention may have caused a selection bias. Another potential bias of this study is that a five-year time difference exists between the groups that were being compared, and technology and medical practice have improved with time, as have surgical mortality rates. The study is non-randomized and consequently statistical adjustment is required to correct for the differences between the current study population and the historical ARTS-I population.

However, the results of the study after adjustment for differences in risk factors did not substantially differ from the unadjusted outcome, since the patients enrolled in ARTS-II were in fact more complex in terms of demographics and lesion characteristics than those included in ARTS-I. In addition, some of the factors such as stent length used or operator's willingness to treat more complex lesions with drug eluting stents or use of dual anti-platelet agents could not be adjusted for and can be a

confounding factor in the analysis. Given low numbers of events in some of the subgroups the multivariate model may have been over-fitted.

CONCLUSIONS

At 5-year follow-up, CABG has comparable safety, and superior efficacy in terms of reducing repeat revascularization compared to BMS and SES in the treatment of diabetic patients with multivessel disease.

REFERENCES

1. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229-34.
2. Flaherty JD, Davidson CJ. Diabetes and coronary revascularization. Jama 2005;293:1501-8.
3. Daemen J, Kuck KH, Macaya C, et al. Multivessel coronary revascularization in patients with and without diabetes mellitus: 3-year follow-up of the ARTS-II (Arterial Revascularization Therapies Study-Part II) trial. J Am Coll Cardiol 2008;52:1957-67.
4. Banning AP, Westaby S, Morice MC, et al. Diabetic and Nondiabetic Patients With Left Main and/or 3-Vessel Coronary Artery Disease Comparison of Outcomes With Cardiac Surgery and Paclitaxel-Eluting Stents. J Am Coll Cardiol.
5. Weintraub WS, Stein B, Kosinski A, et al. Outcome of coronary bypass surgery versus coronary angioplasty in diabetic patients with multivessel coronary artery disease. J Am Coll Cardiol 1998;31:10-9.
6. King SB, 3rd, Lembo NJ, Weintraub WS, et al. A randomized trial comparing coronary angioplasty with coronary bypass surgery. Emory Angioplasty versus Surgery Trial (EAST). N Engl J Med 1994;331:1044-50.
7. Macaya C, Garcia-Garcia HM, Colombo A, et al. One-year results of coronary revascularization in diabetic patients with multivessel coronary artery disease.Sirolimus stent vs. coronary artery bypass surgery and bare metal stent: insights from ARTS-II and ARTS-I. EuroIntervention 2006;2:69-76.
8. Kapur A, Malik IS, Bagger JP, et al. The Coronary Artery Revascularisation in Diabetes (CARDia) trial: background, aims, and design. Am Heart J 2005;149:13-9.
9. Kapur A, Hall RJ, Malik IS, et al. Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial. J Am Coll Cardiol;55:432-40.
10. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961-72.
11. Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 2001;344:1117-24.
12. Serruys PW, Ong ATL, Morice M-C, et al. Arterial Revascularisation Therapies Study Part II - Sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. Eurointervention 2005;1:147-156.
13. Legrand VM, Serruys PW, Unger F, et al. Three-year outcome after coronary stenting versus bypass surgery for the treatment of multivessel disease. Circulation 2004;109:1114-20.
14. Serruys PW, Ong AT, Morice MC, et al. Arterial Revascularisation Therapies Study Part II - Sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. EuroIntervention 2005;1:147-56.
15. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-51.
16. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.
17. Serruys PW, Onuma Y, Garg S, et al. 5-year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. J Am Coll Cardiol;55:1093-101.

Chapter 8.4

Long term clinical results following stenting of the left main stem - Insights from RESEARCH and T-SEARCH registries

J Am Coll Cardiol Intv 2010; 3(6):584-594

Yoshinobu Onuma, Chrysafios Girasis, Nicolo Piazza, Hector M. Garcia-Garcia, Scot Garg, Neville Kukreja, Janet Eindhoven, Jin-Ming Chen; Marco Valgimigli, Ron van Domburg, Patrick W Serruys

FOCUSED UPDATE ON PCI FOR UNPROTECTED LEFT MAIN CAD

Long-Term Clinical Results Following Stenting of the Left Main Stem

Insights From RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) and T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) Registries

Yoshinobu Onuma, MD,* Chrysafios Girasis, MD,* Nicolo Piazza, MD,* Hector M. Garcia-Garcia, MD,* Neville Kukreja, MA,* Scot Garg, MD,* Jannet Eindhoven, MSc,* Jin-Ming Cheng, MSc,* Marco Valgimigli, MD, PhD,† Ron van Domburg, PhD,* Patrick W. Serruys, MD, PhD,* on behalf of Interventional Cardiologists at Thoraxcenter 2000–2005

Rotterdam, the Netherlands; and Ferrara, Italy

Objectives We investigated the long-term clinical outcomes and independent predictors of major cardiac events in unprotected left main coronary artery disease (ULMCA) patients treated by percutaneous coronary intervention with drug-eluting stent (DES).

Background There is limited information on long-term (>3 years) outcomes after DES implantation for ULMCA. Furthermore, bifurcation angle and SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score are emerging as parameters for patient risk stratification, and their prognostic implications have still to be elucidated.

Methods One hundred forty-eight patients with ULMCA treated with DES were analyzed and compared with a historical cohort of 79 patients who received bare-metal stents for the treatment of ULMCA. Patient-oriented composite end point was defined as the occurrence of all-cause death, any myocardial infarction, or any revascularization.

Results The 4-year cumulative incidence of all-cause death, any myocardial infarction, any revascularization, and patient-oriented composite were 35.6%, 3.8%, 25.2%, and 54.4%, respectively. These end points had relatively increased from 1 year to 4 years by Δ70%, Δ5%, Δ50%, and Δ68%, respectively. When compared with a historical cohort who received bare-metal stents for ULMCA treatment, landmark analysis performed after the first 2 years of follow-up demonstrated that the DES cohort had significantly higher patient-oriented composite end point over the last 2 years of follow-up (26% vs. 8%, $p = 0.02$). EuroSCORE (European System for Cardiac Operative Risk Evaluation), cardiogenic shock, and SYNTAX score were identified as independent predictors for the 4-year patient-oriented composite, whereas bifurcation angle was not.

Conclusions Late increase in patient-oriented composite end points after DES implantation for ULMCA warrants careful and long-term follow-up. SYNTAX score and EuroSCORE appear to have a significant prognostic value in long-term patient risk. (J Am Coll Cardiol Intv 2010;3:584–94) © 2010 by the American College of Cardiology Foundation

From the *Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands; and †The Cardiovascular Institute, University of Ferrara, Ferrara, Italy.

Manuscript received February 11, 2010, accepted March 4, 2010.

The prevalence of left main disease in patients with coronary artery atherosclerosis varies from 2.5% to 10% (1). Coronary artery bypass graft (CABG) remains the treatment of choice in patients with unprotected left main coronary artery disease (ULMCA) (2,3). Although percutaneous coronary intervention (PCI) using bare-metal stent (BMS) in patients having 2- or 3-vessel disease is associated with no significant difference in long-term mortality compared with CABG, restenosis and need for repeat revascularization remain major limitations of this mode of revascularization. These latter limitations have precluded the widespread use of PCI, not only in multivessel disease, but also in LM disease (4). Reduction of restenosis with drug-eluting stents (DES), however, has raised the possibility of their use for multivessel treatment as well as LM treatment. So far, several registries and randomized trials have investigated the short- and mid-term clinical outcomes of PCI using DES for ULMCA treatment (5–14), but little is known about its long-term safety and efficacy beyond 3 years (15). In addition, the rate of potentially fatal consequences of stent thrombosis or in-stent restenosis in this patient subset has not fully been investigated (16,17).

See page 642

Several clinical and angiographic parameters for risk stratification after PCI are emerging. Recently, EuroSCORE (European System for Cardiac Operative Risk Evaluation), a typically surgical risk stratification score, has been applied to the PCI population (18). As angiographic analysis, the angle between bifurcated branches has been recognized as a significant prognostic factor for immediate procedural outcomes as well as for intermediate-term outcomes (19–21). In addition, a comprehensive, angiographic scoring system, the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score (22,23) based on morphology and location of coronary artery stenoses in the coronary tree has been proven to predict clinical outcomes in high-risk patients (9,24,25).

The main aim of this study was to report the long-term clinical outcomes of patients receiving DES for unprotected LM lesions in a daily practice of a tertiary medical center. In addition, we assessed the prognostic value of recently emerging predictors of adverse outcomes for PCI treatment of multivessel disease and ULMCA, such as EuroSCORE, the bifurcation angle, and SYNTAX score.

Methods

Study design and patient population. Between April 2002 and December 31, 2005, 210 consecutive patients underwent PCI for LM stenting (7,8). Sixty-two patients with a history of CABG were not retained in this analysis. The remaining 148 patients are the subject of the present investigation. On April 16, 2002, our institution adopted the use of sirolimus-eluting stents (Cypher, Cordis, Warren, New Jersey) as the default strategy for all coronary interventions, as part of RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) registry (26). On February 16, 2003, sirolimus-eluting stents were replaced by paclitaxel-eluting stents (Taxus Express2, Boston Scientific, Natick, Massachusetts) as the default stent, as part of the T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) registry (27). For evaluation of long-term outcomes, this DES group was compared with a historical cohort who received BMS in the unprotected LM trunk before April 2002 (n = 79).

In this study, the decision to intervene in the patients with PCI was based on a consensus reached during a multidisciplinary medical surgical conference (the so-called heart-team conference) involving surgeon, interventionalist, and referring physician (28), except for patients who presented with ST-segment elevation myocardial infarction (STEMI), considering the emergent character of the clinical presentation. All procedures were performed according to standard clinical guidelines at the time. All patients were pretreated with 300 mg of clopidogrel. At least 1 month of clopidogrel treatment (75 mg/day) was recommended for patients treated with BMS. Clopidogrel was prescribed for at least 3 months for patients with DES. Life-long aspirin therapy was recommended in all patients.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CABG = coronary artery bypass graft
CI = confidence interval
DES = drug-eluting stent(s)
HR = hazard ratio
LM = left main
MACCE = major adverse cerebrovascular cardiac event
MACE = major adverse cardiac events
PCI = percutaneous coronary intervention
QCA = quantitative coronary angiography
STEMI = ST-segment elevation myocardial infarction
TVR = target vessel revascularization
ULMCA = unprotected left main coronary artery disease

QCA analysis. To assess the bifurcation angle between the left anterior descending and left circumflex arteries, 3-dimensional quantitative coronary angiography (QCA) analyses were performed by 2 observers blinded to the patient data and clinical outcomes. A validated program was used to reconstruct 3-dimensional images from 2 different projections at least 30° apart from each other (CardiOp-B system version 2.1.0.151, Paieon Medical Ltd., Park Afek, Israel) (29–31). Separate 3-dimensional angiographic images were constructed for systolic and diastolic phases. The bifurcation angle was defined as the angle between the left anterior descending and left circumflex arteries (32). In cases where the separate projections were not available, 2-dimensional bifurcation software (CAAS version 5.6, Pie Medical, Maastricht, the Netherlands) was used to calculate bifurcation angle (33). In primary PCI cases where TIMI (Thrombolysis In Myocardial

Infarction) flow grade was 0 or 1 pre-procedure, the cineangiography following the first balloon angioplasty was analyzed for the determination of the angle.

SYNTAX score. Two analysts blinded to patient characteristics and clinical outcomes reviewed the angiograms to calculate the SYNTAX score (22,23). In case of disagreement, the opinion of a third observer was obtained and the final decision was made by consensus. Each coronary lesion producing >50% luminal obstruction in vessels >1.5 mm was separately scored and added to provide the overall SYNTAX score. The SYNTAX score was calculated using dedicated software that integrates the following: 1) the number of lesions with their specific weighting factors based on the amount of myocardium distal to the lesion according to the score of Leaman et al. (34); and 2) the morphologic features of each single lesion (35,36). The reproducibility of the SYNTAX score was recently reported (22).

Clinical follow-up. Survival data for all patients were obtained from municipal civil registries on a yearly basis. A questionnaire was subsequently sent to all living patients with specific enquiries on rehospitalization and major adverse cardiac events (MACE). As the principal regional cardiac referral center, most repeat revascularization (either percutaneous or surgical) is normally performed at our institution and recorded prospectively in our database. For patients who suffered an adverse event at another center, medical records or discharge letters from the other institutions were systematically reviewed. General practitioners and referring physicians were contacted for additional information if necessary. Causes of death were obtained from medical records when they happened during hospitalization, and otherwise from the Central Bureau of Statistics, The Hague, the Netherlands (37,38). Causes of death were classified according to the International Classification of Diseases and Related Health Problems-10th Revision. For the present analysis, death from ischemic heart disease (I-20 to I-25), sudden cardiac death (I-46), sudden death undefined (R-96), or death from heart failure (I-50) were considered to be cardiac. Death from cancer was defined as any death from malignant neoplasm (C-009 to C-97). All the remaining deaths were classified as being due to other causes, and no further distinction was made. In this study, there was no mandatory angiographic follow-up.

End point definitions. The primary end point was a patient-oriented composite defined as all-cause death or any myocardial infarction (MI) or any revascularization (all surgical and percutaneous, target lesion, target vessel, and non–target vessel revascularization) according to the Academic Research Consortium definitions (39). The secondary end point was the device-oriented composite end point defined as cardiac death, MI in the target vessel territory, or a target lesion revascularization. In addition, each individual component end point was analyzed in a nonhierarchical way. Definite stent thrombosis was also considered as a separate secondary end point.

Myocardial infarction included periprocedural MI (diagnosed by a rise in creatine kinase-myocardial band fraction of 3 times the upper limit of normal), reinfarction (defined as recurrence of symptoms together with ST-segment elevation or new left bundle branch block and an increase in cardiac enzymes following stable or decreasing values), or spontaneous MI (diagnosed by any rise in creatine kinase-myocardial band fraction above the upper limit of normal) (40). Target lesion revascularization was defined as a repeat revascularization of in-stent or within 5 mm proximal or distal to the stent implanted in the index procedure (41). Target vessel revascularization (TVR) was defined as any revascularization in the same epicardial vessel treated in the index procedure. Definite stent thrombosis was defined as TIMI flow grade 0 or 1 or the presence of a flow-limiting thrombus, accompanied by acute symptoms, irrespective of whether there had been an intervening reintervention (42). The timing of stent thrombosis was categorized as early (within 30 days after implantation), late (between 30 days and 1 year), or very late (more than 1 year) (39).

Statistical analysis. Continuous variables are presented as mean ± SD, whereas categorical variables are expressed as percentages. Comparisons among groups were performed by the independent t test for continuous variables and Pearson chi-square test for categorical variables. All statistical tests were 2-tailed, and p value of <0.05 was considered as statistically significant. The incidence of events over time was studied with the use of the Kaplan-Meier method, whereas log-rank tests were applied to evaluate differences between the current cohort and the historical control. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Cox regression models were built to elucidate independent predictors of clinical end points. Significant variables in univariate analysis ($p < 0.1$) were selected to put in the multivariate model. The following pre-procedural variables were included in the initial univariate analysis: gender, diabetes, current smoking habit, hypertension, hypercholesterolemia, age, previous history of myocardial infarction or PCI, SYNTAX score, EuroSCORE, shock at entry, clinical presentation, and bifurcation angle. Clinical presentation (STEMI, unstable angina or non-STEMI, and stable angina) was coded as a categorical variable. Bifurcation angle was partitioned according to tertiles (lowest tertile as a reference). The results are presented as adjusted hazard ratios (HR) with 95% confidence intervals (CI). Statistical analysis was performed with SPSS version 16 for windows (SPSS Inc., Chicago, Illinois).

Results

Baseline and procedural characteristics. The baseline and procedural characteristics of the patients are shown in Table 1.

Table 1. Baseline Characteristics

	Current Cohort With DES (n = 148)	Historical Cohort With BMS (n = 79)	p Value
Demographics			
Age, yrs	64.9 ± 12.1	65.1 ± 11.2	0.96
Men	108 (73)	49 (62)	0.10
Diabetes	24 (16.2)	15 (19)	0.59
Hypertension	61 (41)	34 (43)	0.89
Hypercholesterolemia	80 (54)	34 (43)	0.13
Family history of coronary artery disease	47 (32)	15 (19)	0.04
Current smoking	27 (18)	14 (18)	1.00
Previous PCI	32 (22)	25 (32)	0.11
Previous MI	49 (33)	24 (30)	0.77
Additive EuroSCORE	4.26 ± 3.54	4.37 ± 3.57	0.82
SYNTAX score	39.4 ± 22.9	36.8 ± 24.6	0.96
LVEF, %	45.3 ± 13.6	41.8 ± 16.9	0.48
Presentation			
STEMI	36 (24.3)	22 (27.8)	0.64
Stable angina	60 (40.5)	30 (33.3)	0.78
Unstable angina/non-STEMI	52 (35.1)	27 (34.2)	1.00
Shock at entry	13 (8.8)	6 (7.6)	1.00
Pre-procedural quantitative angiographic analysis			
Bifurcation angle in diastole, °	94.1 ± 25.5	89.5 ± 25.3	0.29
Bifurcation angle in systole, °	84.9 ± 26.6	81.42 ± 23.8	0.42
Minimal lumen diameter, mm	1.09 ± 0.32	1.08 ± 0.27	0.92
Reference vessel diameter, mm	3.35 ± 2.49	3.31 ± 0.36	0.69
Procedural characteristics			
Number of implanted stents	3.08 ± 0.37	2.85 ± 0.47	<0.0001
Total stented length per patient	59.9 ± 40.4	42.4 ± 28.4	<0.0001
Average stent diameter	3.08 ± 0.37	3.52 ± 0.47	<0.0001
Clopidogrel duration in month	7.53 ± 5.32	5.27 ± 4.86	0.01
IVUS use	48 (32)	34 (43)	0.15
Stenting strategy			
Provisional	114 (77)	70 (89)	0.07
Culotte	13 (9)	1 (1)	
T-stenting	15 (10)	8 (10)	
Crush stenting	4 (3)	0	
Kissing technique	2 (1)	0	
Post-procedural bifurcation angle			
Bifurcation angle in diastole, °	85.1 ± 24.8	84.2 ± 25.9	0.83
Bifurcation angle in systole, °	80.0 ± 23.7	76.7 ± 21.2	0.38

Values are expressed as n (%) or mean ± SD.

BMS = bare-metal stents; DES = drug-eluting stents; EuroSCORE = European System for Cardiac Operative Risk Evaluation; IVUS = intravascular ultrasound; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; SYNTAX = Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

The mean age of the patients was 64.9 years old, 16.2% of the patients had diabetes, and 33% had previous history of MI. Approximately one-quarter of patients presented with STEMI, and 8% presented with severe hemodynamic compromise at entry. The average additive EuroSCORE and SYNTAX score was 4.26 and 39.4, respectively.

Clinical outcomes. Clinical follow-up was available in all patients, with a median duration of follow-up of 1,473 days (interquartile range: 1,182 to 1,848 days) for patients alive at follow-up. Hierarchical count of adverse events is shown in Table 2. Patient-oriented composite increases from 32.4% at 1 year to 51.4% at 4 years (Δ58%), which was mainly driven by an increase in all-cause mortality from 19.6% at 1 year to 33.1% at 4 years, a relative increase of 68%. There was 1 case of definite late stent thrombosis at 1 year, and there was 1 case of definite very late stent thrombosis at 4 years.

Kaplan-Meier estimates of clinical end points are presented in Figures 1A to 1C. At 4 years, the cumulative

Table 2. Hierarchical Count of Patient-Oriented Composite After DES Implantation Compared With the Historical Cohort With BMS

	Current Cohort With DES (n = 148)	Historical Cohort With BMS (n = 79)	p Value
1 yr			
All-cause death	29 (19.6)	23 (29.1)	0.14
Any MI	2 (1.4)	1 (1.3)	1.00
Any revascularization	17 (11.5)	10 (12.7)	1.00
Patient-oriented composite	48 (32.4)	34 (43)	0.15
2 yrs			
All-cause death	35 (23.6)	27 (34.2)	0.11
Any MI	3 (2.0)	1 (1.3)	1.00
Any revascularization	19 (12.8)	11 (13.9)	0.84
Patient-oriented composite	57 (38.5)	39 (49.4)	0.12
3 yrs			
All-cause death	41 (27.7)	29 (36.7)	0.18
Any MI	3 (2.0)	1 (1.3)	1.00
Any revascularization	23 (15.5)	11 (13.9)	0.85
Patient-oriented composite	67 (45.3)	41 (51.9)	0.4
4 yrs			
All-cause death	49 (33.1)	30 (38)	0.47
Any MI	3 (2.0)	1 (1.3)	1.00
Any revascularization	24 (16.2)	11 (13.9)	0.7
Patient-oriented composite	76 (51.4)	42 (53.2)	0.9

Event rates were calculated as number of events divided by total number of patients and therefore differ from those in the figures, where event rates were calculated by Kaplan-Meier methods. In this table, comparison was made with the chi-square or Fisher exact test.

Abbreviations as in Table 1.

incidence of all-cause death, MI, any revascularization, and patient-oriented composite were 35.6% (95% CI: 27.3% to 43.8%), 3.8% (95% CI: 0.5% to 7.1%), 25.2% (95% CI: 16.9% to 33.6%), and 54.4% (95% CI: 45.8% to 63.1%), respectively. Cardiac mortality, all-cause mortality, and any revascularization rate relatively increased from 1 year to 4 years by Δ68%, Δ82%, and Δ49%, respectively, whereas the changes in target lesion revascularization and MI was less increased from 1 year to 4 years (Δ5% and Δ28%, respectively) (Figs. 1A and 1B). In summary, the device-oriented and patient-oriented composite increased from 1 year to 4 years by Δ56% and Δ68%, respectively (Fig. 1C). If stratified by the presentation with STEMI versus others (non-STEMI, unstable angina, and stable angina), the patient-oriented composite was higher in STEMI patients (68.6%) than the others (49%, $p < 0.001$), also the device-oriented composite, all-cause death, and cardiac death were higher in the STEMI patients than the others (53% vs. 30%, $p < 0001$; 55% vs. 29%, $p < 0.001$; 48% vs. 16%, $p < 0.001$) (Fig. 2A). With stratification according to the tertiles of EuroSCORE (<2, ≥2 and <5, ≥5), the patient-oriented composite was higher in the high tertile (76.8%) than in the low (41.2%, log-rank $p < 0.001$) or intermediate tertiles (51.8%, log-rank $p < 0.001$) (Fig. 2B). If stratified according to type of DES (Cypher and Taxus), the patient-oriented composite was

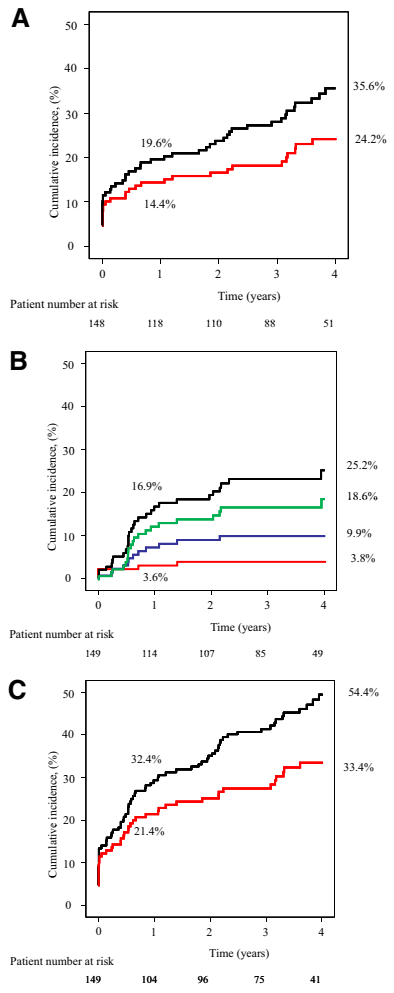


Figure 1. Kaplan-Meier Estimates After Implantation of DES

(A) Kaplan-Meier estimates demonstrate all-cause mortality **(black line)** and cardiac mortality **(red line)**. **(B)** Kaplan-Meier estimates present the end points of any myocardial infarction **(red line)**, target lesion revascularization **(blue line)**, target vessel revascularization **(green)**, and any revascularization including target and non–target vessel revascularization **(black line)**. **(C)** Kaplan-Meier estimates show the composite end point **(red line)** of cardiac mortality, myocardial infarction in the stented vessel territory, or target lesion revascularization and the composite end point **(black line)** of all-cause mortality, any myocardial infarction, or any revascularization. DES = drug-eluting stent.

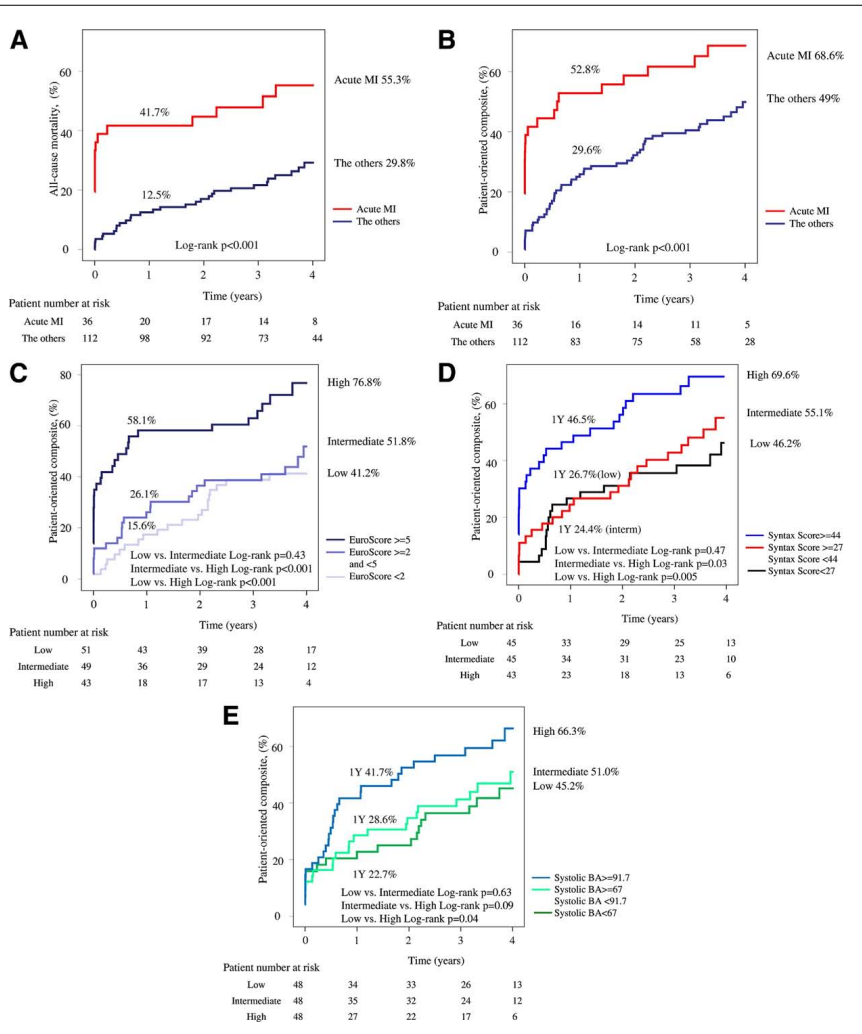


Figure 2. Kaplan-Meier Estimates After Implantation of DES With Stratification of Subgroups

(A) All-cause mortality and **(B)** patient-oriented composite end point (all-cause mortality, any myocardial infarction [MI]), or any revascularization) according to a presentation of ST-segment elevation myocardial infarction or the others (stable angina, non–ST-segment elevation myocardial infarction, or unstable angina). Patient-oriented composite end point stratified by **(C)** tertile division of EuroSCORE (European System for Cardiac Operative Risk Evaluation) with cutoff values of 2 and 5 and **(D)** tertiles of SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score of the current cohort (cutoff values of 27 and 44). **(E)** The patient-oriented composite end points were classified according to tertiles of bifurcation angle (BA) between the left anterior descending and circumflex arteries (cutoff values of 67 and 91.7). Abbreviations as in Figure 1.

53.8% in Cypher and 54.8% in paclitaxel-eluting stent (p = 0.83), whereas the all-cause mortality was 30.8% versus 36.5%, respectively (p = 0.56).

Comparison with historical cohort. Patient demographics in the historical control (n = 79) were similar to the current cohort except for a lower frequency of family history of coronary artery disease (32% vs. 19%, p = 0.04), reflecting that the changes in clinical practice, number of implanted stents, stent length, stent diameter, and clopidogrel duration are higher in the current cohort than in the historical control group.

Figure 3 shows the Kaplan-Meier estimates of all-cause mortality and the patient-oriented composite end point of the current cohort with DES and the historical control with BMS. At 1 year, the rate of all-cause death (current cohort 19.6% vs. historical cohort 29.1%) and patient-oriented composite (32.4% vs. 43.0%) was lower in the current cohort than in the historical cohort (Figs. 3A and 3B). At 4 years the events rate, however, became comparable between the 2 groups (all-cause mortality: 38.0 vs. 35.6%, p = 0.48; patient-oriented composite: 54.4 vs. 53.2%, p = 0.64) as a result from a late increase of events in the current cohort. Kaplan-Meier estimate before 2 years yielded a numerically higher patient-oriented composite end point in the historical cohort (log-rank p = 0.1), whereas landmark analysis (Fig. 3B) after the second year demonstrated a significantly higher event rate in the current cohort than the historical cohort (log-rank p = 0.02).

SYNTAX score. In the current cohort, the SYNTAX score ranged from 7 to 104 with median of 33.0. If the SYNTAX score is divided into tertiles, the cutoff values were 27.0 and 44.0. The Kaplan-Meier curves of device-oriented composite stratified by these tertiles of SYNTAX score are presented in Figure 2C. The 4-year event rates were 46.2%, 55.1%, and 69.6% in low, intermediate, and high tertile groups, respectively. High tertile group demonstrated significantly higher event rates than intermediate tertile (log-rank p = 0.03) and low tertile (log-rank p = 0.005) groups did.

Three-dimensional QCA analysis. Three-dimensional QCA analysis was feasible in only 50.7% of patients due to the unavailability of 2 separate angiographic views of more than 30° that is a prerequisite for 3-dimensional QCA; in the remaining patients, 2-dimensional QCA was performed. The results are shown in Table 1. In the patient receiving DES, the Kaplan-Meier curves of patient-oriented composite were separated according to the tertiles of systolic bifurcation angle (high >91.7, intermediate ≤91.7 and >67, low ≤67) as shown in Figure 2E. High tertile group demonstrated higher patient-oriented composite at 4 years (66.3%) than the intermediate (51.0%) and the low (45.2%) groups did (log-rank high vs. low: p = 0.04; high vs. intermediate: p = 0.09).

Predictor of adverse events. Table 3 shows the results of the univariate and multivariate analyses to identify the predictors for all-cause mortality and for patient-oriented composite. Bifurcation angle did not remain as a significant predictor of either all-cause mortality or patient-oriented end point in the multivariate analysis.

At 1 year, multivariate analysis demonstrated that EuroSCORE, age, shock at entry, and SYNTAX score were independent predictors for all-cause mortality and patient-

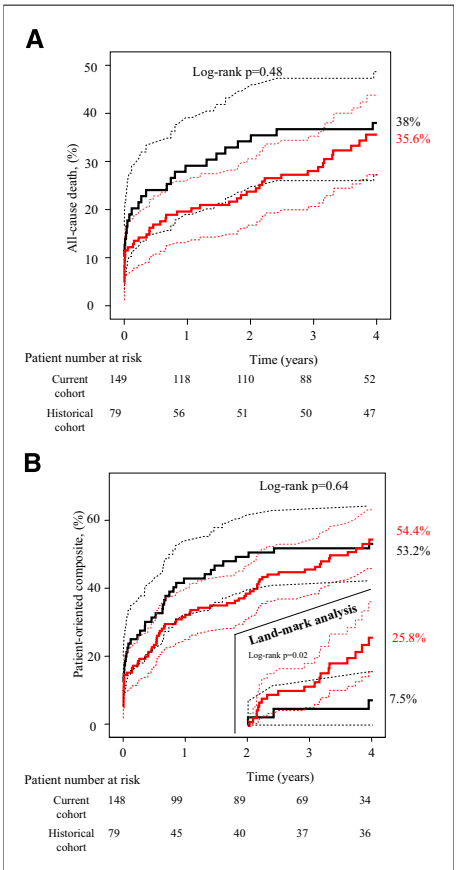


Figure 3. Kaplan-Meier Estimates of DES and BMS Cohorts

Kaplan-Meier estimates of the current cohort treated with drug-eluting stent **(red line)** or historical cohort treated with bare-metal stent **(black line).** All-cause mortality is demonstrated in **(A)**, whereas **(B)** demonstrates patient-oriented composite end point (all-cause mortality, any myocardial infarction, or any revascularization) with a landmark analysis more than 2 years after implantation. **Dotted lines** = 95% confidence interval. BMS = bare-metal stent(s); other abbreviations as in Figure 1.

Table 3. Univariate and Multivariate Analysis for Predictors of All-Cause Mortality and Patient-Oriented Composite After DES Implantation in the Left Main Trunk

	All-Cause Mortality				Patient-Oriented Composite			
	Univariate Hazard Ratio (95% CI)	p Value	Multivariate Hazard Ratio (95% CI)	p Value	Univariate Hazard Ratio (95% CI)	p Value	Multivariate Hazard Ratio (95% CI)	p Value
1-year outcome								
EuroSCORE	1.26 (1.17–1.36)	<0.001	1.24 (1.11–1.39)	<0.001	1.19 (1.12–1.26)	<0.001	1.13 (1.03–1.24)	0.009
Presentation of STEMI*	6.77 (3.56–18.66)	<0.001			4.38 (2.08–9.23)	<0.001		
Age	1.06 (1.02–1.09)	0.003	1.05 (1.01–1.10)	0.03	1.05 (1.03–1.08)	<0.001	1.04 (1.01–1.08)	0.009
Shock at entry	8.56 (3.83–19.1)	<0.001	4.21 (1.50–1.82)	0.006	8.26 (4.09–16.68)	<0.001	5.46 (2.35–12.69)	<0.001
SYNTAX score†	1.35 (1.17–1.56)	<0.001	1.23 (1.06–1.42)	0.006	1.27 (1.13–1.42)	<0.001	1.15 (1.02–1.30)	0.03
Hypercholesterolemia	0.33 (0.15–0.73)	0.006			0.43 (0.24–0.76)	0.004		
Hypertension	0.41 (0.18–0.96)	0.04	0.34 (0.13–0.88)	0.03	0.45 (0.24–0.84)	0.01		
4-year outcome								
EuroSCORE	1.19 (1.12–1.26)	<0.001	1.13 (1.03–1.24)	0.009	1.16 (1.09–1.24)	<0.001	1.09 (1.02–1.16)	0.02
Presentation of STEMI*	4.38 (2.08–9.23)	<0.001			3.42 (1.69–6.94)	0.001		
Age	1.05 (1.03–1.08)	<0.001	1.04 (1.01–1.08)	0.009	1.04 (1.01–1.070)	0.004		
Shock at entry	8.26 (4.09–16.68)	<0.001	5.46 (2.35–12.69)	<0.001	4.61 (2.21–6.61)	<0.001	2.74 (1.30–5.80)	0.008
SYNTAX score†	1.27 (1.13–1.42)	<0.001	1.15 (1.02–1.30)	0.03	1.22 (1.08–1.38)	0.001	1.12 (1.01–1.24)	0.4
High bifurcation angle‡					1.99 (0.93–4.26)	0.075		

Univariate or multivariate hazard ratios were calculated by Cox regression models.
*Stable angina used as a reference. †Each 10-point increase of SYNTAX score. ‡Low tertile bifurcation angle used as a reference.
Abbreviations as in Table 1.

oriented composite. At 4 years, in the final multivariate models, age, shock at entry, the SYNTAX score and EuroSCORE remained as independent predictors for all-cause mortality, whereas EuroSCORE, shock at entry, and SYNTAX score were identified as independent predictors for patient-oriented composite.

Discussion

The main findings of the current study are the following: 1) At 4-year follow-up after DES implantation in ULMCA, patient-oriented composite end point was 51.4% with a 58% relative increase of events from 1 year to 4 years. 2) A landmark analysis of the last 2 years of follow-up indicated a higher composite end point for the current cohort with DES when compared with the historical cohort with BMS (25% vs. 8%, p = 0.02). 3) EuroSCORE and SYNTAX score were independent predictors for both all-cause mortality and the patient-oriented composite end point up to 4 years, whereas pre-procedural bifurcation angle between the left circumflex and left anterior descending arteries was not.

According to the current guidelines of the European Society of Cardiology and the American Heart Association and American College of Cardiology guidelines (40,43), the presence of a stenosis in the LMCA is a class IIB or III indication for PCI unless the patient is not eligible for CABG in presence of extreme comorbidities and STEMI. In the recent U.S. criteria for appropriateness of revascularization, percutaneous treatment of LM disease is considered "inappropriate" (2). In European daily practice, however, 4.6% of patients treated in the catheterization lab have LM stenosis, and 58% of those are treated by percutaneous means (44).

Up to now, 2 randomized trials have been performed to compare CABG and PCI using DES in patients undergoing treatment for LM disease. In the LE MANS (Left Main Coronary Artery Stenting) study by Buszman et al. (10), PCI was associated with a lower 30-day risk of major adverse cerebrovascular cardiac event (MACCE) (p = 0.03) and had comparable 1-year mortality or MACCE to surgery. In the more recent SYNTAX trial (9), which randomized 1,800 patients with 3-vessel or LM coronary artery disease to either CABG or PCI, the use of PCI at 1 year was associated with safety end points (death, cerebrovascular accident, and MI) but a higher rate of MACCE than CABG, due to a significantly higher rate of revascularization. However, in the subgroup of patients with LM disease with an average SYNTAX score of 28.1, PCI and CABG were associated with similar MACCE rates at 1 year (PCI 15.8% vs. CABG 13.6%). In the DES cohort of the present study, the 1-year all-cause mortality and revascularization rate of patients treated with DES (19.6% and 16.9%, respectively) were higher than rates reported in the LM subgroup of the randomized cohort in the SYNTAX trial (4.2% and 12.0%, respectively). This is likely due to the high-risk nature of our all-comers registry (e.g., including 24% STEMI patients with a mean EuroSCORE of 4.26 and an average SYNTAX score of 39.4).

In this analysis, we selected a patient-oriented composite end point as a primary end point, because it represents the most critical clinical approach for a population undergoing a new form of treatment. The Academic Research Consortium defined 2 methodological approaches to report clinical follow-up: 1) the device-oriented composite end point; and 2) the patient-oriented composite end point. The device-oriented approach put the accent on the efficiency and efficacy of a new device, therefore, focusing on the cardiac death, MI, and reintervention related to the device. The patient-oriented end point is a follow-up, which specifically considers the welfare of the patient, and includes all-cause death, any MI, and any revascularization.

In the current analysis, we entered only the pre-procedural parameters in the multivariate analysis and excluded the procedural variables such as angulation after stenting, technique of stenting, number of stent, length of stent, and so forth, because they are factors reflecting the treatment modalities rather than the anticipated prognosis of the treatment. Parameters describing lesion characteristics were also excluded because they were incorporated in the SYNTAX score: for example, Medina classification, chronic total occlusion, American College of Cardiology/American Heart Association lesion classification (45).

Long-term outcomes after PCI in the LM population are limited. Park et al. (46) reported the 3-year safety composite rate (death, Q-wave MI, or stroke) of 9.7% with TVR rate of 12.6%. Vaquerizo et al. (12) demonstrated the device-oriented composite end point at 2 years of 12.6% after UCLMA stenting with paclitaxel-eluting stents in 291 patients from multicenter registry. In these registries, the patients with acute MI or cardiogenic shock were excluded; whereas in our registry, such patients were included and had a negative impact on clinical outcomes. Also, frequent use of intravascular ultrasound might contribute the relatively lower mortality in the Korean registry than in our European registry (46). In one of largest "all-comer" DELFT (Drug-Eluting Stent for Left Main) registries exclusively using DES in ULMCA with 3-year complete follow-up, Meliga et al. (15) demonstrated 3-year MACE rate (a composite of cardiac mortality, MI, and TVR) of 26.5%, cardiac mortality of 9.2%, and TVR of 14.2%. If the same composite definition were applied to the present study, the 3-year MACE rate in our study (26.0%) would be similar to the DELFT registry (26.5%). Wood et al. (47) reported a long-term outcome of 100 patients with high surgical risk after PCI. All-cause mortality at 28 months was 21%; event-free survival was around 65% at 27 months (47).

In the current study, the baseline patient demographics are comparable between the current and the historical cohorts. Although the anatomical complexity reflected by SYNTAX score was comparable between the 2 cohorts (the current cohort 39.4 vs. the historical control 36.8, $p = 0.96$), the cohort with DES was more aggressively treated than the historical cohort with BMS, as indicated by a higher incidence of bifurcation stenting (48% vs. 57%, $p = 0.04$), by a larger number of stents implanted (2.85 ± 0.47 vs. 3.08 ± 0.37), and by on average a longer stented length (42.4 ± 28.4 mm vs. 59.9 ± 40.4 mm).

The source of our concerns is the increase of the patient-oriented composite in the DES group between 2 and 4 years, which was significantly higher than in the historical cohort of BMS, and the long-term safety of DES in the treatment of patients with ULMCA remains an unanswered question. One possible explanation for unfavorable follow-up could be the occurrence of occult stent thrombosis. Occlusion of the LM trunk with thrombus is likely to be lethal. Thus, patients can present with sudden and/or out-of-hospital death rather than with angiographically proven stent thrombosis. The very late stent thrombosis presenting with out-of-hospital death, however, can be undiagnosed and under-reported. The cause of death was obtained from the civil registry, and it is up to the general practitioners to classify the cause of mortality according to International Classification of Diseases and Related Health Problems-10th Revision unless the patient passed away in the hospital. Therefore, no attempt was made to impute death to possible or probable stent thrombosis.

In the large multicenter registry ($n = 731$) by Chieffo et al. (17), the cumulative incidence of stent thrombosis at 29.5 months after LM stenting was reported to be 0.95% for definite stent thrombosis and 2.7% for possible stent thrombosis. In DELFT registry (15) ($n = 358$) at ≥3-year follow-up, the incidence of definite, probable, and possible stent thrombosis were 0.6%, 1.1%, and 4.4%. In ISAR-LEFT MAIN (Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions) trial (48) ($n = 607$), the 2-year rate of definite or probable stent thrombosis was about 0.5% to 1.0%. In a series of high surgical risk patients, Wood et al. (47) reported a 5% possible stent thrombosis presenting as sudden death. Taking into account the late increase in mortality shown in our study, follow-up extending beyond 3 years is warranted for patients receiving DES in the setting of ULMCA.

The bifurcation angle has been shown to relate not only to the difficulty level of the procedure but is also associated with intermediate outcomes. Dzavik et al. (19) reported that a bifurcation angle ≥50 was an independent predictor of MACE at 1 year after bifurcation crush stenting in 133 patients. In 132 patients receiving Cypher stents in bifurcations excluding LM lesions, Adriaenssens et al. (49) reported that increasing bifurcation angles is an independent predictor of binary restenosis (HR: 1.53 [95% CI: 1.04 to 2.23] per 10° increase in angulation) after culotte stenting. The worse outcomes in high-angulated bifurcation lesions might be the result of the adjacent presence of low and high shear stress found in bifurcation lesions. High

shear stress possibly stimulates platelet activation and aggregation, and low shear stress might enhance deposition of platelets. This mechanism can be potentially exaggerated in higher bifurcation angles. Furthermore, when bifurcation stenting is performed in high-angle lesions, the stent will likely not appose against the wall of bifurcation (50), especially in the ostium of the left circumflex artery (20). In the present study, however, we observed that the bifurcation angle between the left anterior descending and left circumflex arteries was not an independent predictor for adverse events, although there is a weak statistical association with 4-year composite end points in the univariate analysis (HR: 1.99 [95% CI: 0.93 to 4.26], p = 0.07).

Study limitations. This study has several limitations. This is a single center, observational study that included a modest number of patients. The results of this landmark analysis (reporting a higher event rate in patients treated with DES compared with BMS after 2 years) would need to be confirmed in a larger study. In addition, the low 1-year mortality rate compelled us to include only 2 or 3 independent variables in the Cox regression model, resulting in overfitting of the model. Confounding factors, such as procedural variables, might have been overlooked. Although baseline characteristics were similar in the historical BMS and current DES groups, some procedural variables were in fact different and as a result might have influenced outcomes.

Conclusions

Our study reports a late increase in adverse events up to 4 years, which warrants careful follow-up of the patient receiving DES in the LM trunk. The SYNTAX score and EuroSCORE can be considered important components of risk stratification.

Acknowledgments

The authors would like to acknowledge the senior cardiologists involved in the PCI procedures: E. McFadden, MD, PhD; P. J. de Feyter, MD, PhD; P. P. T. de Jaegere, MD, PhD; S. H. Hofma, MD, PhD; E. Regar, MD, PhD; G. Sianos, MD, PhD; P. C. Smits, MD, PhD; H. Duckers, MD, PhD; M. J. van der Ent, MD, PhD; W. J. van der Giessen, MD, PhD; R. J. van Geuns, MD, PhD; and C. A. van Mieghem, MD, PhD.

Reprint requests and correspondence: Prof. Patrick W. Serruys, Thoraxcenter, Ba-583, 's Gravendijkwal 230, Rotterdam 3015 CE, the Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl.

REFERENCES

1. Proudfit WL, Shirey EK, Sones FM Jr. Distribution of arterial lesions demonstrated by selective cinecoronary arteriography. Circulation 1967;36:54–62.
2. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 appropriateness criteria for coronary revascularization: a report by the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol 2009;53:530–53.
3. Taggart DP, Kaul S, Boden WE, et al. Revascularization for unprotected left main stem coronary artery stenosis stenting or surgery. J Am Coll Cardiol 2008;51:885–92.
4. Daemen J, Boersma E, Flather M, et al. Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. Circulation 2008;118:1146–54.
5. Chieffo A, Stankovic G, Bonizzoni E, et al. Early and mid-term results of drug-eluting stent implantation in unprotected left main. Circulation 2005;111:791–5.
6. Park SJ, Kim YH, Lee BK, et al. Sirolimus-eluting stent implantation for unprotected left main coronary artery stenosis: comparison with bare metal stent implantation. J Am Coll Cardiol 2005;45:351–6.
7. Valgimigli M, Malagutti P, Aoki J, et al. Sirolimus-eluting versus paclitaxel-eluting stent implantation for the percutaneous treatment of left main coronary artery disease: a combined RESEARCH and T-SEARCH long-term analysis. J Am Coll Cardiol 2006;47:507–14.
8. Valgimigli M, van Mieghem CA, Ong AT, et al. Short- and long-term clinical outcome after drug-eluting stent implantation for the percutaneous treatment of left main coronary artery disease: insights from the Rapamycin-Eluting and Taxus Stent Evaluated At Rotterdam Cardiology Hospital registries (RESEARCH and T-SEARCH). Circulation 2005;111:1383–9.
9. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.
10. Buszman PE, Kiesz SR, Bochenek A, et al. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. J Am Coll Cardiol 2008;51:538–45.
11. Biondi-Zoccai GG, Lotrionte M, Moretti C, et al. A collaborative systematic review and meta-analysis on 1278 patients undergoing percutaneous drug-eluting stenting for unprotected left main coronary artery disease. Am Heart J 2008;155:274–83.
12. Vaquerizo B, Lefevre T, Darremont O, et al. Unprotected left main stenting in the real world: two-year outcomes of the French Left Main Taxus Registry. Circulation 2009;119:2349–56.
13. Tamburino C, Angiolillo DJ, Capranzano P, et al. Long-term clinical outcomes after drug-eluting stent implantation in unprotected left main coronary artery disease. Catheter Cardiovasc Interv 2009;73:291–8.
14. Pavei A, Oreglia JA, Martin G, et al. Long-term follow-up of percutaneous coronary intervention of unprotected left main lesions with drug eluting stents: predictors of clinical outcome. EuroIntervention 2009;4:457–63.
15. Meliga E, Garcia-Garcia HM, Valgimigli M, et al. Longest available clinical outcomes after drug-eluting stent implantation for unprotected left main coronary artery disease: the DELFT (Drug Eluting stent for LeFT main) Registry. J Am Coll Cardiol 2008;51:2212–9.
16. Palmerini T, Marzocchi A, Tamburino C, et al. Temporal pattern of ischemic events in relation to dual antiplatelet therapy in patients with unprotected left main coronary artery stenosis undergoing percutaneous coronary intervention. J Am Coll Cardiol 2009;53:1176–81.
17. Chieffo A, Park SJ, Meliga E, et al. Late and very late stent thrombosis following drug-eluting stent implantation in unprotected left main coronary artery: a multicentre registry. Eur Heart J 2008 June 18 [E-pub ahead of print].
18. Kim YH, Dangas GD, Solinas E, et al. Effectiveness of drug-eluting stent implantation for patients with unprotected left main coronary artery stenosis. Am J Cardiol 2008;101:801–6.

19. Dzavik V, Kharbanda R, Ivanov J, et al. Predictors of long-term outcome after crush stenting of coronary bifurcation lesions: importance of the bifurcation angle. Am Heart J 2006;152:762–9.
20. Murasato Y. Impact of three-dimensional characteristics of the left main coronary artery bifurcation on outcome of crush stenting. Catheter Cardiovasc Interv 2007;69:248–56.
21. Rodriguez-Granillo GA, Rosales MA, Degrossi E, Durbano I, Rodriguez AE. Multislice CT coronary angiography for the detection of burden, morphology and distribution of atherosclerotic plaques in the left main bifurcation. Int J Cardiovasc Imaging 2007;23:389–92.
22. Serruys PW, Onuma Y, Garg S, et al. Assessment of the SYNTAX score in the SYNTAX study. EuroIntervention 2009;5:50–6.
23. Sianos G, Morel M-A, Kappetein AP, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005:219–27.
24. Serruys PW, Daemen J, Morice M-C, et al. Three-year follow-up of the ARTS-II—sirolimus-eluting stents for the treatment of patients with multivessel coronary artery disease. EuroIntervention 2007;3:450–9.
25. Valgimigli M, Serruys PW, Tsuchida K, et al. Cyphering the complexity of coronary artery disease using the syntax score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. Am J Cardiol 2007;99:1072–81.
26. Lemos PA, Hoye A, Goedhart D, et al. Clinical, angiographic, and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation in complex patients: an evaluation from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) study. Circulation 2004;109:1366–70.
27. Ong AT, Serruys PW, Aoki J, et al. The unrestricted use of paclitaxel-versus sirolimus-eluting stents for coronary artery disease in an unselected population: one-year results of the Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry. J Am Coll Cardiol 2005;45:1135–41.
28. Kappetein AP, Dawkins KD, Mohr FW, et al. Current percutaneous coronary intervention and coronary artery bypass grafting practices for three-vessel and left main coronary artery disease. Insights from the SYNTAX run-in phase. Eur J Cardiothorac Surg 2006;29:486–91.
29. Dvir D, Marom H, Assali A, Kornowski R. Bifurcation lesions in the coronary arteries: early experience with a novel 3-dimensional imaging and quantitative analysis before and after stenting. EuroIntervention 2007;3:95–9.
30. Tsuchida K, van der Giessen WJ, Patterson M, et al. In vivo validation of a novel three-dimensional quantitative coronary angiography system (CardiOp-B^{TM}): comparison with a conventional two-dimensional system (CAAS II^{TM}) and with special reference to optical coherence tomography. EuroIntervention 2007;3:100–8.
31. Ramcharitar S, Daeman J, Patterson M, et al. First direct in vivo comparison of two commercially available three-dimensional quantitative coronary angiography systems. Catheter Cardiovasc Interv 2008;71:44–50.
32. Girasis C, Serruys PW, Onuma Y, et al. 3-dimensional bifurcation angle analysis in patients with left main disease a substudy of the SYNTAX Trial (SYNergy Between Percutaneous Coronary Intervention With TAXus and Cardiac Surgery). J Am Coll Cardiol Intv 2010;3:41–8.
33. Ramcharitar S, Onuma Y, Aben JP, et al. A novel dedicated quantitative coronary analysis methodology for bifurcation lesions. EuroIntervention 2008;3:553–7.
34. Leaman DM, Brower RW, Meester GT, Serruys P, van den Brand M. Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. Circulation 1981;63:285–99.
35. Ryan TJ, Faxon DP, Gunnar RM, et al. Guidelines for percutaneous transluminal coronary angioplasty. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). Circulation 1988;78:486–502.
36. Smith SC Jr., Dove JT, Jacobs AK, et al. ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines)—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1993 Guidelines for Percutaneous Transluminal Coronary Angioplasty). J Am Coll Cardiol 2001;37:2215–39.
37. World Health Organization. International Statistical Classification of Diseases and Related Health Problems. 10th revision. Geneva, Switzerland: World Health Organization, 1992.
38. Daemen J, van Twisk PH, Kukreja N, et al. The relative safety and efficacy of bare-metal and drug-eluting stents in low and high-risk patient subsets. An epidemiological analysis of three sequential cohorts of consecutive all comers (n = 6129). EuroIntervention 2009;4:464–74.
39. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
40. Smith SC Jr., Feldman TE, Hirshfeld JW Jr. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). J Am Coll Cardiol 2006;47:216–35.
41. Lemos PA, Lee CH, Degertekin M, et al. Early outcome after sirolimus-eluting stent implantation in patients with acute coronary syndromes: insights from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. J Am Coll Cardiol 2003;41:2093–9.
42. Ong AT, McFadden EP, Regar E, de Jaegere PP, van Domburg RT, Serruys PW. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. J Am Coll Cardiol 2005;45:2088–92.
43. Silber S, Albertsson P, Aviles FF, et al., on behalf of Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Eur Heart J 2005;26:804–47.
44. Onuma Y. Interventional treatment in left main disease in the era of drug-eluting stents—lessons learned from the Euro Heart Survey Programme. Abstract presented at: European Society of Cardiology. September 2, 2008; Munich, Germany.
45. Serruys PW, Onuma Y, Garg S, et al. Assessment of the SYNTAX score in the SYNTAX study. EuroIntervention 2009;5:50–6.
46. Park SJ, Kim YH, Park DW, et al. Impact of intravascular ultrasound guidance on long-term mortality in stenting for unprotected left main coronary artery stenosis. Circ Cardiovasc Interv 2009;2:167–77.
47. Wood FO, Saylors EK, Schneider JE, Jobe RL, Mann JT 3rd. Unprotected left main disease managed with drug-eluting stents: long-term outcome of 100 patients with increased surgical risk. Catheter Cardiovasc Interv 2008;71:533–8.
48. Mehilli J, Kastrati A, Byrne RA, et al. Paclitaxel- versus sirolimus-eluting stents for unprotected left main coronary artery disease. J Am Coll Cardiol 2009;53:1760–8.
49. Adriaenssens T, Byrne RA, Dibra A, et al. Culotte stenting technique in coronary bifurcation disease: angiographic follow-up using dedicated quantitative coronary angiographic analysis and 12-month clinical outcomes. Eur Heart J 2008;29:2868–76.
50. Gijsen FJ, Oortman RM, Wentzel JJ, et al. Usefulness of shear stress pattern in predicting neointima distribution in sirolimus-eluting stents in coronary arteries. Am J Cardiol 2003;92:1325–8.

Key Words: coronary disease ■ stents ■ atherosclerosis.

Chapter 8.5

Five-year clinical outcomes after coronary stenting of chronic total occlusions using sirolimus-eluting stents: Insights from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital-(RESEARCH) Registry

Catheter Cardiovasc Interv 2009; 74(7):979-986

ZJ Shen, Hector M. Garcia-Garcia, Scot Garg, Yoshi Onuma, L Schenkeveld, Ron van Domburg, Patrick W. Serruys on behalf of the Interventional Cardiologists at Thoraxcentre in 2000–2003

CORONARY ARTERY DISEASE

Original Studies

Five-Year Clinical Outcomes After Coronary Stenting of Chronic Total Occlusion Using Sirolimus-Eluting Stents: Insights From the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital—(Research) Registry

Zhu Jun Shen, MD, Hector M. García-García, MD, PhD, Scot Garg, MBChB, MRCP, Yoshinobu Onuma, MD, Lisanne Schenkeveld, MSc, Ron T. van Domburg, PhD, and Patrick W. Serruys,* MD, PhD, on behalf of the Interventional Cardiologists at Thoraxcentre in 2000–2003

Background: The use of drug eluting stents (DES) in patients with a successfully recanalized chronic total occlusion (CTO) has been associated with a significant decrease in the need for repeat revascularization, and a favorable short-term clinical outcome when compared with the use of bare metal stents (BMS). Our group, however, has previously reported similar rates of target lesion revascularisation (TLR) and major adverse cardiovascular events (MACE) at 3 years follow-up in patients with a successfully opened CTO who were treated with either a sirolimus eluting stent (SES) or a BMS. The objective of this report was to evaluate the outcomes of these patients at 5-years clinical follow-up. Methods and Results: A total of 140 (BMS 64, SES 76) patients with successfully opened CTOs were included. Seven patients died in the BMS group whilst nine patients died in the SES group ($P = 0.90$). Noncardiac death was the major component of all-cause mortality (11 noncardiac deaths vs. 5 cardiac). There were two and three myocardial infarctions (MI) in the BMS and SES group, respectively ($P = 1.0$). The composite of death and MI occurred in seven (10.9%) and eleven (14.5%) patients in the BMS and SES group, respectively ($P = 0.53$). Clinically driven TLR was performed in eight patients (12.5%) in the BMS group, and five (6.6%) in the SES group ($P = 0.26$). Non-TLR target vessel revascularization was performed in one patient in the BMS group, and four in the SES group ($P = 0.37$). The 5-year device-oriented cumulative MACE rate was 15.6% and 11.8% in the BMS and SES group, respectively ($P = 0.56$). Conclusion: In patients with a successfully treated CTO, clinical outcome after 5 years was similar between SES and BMS, however, clinically driven TLR was slightly higher in the BMS group. © 2009 Wiley-Liss, Inc.

Key words: total occlusions; percutaneous coronary intervention; angiography coronary

INTRODUCTION

Chronic total occlusions (CTO) are one of the remaining challenges for interventional cardiologists. In recent times, the use of drug eluting stents (DES) in patients with a successfully recanalized CTO has been associated with a significant decrease in the need for repeat revascularization, and a favorable short-term clinical outcome when compared with the use of bare metal stents (BMS) [1–4]. However, despite this, in the DES era, CTOs still remain an independent predictor of restenosis [5].

Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands

Conflict of interest: Nothing to report.

*Correspondence to: Patrick W. Serruys, MD, PhD, Thoraxcenter, Ba-583, 's-Gravendijkwal 230, Rotterdam 3015- CE, The Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl

Received 23 June 2009; Revision accepted 14 July 2009

DOI 10.1002/ccd.22230
Published online 14 September 2009 in Wiley InterScience (www.interscience.wiley.com).

Our group has previously reported the 6 month and 3 year angiographic and clinical outcomes of the use of the sirolimus-eluting stent (SES) in patients with a CTO. At 6-months, there was a marked reduction in the rate of restenosis, and major adverse cardiac events (MACE) with the use of SES, compared with BMS [6]; however, this difference was not maintained at 3-year follow-up [7]. The long-term outcomes (>3 years) in patients with a CTO successfully treated with DES have not yet been reported in the literature, and therefore, the aim of this study was to compare the 5 year clinical outcomes of patients with a CTO treated with a SES, to historical controls treated with BMS.

MATERIALS AND METHODS

From April 2002 to February 2003, SES (Cypher®; Cordis Corporation, Warren, NJ) was the first choice device of for all percutaneous coronary intervention (PCI) performed in our institution as part of the Rapamycin Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. The RESEARCH registry was a prospective single center study set-up with the aim of evaluating the safety and efficacy of SES in the "real world," following the dynamic registry design described by Rothman et al [8,9]. The major reasons for not using a SES stent were as follows: unavailability of an appropriately sized SES; or participation in another ongoing study [8].

For this substudy, all consecutive patients with a successfully treated CTO were enrolled irrespective of clinical presentation or CTO lesion characteristics. During the study period, 76 patients with a CTO were treated with SES, and these patients were compared with a cohort of consecutive CTO patients, who were treated with BMS in the year preceding the introduction of SES.

Angioplasty Procedure

Patients in both cohorts were treated by the same group of operators, who were permitted to use whatever equipment was available at the time of the procedure. The PCI technique was left to the operator's discretion, apart from the choice of stent. All patients were pretreated with 300 mg of clopidogrel, which was then prescribed at a dose of 75 mg/day for at least 1 month in the pre-SES phase and 6 months in the SES phase. All patients were advised to maintain aspirin (≥80 mg/day) lifelong.

Clinical Endpoint Definition

A CTO was defined as a total (100%) occlusion of the coronary artery, with the absence of intraluminal antegrade blood flow for at least 3 months. The duration of the occlusion was assessed by using clinical data such as follows: (i) the date of any previous Q wave myocardial infarction (MI) in the vascular territory severed by the occluded artery, (ii) any previous angiography or angioplasty procedures, and (iii) the duration of angina symptoms or deterioration in symptoms. Complete revascularization was defined as the treatment of all coronary lesions greater than 50% diameter stenosis at time of the index CTO procedure, and/or those planned for treatment within 4 weeks of the CTO procedure. Primary endpoint was the device-oriented MACE, calculated as recommended by Academic Research Consortium (ARC) consensus [10]: defined as cardiac death, MI (not clearly attributable to a nontarget vessel), and clinically driven target lesion revascularization (TLR). The secondary endpoints were the following: all-cause death, cardiac death, death from cancer, MI, clinically driven TLR, non-TLR target-vessel revascularization (TVR), stent thrombosis, and the patient-oriented MACE which was defined as a composite of all-cause mortality, any MI (including nontarget vessel territory), and any repeat revascularization (including all target and nontarget vessel).

The cause of death was classified according to the International Classification of Disease and Related Health Problems, 10th Revision (ICD-10). For the present analysis, death from ischemic heart disease (ICD I-20-I-25), sudden cardiac death (I-46), sudden death undefined (R-96), or death from heart failure (I-50) were all considered to be cardiac. Death from cancer was defined as any death from malignant neoplasms (C-00-C-97). All the remaining deaths were classified as being due to other causes and no further distinctions were made. MI and TLR definitions follow the ARC consensus on stent trials [10]. Clinically driven TLR was defined as treatment with either PCI or CABG of the same lesion, or a 5 mm margin proximal or distal to the index lesion, which on follow-up angiography had a percent diameter stenosis ≥50% and one of the following occurs: (1) a positive history of recurrent angina pectoris, presumably related to the target vessel; (2) objective signs of ischemia at rest (ECG changes) or during an exercise test (or equivalent), presumably related to the target vessel; or (3) abnormal results of any invasive functional diagnostic test (e.g., Doppler flow velocity reserve, fractional flow reserve); or a TLR or TVR with a diameter stenosis ≥70% even in the absence of the aforementioned ischemic signs or symptoms. TVR was defined as repeat PCI, or coronary artery bypass grafting (CABG) of a lesion in the same epicardial vessel. Stent thrombosis was defined angiographically as thrombosis with TIMI grade 0 or 1 flow, or the presence of a flow limiting thrombus

Catheterization and Cardiovascular Interventions DOI 10.1002/ccd.
Published on behalf of The Society for Cardiovascular Angiography and Interventions (SCAI).

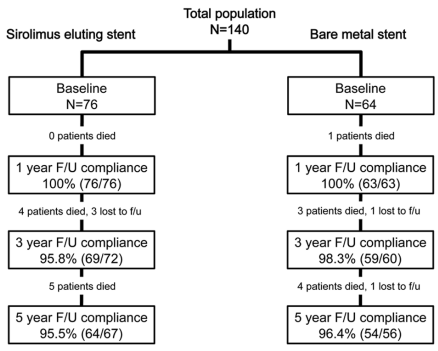


Fig. 1. Flow chart of clinical follow-up.

within a stent accompanied by acute symptoms, irrespective of whether there had been an intervening intervention [11].

Five-Year Follow-Up Data

Patients were followed-up prospectively, and MACE-free survival was evaluated using both municipal civil registries, and questionnaires sent to patient's homes inquiring about postdischarge repeat coronary interventions (either percutaneous or surgical) and MI. Our institution is the tertiary referral center for our region; therefore, most repeat interventions were performed at our institution. The medical records and discharge letters of those patients who had an MI or a reintervention at another center were requested and systematically reviewed. Local cardiologists or general practitioners were also contacted as necessary. Causes of death were obtained from medical records where death occurred during hospitalization or from the Central Bureau of Statistics, The Hague, The Netherlands.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation and were compared by the Student's *t* test. Categorical variables are presented as counts and percentages and compared by the Pearson Chi-Square test or Fisher's exact test. The cumulative incidence of adverse events was estimated according to the Kaplan–Meier method, and curves were compared using the log-rank test. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. The Cox regression analysis was used to find the independent predictors of MACE, and those variables with a P value of <0.10 in univariate analysis were included in the multivariate model. The final results are presented as adjusted hazard ratios (HRs). A P value of <0.05 was considered significant, and all tests were two-tailed. Data were analyzed with SPSS version 16.0 software (SPSS, Chicago, IL).

TABLE I. Baseline Patient Characteristics

	BMS $n = 64$	SES $n = 76$	P value
Mean age (years)	60.3 ± 10.5	61.0 ± 10.6	0.69
Male sex (%)	75.0	65.8	0.24
Current smoker (%)	29.7	18.4	0.12
Diabetes mellitus (%)	4.7	14.5	0.06
Hypertension (%)	34.4	44.7	0.21
Hypercholesterolemia (%)	59.4	65.8	0.43
Previous MI (%)	53.1	48.7	0.60
Previous CABG (%)	0	2.6	0.19
Target vessel (%)			0.25
LAD	27.5	43.4	
LCX	27.5	19.7	
RCA	44.9	36.8	
Vessel diseased (%)			0.41
1	42.2	48.7	
2	43.8	32.9	
3	14.1	18.4	
Mean number of stents	2.6 ± 0.8	3.1 ± 1.2	0.07
Mean diameter of the stent (mm)	3.1 ± 0.58	2.8 ± 0.3	<0.001
Total length of stent (mm)	45.5 ± 26.6	56.5 ± 30.8	0.027

SES, sirolimus-eluting stents; BMS, bare metal stents; MI, myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; LAD, left anterior descending artery; LCX, circumflex artery; RCA, right coronary artery.

RESULTS

Study Population

From March 2001 to February 2003, 186 consecutive patients had a CTO which was initially attempted by PCI and of these 140 (75.3%) were successfully recanalized and used in the final analysis: 64 patients were treated with BMS and 76 patients were treated with SES. The flow of patients through the registry is shown in Fig. 1. The overall mean age was 60.7 ± 10.2 years (range 40–82), and 70% of patients were male. Seventy-one patients (50.7%) had had a previous MI whilst two patients had a previous CABG. There were no significant differences between the groups with respect to baseline patient characteristics (Table I). Although not statistically significant, there were a greater number of patients in the SES group who were diabetic and had treatment in the left anterior descending artery (LAD). As defined by protocol, duration of clopidogrel treatment was longer in SES group

TABLE II. Clinical Events Upto 5-Year Follow-Up

	BMS $n = 64$	SES $n = 76$	P value
Patient-oriented composite MACE			
Hierarchical ranking n (%)			
All-cause death	7 (10.9)	9 (11.8)	0.87
Any MI	0 (0)	2 (2.6)	
Reintervention	7 (10.9)	8 (10.5)	
MACE	14 (21.9)	19 (25.0)	0.71
Device-oriented composite MACE			
Hierarchical ranking n (%)			
Cardiac death	2 (3.1)	3 (4.3)	1.0
MI	0 (0)	2 (2.6)	
Reintervention			
Clinically driven TLR	8 (12.5)	4 (5.3)	
MACE	10 (15.6)	9 (11.8)	0.56
Non-Hierarchical ranking n (%)			
Death	7 (10.9)	9 (11.8)	0.87
Cardiac death	2 (3.1)	3 (4.3)	1.0
Cancer death	3 (4.7)	5 (6.6)	0.73
Other causes of death	2 (3.1)	1 (1.3)	0.59
MI	2 (3.1)	3 (4.3)	1.0
Definite stent thrombosis	0 (0)	1 (2.6)	1.0
Reintervention			
Clinically driven TLR-PCI	7 (10.9)	4 (5.3)	0.26
Clinically driven TLR-CABG	1 (1.6)	1 (1.3)	0.37
Clinically driven non-TLR, TVR-PCI	1 (1.6)	3 (4.3)	
Clinically driven non-TLR, TVR-CABG	0 (0)	1 (2.6)	

SES, sirolimus-eluting stents; BMS, bare metal stents; MI, myocardial infarction; MACE, major adverse cardiac events; TLR, target lesion revascularization; TVR, target-vessel revascularization; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

(6 months) when compared with the BMS group (1 month).

Angiographic and Procedural Variables

The target vessel was the LAD in 56 patients, the circumflex artery in 34, and the right coronary artery in 57. There was no significant difference in the number of diseased vessels in both groups ($P = 0.41$); 106 (75.7%) patients had single vessel disease, and 23 (16.4%) and 11(7.8%) had two vessel disease and three vessel disease, respectively. A staged PCI was performed in those with multivessel disease such that within 1 month of the index CTO PCI, 136 patients (97.1%) were fully revascularised. Of the four patients who were not completely revascularised, three had disease in small vessels which were not suitable for PCI and one had a CTO which was attempted unsuccessfully. None of these patients experienced a MACE event out to 5-years follow-up.

Stent length as well as stent number was larger in SES group when compared with BMS group ($P = 0.027$ for stent length and $P = 0.07$ for stent number) (Table I). Glycoprotein IIb/IIIa inhibitors were used in 15 cases.

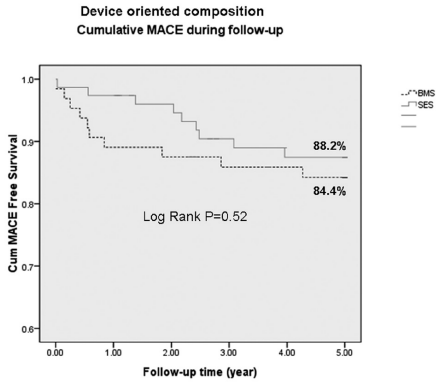


Fig. 2. Kaplan-Meier curve of device-oriented MACE between BMS and SES.

Five-Year Clinical Follow-Up

In total, five patients (three SES group vs. two BMS group) were lost to follow-up (four of them emigrated from this country); four patients were lost after 1-year and one patient was lost after 3-years follow-up. All other patients were evaluated after an overall follow-up of 5 years, with no difference in 5 years follow-up rate between the study groups (95.5% versus 96.4% in BMS and SES, $P = 1.0$). In SES group, 59% and 40% had angiographic follow-up at 6 months and 3 years, respectively. There was no routine follow-up coronary angiography at 5 years.

Composite clinical endpoint. Table II shows the clinical events with and without hierarchical ranking at 5-year follow-up. Device-oriented composite MACE and patient-oriented composite MACE were calculated separately. The overall patient-oriented composite 5-year cumulative MACE rate for this group of CTO patients was 23.6%, with 21.9% and 25.0% in BMS group and SES group, respectively ($P = 0.71$); the device-oriented cumulative MACE rate was 15.6% and 11.8% in the BMS and SES group, respectively ($P = 0.56$) (Fig. 2).

Death. all-cause death occurred in 16 patients, seven in the BMS group and nine in the SES group, ($P = 0.87$). Five patients died from a definite cardiac event, with two and three in BMS group and SES group, respectively ($P = 1.0$). Eight patients died of cancer, and three died from other causes. Noncardiac death

Catheterization and Cardiovascular Interventions DOI 10.1002/ccd.
Published on behalf of The Society for Cardiovascular Angiography and Interventions (SCAI).

TABLE III. MI Events During Follow-Up

Patient no.	Stent	MI timing after index PCI (days)	Angiogram	Outcome
1	BMS	1	Periprocedural MI due to another vessel intervention	Died
2	SES	11	Subacute ST	re-PCI
3	BMS	669	No	Died
4	SES	904	Periprocedural MI during another vessel reintervention	Recovered
5	SES	975	Yes, PCI done in another vessel	Recovered, died 1 year later

PCI, percutaneous coronary intervention; BMS, bare metal stents; SES, sirolimus eluting stents; MI, myocardial infarction; ST, stent thrombosis.

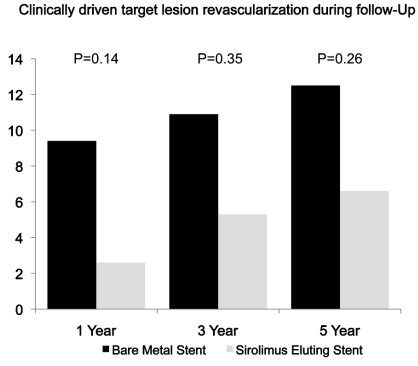


Fig. 3. Cumulative rate of clinically driven target lesion revascularization during follow-up. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

was the main component of all-cause mortality (11/16, 68.8%).

Myocardial infarction and stent thrombosis. There were five MIs during the follow-up period (Table III); with two and three MIs occurring in the BMS and SES group, respectively ($P = 1.0$). One patient in BMS group had successful recanalization of the right coronary artery, but experienced a spiral dissection of the left main stem during PCI of the LAD. This was successfully treated with stenting, but the patient died 48 hr later following a MI and cardiogenic shock. Another patient in BMS group had an MI 669 days after the index PCI and died of the event. Three patients treated with SES had an MI: one had an MI within 11 days of the index PCI which was a definite stent thrombosis confirmed on angiogram; one patient had an MI after 975 days due to a de novo lesion, which was confirmed on angiography and successfully treated with PCI; the final patient experienced a periprocedural MI during a nontarget vessel reintervention at 904 days follow-up. The composite of death and MI occurred in seven (10.9%) and eleven (14.5%) patients in the BMS and SES group, respectively ($P = 0.53$).

TABLE IV. Cumulative Clinically Driven Target Lesion Revascularisation (TLR) Events During Follow-Up Between Sirolimus-Eluting Stents and Bare Metal Stents

Clinically driven TLR n [(%); years]	Bare metal stent ($n = 64$)	Sirolimus-eluting stent ($n = 76$)	P value
1	6 (9.4)	2 (2.6)	0.14
3	7 (10.9)	4 (5.3)	0.35
5	8 (12.5)	5 (6.6)	0.26

Clinically driven TLR and non-TLR TVR. Non-hierarchical clinically driven TLR during the follow-up period is shown in Fig. 3 and Table IV. Clinically driven TLR was performed in eight patients in the BMS and five in the SES group ($P = 0.26$); while non-TLR TVR was performed in one patients in the BMS and four in the SES group ($P = 0.37$). In the first year, there was more clinically driven TLR in the BMS group (6/64 vs. 2/76, $\Delta = 6.8\%$, $P = 0.14$), however, by year three, the difference in clinically driven TLR between the two groups had became smaller (7/64 vs. 4/76, $\Delta = 5.6\%$, $P = 0.35$). Between years three and five, there was no further progression in the difference between the two groups ($\Delta = 5.9\%$).

Multivariate analysis for MACE. Age and diabetes were the only variables in the univariate analysis with a $P < 0.10$ and were subsequently included in the Cox regression analysis. The only variable that was an independent predictor of device-oriented MACE was age (HR 1.06, 95%C.I.: 1.01 to 1.11, $P = 0.014$). The stent type was not an independent predictor of device-oriented MACE (HR 0.68, 95% C.I.: 0.36 to 1.28, $P = 0.23$).

DISCUSSION

This study reports the longest available clinical follow-up of DES in the management of patients with a successfully recanalized CTO. The main finding of this study is that, at 5-years follow-up, clinical outcome is similar between SES and BMS, however, clinically driven TLR is slightly less in patients with CTOs treated with SES.

Long-Term Follow-Up in Patients Treated With PCI for CTO Lesion

The initial success of the PCI procedure for a CTO lesion may influence long-term outcomes. PCI for a CTO is associated with lower procedural success when compared with nonocclusive lesions, with the inability to cross a CTO with a wire as the commonest cited reason for procedural failure [12]. There is a wide variation in published rates of procedural success rate, which vary from 54–90% [13] of all attempted PCI for CTOs, this variability reflecting differing definitions of what constitutes a CTO, duration of occlusion, operator experience and technique, available technology, and case selection [12]. Furthermore, improvements in technology, technique, and understanding of the underlying disease processes have lead to increasing confidence in tackling CTOs resulting in more complex lesions being attempted. Fortunately, this has not increased procedural complications but may account for a recent plateau in CTO success rates [14,15].

Studies have shown conflicting long-term results when comparing outcomes depending on the success of the CTO procedure. Suero et al. demonstrated significant long-term survival advantages in those with a successful procedure [14,16], however, more recently Prasad et al., who reviewed outcomes over 25-years in a single center, reported that an unsuccessful procedure was not an independent predictor of long-term mortality [15]. de Labriolle et al. also reported that patients with a successful CTO procedure had no survival or MI benefit compared with those with an unsuccessful procedure [17].

Previously, our institution has published a success rate for recanalization of a CTO of ~65% during the period 1992–2002. Furthermore, during this period, we demonstrated that in patients with a successfully opened CTO, there is a benefit in 5-year long-term survival (93.5% vs. 88.0%, $P = 0.02$) and MACE-free survival (5.5% vs. 14.8%, $P < 0.001$) [16].

Clinical Follow-Up of Successfully Recanalized CTO Patients

In contrast to procedural success, the use of DES in patients with a CTO lesion has only been shown to lead to improved short-term outcomes. The only randomized data is limited to the PRISON II study, which compared outcomes in 200 patients with a CTO randomized to either BMS or SES. The results showed a significant reduction in TLR, binary restenosis, and target-vessel failure at 6 months follow-up with the use of SES compared with BMS [18]; however, a major limitation of the study was that only 45% of patients had an occlusion which was greater than 3-month-old. Numerous registries report similar results at 12-months follow-up [3,4,19], whilst De Felice showed that DES leads to a significant reduction in TLR when compared with BMS out to 18-months follow-up. In addition, they showed that the use of DES is a significant independent protective factor of MACE (HR 0.16; 95% CI 0.05–0.52, $P = 0.002$) [20]. No studies as yet have demonstrated a reduction in all-cause death or MI.

Long-term studies with the use of DES compared with BMS are limited; our group previous published 3-year clinical outcomes showing no difference in MACE rate and TLR [7]. In addition, Han et al. recently reported the results of 1,184 patients treated with BMS and DES demonstrating an improved outcome with DES out to 5-years [21]. The 3-year results of the PRISON II study also show benefit with SES in terms of reduced rates of TLR and MACE, with similar results in the CTO subgroup [22].

The greatest benefit of DES in treating coronary lesions is decreasing the need for repeat revascularization, however, there are always concerns about a late catch-up in restenosis amongst those treated with DES[23–25]. Data currently available for the first generation of DES, namely the Cypher® SES and TAXUS® paclitaxel eluting stent (Boston Scientific, Natick), demonstrate that in patients without a CTO, the initial benefits of DES in terms of lower TLR are preserved out to 5-year follow-up [26–28]. At 4-year follow-up intravascular ultrasound in SES-treated patients has shown that there is a continuous late chronic artery response, however, no significant increase in the neointimal volume was observed from 2 to 4 years [29]. This late gradual increase in neointima with SES did not convert into clinical events.

In this study of CTO patients treated with SES, at the end of 5-year follow-up, there was a nonsignificant reduction in non-hierarchical clinically driven TLR. There was also no difference in device oriented or patient-oriented MACE rate. In addition, no significant difference in clinically driven TLR was observed during either short or long-term; this may be the result of the small numbers of patients in this study, such that it was underpowered for this endpoint.

The difference in clinically driven TLR rate between BMS and SES was 6.8%, 5.6%, and 5.9% at 1-, 3-,

and 5-year follow-up. Therefore, no obvious "catch up" in TLR rate was observed between year 1 and 3, whilst the difference did not increase between years 3 and 5.

Safety Concerns of DES in CTO Patients

There have been concerns regarding the long-term use of DES with respect to very late stent thrombosis[8]. In our institution, we have previously reported a significantly higher rate of definite ST with DES compared with BMS out to 4 years follow–up (3.3% vs. 1.6%, $P = 0.002$) [30]. Conversely, three recent reports from trials of PES and SES reported no difference in rates of death, MI, and ST at 5-year follow-up compared with BMS [26–28]. In patients with a CTO treated with SES, the rate of ST was 1.3% lower than the overall population treated with a DES (3.3%). Similarly, in previous studies of CTO lesions, there have been few reported stent thrombosis events. These low rates may be secondary to the small numbers of patients which have been recruited, or the definition used for ST. In this study, ST was defined on the basis of symptoms, however, it has been shown that reocclusion of a successfully opened CTO can be asymptomatic, and therefore, ST may be under reported. For example, Valenti et al. reported a rate of reocclusion in successfully opened CTO lesions of 11.2% in the 282 patients who return for angiographic follow-up at 8 months, however, only three patients experienced an MI [31], the rate of stent thrombosis was not reported.

LIMITATIONS

This study has the following limitations. First of all, it is a nonrandomized, observational study having a historical cohort as a control; additionally, the patient numbers are relatively small to enable any definite conclusions to be drawn.

Our data is limited by not being collected by direct patient contact. We relied on patient's to remember all pertinent information. It is conceivable in view of the long duration of follow-up that some events were forgotten or omitted, although the annual follow-up ensured that this was kept to a minimum.

Another limitation is the comparison between two stents over different time periods, which makes it impossible to control for changes in procedural technique and developments in available equipment, such as lower profile balloons and stents.

Stent length was longer in SES group when compared with BMS group, but nevertheless despite this, no other difference in the two stents was noted. Restenosis or even reocclusion within the CTO lesion may not have been clinical apparent, which makes the evaluation of clinical events at follow-up less sensitive and also affects the assessment of the status of the stent. Angiogram follow-up was shown to bias data assessment during clinical follow-up in the TAXUS IV trial [32]. In our study, 59% and 40% of the SES group had angiographic follow-up at 6 months and 3 years, respectively, and therefore, our results may be biased by this angiographic follow-up which occurred only in one group.

CONCLUSIONS

After 5-years, clinically driven TLR was slightly lower in the SES group when compared with a consecutive historical control BMS group but no benefit exists in terms of reducing rates of MI, death, and MACE when compared with the use of BMS.

ACKNOWLEDGMENTS

The authors like to acknowledge the senior cardiologists involved in the PCI procedures:

E. McFadden, MD, PhD; P.J. de Feyter, MD, PhD; P.P.T. de Jaegere, MD, PhD; S.H. Hofma, MD, PhD; E.Regar, MD, PhD; G. Sianos, MD, PhD; P.C. Smits, MD, PhD; H. Duckers, MD, PhD; M.J. van der Ent, MD, PhD; W.J. van der Giessen, MD, PhD; and C.A. van Mieghem, MD.

REFERENCES

1. Ge L, Iakovou I, Cosgrave J, et al. Immediate and mid-term outcomes of sirolimus-eluting stent implantation for chronic total occlusions. Eur Heart J 2005;26:1056–1062.
2. Biondi-Zoccai GG, Sangiorgi GM, Antoniucci D, Grube E, Di Mario C, Reimers B, Tamburino C, Agostoni P, Cosgrave J, Colombo A. Testing prospectively the effectiveness and safety of paclitaxel-eluting stents in over 1000 very high-risk patients: Design, baseline characteristics, procedural data and in-hospital outcomes of the multicenter Taxus in Real-life Usage Evaluation (TRUE) Study. Int J Cardiol 2007;117:349–354.
3. Werner GS, Krack A, Schwarz G, Prochnau D, Betge S, Figulla HR. Prevention of lesion recurrence in chronic total coronary occlusions by paclitaxel-eluting stents. J Am Coll Cardiol 2004; 44:2301–2306.
4. Nakamura S, Muthusamy TS, Bae JH, Cahyadi YH, Udayachalerm W, Tresukosol D. Impact of sirolimus-eluting stent on the outcome of patients with chronic total occlusions. Am J Cardiol 2005;95:161–166.
5. Elezi S, Kastrati A, Wehinger A, Walter H, Schuhlen H, Hadamitzky M, Dirschinger J, Neumann FJ, Schomig A. Clinical and angiographic outcome after stent placement for chronic coronary occlusion. Am J Cardiol 1998;82:803–806.
6. Hoye A, Tanabe K, Lemos PA, et al. Significant reduction in restenosis after the use of sirolimus-eluting stents in the treatment of chronic total occlusions. J Am Coll Cardiol 2004;43: 1954–1958.

7. Garcia-Garcia HM, Daemen J, Kukreja N, Tanimoto S, Van Mieghem CA, Van Der Ent M, Van Domburg RT, Serruys PW. Three-year clinical outcomes after coronary stenting of chronic total occlusion using sirolimus-eluting stents: Insights from the rapamycin-eluting stent evaluated at Rotterdam cardiology hospital-(RESEARCH) registry. Catheter Cardiovasc Interv 2007;70:635–639.
8. Lemos PA, Serruys PW, Van Domburg RT, et al. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": The Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. Circulation 2004;109:190–195.
9. Rothman K, Greenland S. Cohort studies. In: Rothman K, Greenland S, editors. Modern Epidemiology. Lippincott Williams: Philadelphia; 1998. pp 78–80.
10. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: A case for standardized definitions. Circulation 2007;115:2344–2351.
11. Song W, Lee J, Kim H, Shin J, Oh D, Tio F, Wong SC, Hong MK. A new percutaneous porcine coronary model of chronic total occlusion. J Invasive Cardiol 2005;17:452–454.
12. Stone GW, Reifart NJ, Moussa I, et al. Percutaneous recanalization of chronically occluded coronary arteries: A consensus document: Part II. Circulation 2005;112:2530–2537.
13. He LQ, Ma CS, Nie SP, et al. Impact of drug-eluting stents on transferring treatment with coronary surgical revascularization among patients initially admitted to department of internal medicine. Zhonghua Yi Xue Za Zhi 2007;87:1518–1522.
14. Suero JA, Marso SP, Jones PG, Laster SB, Huber KC, Giorgi LV, Johnson WL, Rutherford BD. Procedural outcomes and long-term survival among patients undergoing percutaneous coronary intervention of a chronic total occlusion in native coronary arteries: A 20-year experience. J Am Coll Cardiol 2001;38:409–414.
15. Prasad A, Rihal CS, Lennon RJ, Wiste HJ, Singh M, Holmes DR. Trends in outcomes after percutaneous coronary intervention for chronic total occlusions: A 25-year experience from the Mayo Clinic. J Am Coll Cardiol 2007;49:1611–1618.
16. Hoye A, Van Domburg RT, Sonnenschein K, Serruys PW. Percutaneous coronary intervention for chronic total occlusions: The Thoraxcenter experience 1992–2002. Eur Heart J 2005;26:2630–2636.
17. De Labriolle A, Bonello L, Roy P, et al. Comparison of safety, efficacy, and outcome of successful versus unsuccessful percutaneous coronary intervention in "true" chronic total occlusions. Am J Cardiol 2008;102:1175–1181.
18. Suttorp MJ, Laarman GJ, Rahel BM, et al. Primary Stenting of Totally Occluded Native Coronary Arteries II (PRISON II): A randomized comparison of bare metal stent implantation with sirolimus-eluting stent implantation for the treatment of total coronary occlusions. Circulation 2006;114:921–928.
19. Hoye A, Ong ATL, Aoki J, Van Mieghem CAG, Rodriguez Granillo GA, Valgimigli M, Sianos G, Mcfadden E, Van Der Giessen WJ, De Feyter PJ. Drug-eluting stent implantation for chronic total occlusions: Comparison between the Sirolimus- and Paclitaxel-eluting stent. EuroIntervention 2005;1:193–197.
20. De Felice F, Fiorilli R, Parma A, Nazzaro MS, Dibra A, Musto C, De Santis A, Violini R. Clinical outcome of patients with diabetes mellitus and chronic total occlusion treated with drug-eluting stents. J Invasive Cardiol 2008;20:651–654.
21. Han YL, Zhang J, Li Y, Wang SL, Jing QM, Yi XH, Ma YY, Luan B, Wang G, Wang B. Long-term outcomes of drug-eluting versus bare-metal stent implantation in patients with chronic total coronary artery occlusions. Chin Med J (Engl) 2009;122:643–647.
22. Rahel BM, Laarman GJ, Kelder JC, Ten Berg JM, Suttorp MJ. Three-year clinical outcome after primary stenting of totally occluded native coronary arteries: A randomized comparison of bare-metal stent implantation with sirolimus-eluting stent implantation for the treatment of total coronary occlusions (Primary Stenting of Totally Occluded Native Coronary Arteries [PRISON] II study). Am Heart J 2009;157:149–155.
23. Serruys PW. SPIRIT 2 study: A clinical evaluation of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions. Late-breaking clinical trials 3. American College of Cardiology Scientific Sessions/i2 Summit-SCAI Annual Meeting, Chicago. March 31, 2008.
24. Stone GW, Midei M, Newman W, et al. Randomized comparison of Everolimus-eluting and Paclitaxel-eluting stents. Two-year clinical follow-up from the clinical evaluation of the Xience V Everolimus Eluting Coronary Stent System in the treatment of patients with de novo native coronary artery lesions (SPIRIT) III trial. Circulation 2009;119:680–686.
25. Park DW, Hong MK, Mintz GS, et al. Two-year follow-up of the quantitative angiographic and volumetric intravascular ultrasound analysis after nonpolymeric paclitaxel-eluting stent implantation: Late "catch-up" phenomenon from ASPECT Study. J Am Coll Cardiol 2006;48:2432–2439.
26. Morice MC, Serruys PW, Barragan P, Bode C, Van Es GA, Stoll HP, Snead D, Mauri L, Cutlip DE, Sousa E. Long-term clinical outcomes with sirolimus-eluting coronary stents: Five-year results of the RAVEL trial. J Am Coll Cardiol 2007;50:1299–1304.
27. Grube E, Dawkins K, Guagliumi G, et al. TAXUS VI final 5-year results: A multicentre, randomised trial comparing polymer-based moderate-release paclitaxel-eluting stent with a bare metal stent for treatment of long, complex coronary artery lesions. EuroIntervention 2009;4:572–577.
28. Weisz G, Moses JW. New percutaneous approaches for chronic total occlusion of coronary arteries. Expert Rev Cardiovasc Ther 2007;5:231–241.
29. Aoki J, Abizaid AC, Serruys PW, Ong AT, Boersma E, Sousa JE, Bruining N. Evaluation of four-year coronary artery response after sirolimus-eluting stent implantation using serial quantitative intravascular ultrasound and computer-assisted grayscale value analysis for plaque composition in event-free patients. J Am Coll Cardiol 2005;46:1670–1676.
30. Daemen. J, Twisk P-Hv, Kukreja N, Domburg RTv, Boersma E, Jaegere Pd, Serruys PW. The relative safety and efficacy of bare-metal and drug-eluting stents in low and high-risk patient subsets. An epidemiological analysis of three sequential cohorts of consecutive all comers (n = 6129). EuroIntervention 2008;4:464–474.
31. Valenti R, Migliorini A, Signorini U, Vergara R, Parodi G, Carrabba N, Cerisano G, Antoniucci D. Impact of complete revascularization with percutaneous coronary intervention on survival in patients with at least one chronic total occlusion. Eur Heart J 2008;29:2336–2342.
32. Pinto DS, Stone GW, Ellis SG, et al. Impact of routine angiographic follow-up on the clinical benefits of paclitaxel-eluting stents: Results from the TAXUS-IV trial. J Am Coll Cardiol 2006;48:32–36.

PART IX

Summary and Conclusions

Discussion/Summary

The revascularization of patients with increasing co-morbidities and complex coronary artery disease has reiterated the importance of appropriate risk stratification. Accordingly, after establishing which patients should be revascularized, and discussing contemporary and future coronary stents, this thesis examined the current and newly developed tools available to stratify risk in those patients undergoing percutaneous coronary intervention (PCI). Finally after assessing the impact of clinical factors, coronary anatomy, and coronary stents on clinical outcomes, this thesis concluded by reporting the long-term outcomes of patients with complex disease treated with PCI using drug-eluting stents (DES).

The need for revascularization

In recent times there have been improvements in clinical outcomes following percutaneous or surgical revascularization, which coupled with the increasing number of institutions performing revascularization procedures, has resulted in an overall lower threshold for referring stable patients for mechanical revascularization. The expense of this however is that patients are often on sub-optimal medical therapy, or given insufficient time to stabilize on prescribed medication, before being referred for revascularization. Revascularization procedures carry an inherent procedural risk, and should ultimately only be performed in those patients in whom they improve symptoms and/or prognosis. Chapter 1 of this thesis contains a key discussion comparing the three available treatments for patients with stable angina: medical therapy, PCI and coronary artery bypass surgery (CABG). Importantly in 2007, the COURAGE trial provided data with respect to the benefits of optimal medical therapy in patients with stable angina, challenging the concept that all patients with obstructive coronary lesions require revascularization. As highlighted in the chapter however, there was a clear sub-set of patients (those with objective evidence of ischaemia) who did benefit from mechanical revascularization. Ultimately in those patients in whom revascularization is required, the age old discussion between whether patients should be treated with PCI or CABG still rages on. Fortunately however, the developments and advances in percutaneous techniques, which are discussed extensively in Part 2, have helped to confine a large quantity of this debate to history, and the discussion is now really only applicable to those patients with the most severe disease as explored in Parts 2, 3 and 8.

Coronary stents

Part 2 of this thesis provided an in-depth review of current and future coronary stents, indicating that although there are clear benefits from using DES over historical bare metal stents, their use is not without some associated degree of risk. The first and second generation DES have all been studied in randomized trials, which have now reported long-term data, however most of these studies employed restrictive inclusion criteria, hindering extrapolation of the results to routine practice. There were safety concerns following widespread use of the early DES, which precipitated the development of newer stent platforms, polymer technologies and anti-proliferative agents. Many of these newer stents are still in the early phases of assessment; however results thus far appear promising. Importantly, and as reported later in Chapter 7, some of these newer stents are being assessed in

unrestricted patient populations, enabling the study results to be more reflective of the stent's performance when used in everyday practice. Unfortunately many questions still remain unanswered with respect to one of the major risks of stent implantation – stent thrombosis. Chapter 2.3 included an in-depth discussion of the most pertinent issues regarding this undesirable and frequently fatal complication. It is hoped that an improved understanding of these factors will ultimately facilitate identification of optimal preventive strategies.

Individualized assessment for mechanical revascularization

Part 3 provided an overview of the risk models that are available to physicians to assist in the assessment of patients in need of mechanical revascularization. As discussed, current risk models rely on the assessment of clinical factors, or the complexity of coronary artery disease, whilst the more recently proposed models, which are explored in Part 4, rely on a combination of these two types of variables. Ultimately this chapter reiterates that patients in need of revascularization require an individual assessment, and moreover the modality of revascularization needs to be tailored after considering the patient's co-morbidities, disease complexity, and personal preferences, whilst also taking into account the expertise of the physicians/surgeons performing the procedure.

Tools for risk assessment in patients treated by PCI

Continuing on from the general discussion on risk models, Part 4 examined in greater detail those models which are appropriate for patients having PCI. In particular the benefits of using the euroSCORE and the SYNTAX score, together with an assessment of the SYNTAX score's reproducibility are examined in Chapters 4.1 to 4.3, respectively. Following this were a series of studies assessing the utility of using newer risk models in a variety of different patient populations. The ACEF score, which represents a simple clinical based score that has only previously been validated in patients undergoing CABG, was shown to be effective in risk stratifying patients undergoing PCI who were enrolled in the all-comers LEADERS study. Intuitively, a complete assessment of risk should consider both clinical and angiographic characteristics. Consequently the combined scores – Clinical SYNTAX score, and Global Risk Classification – have been developed, both of which utilise a clinical based score such as the ACEF score or the euroSCORE, in combination with the SYNTAX score. As reported in Chapter 4.5, the first assessment of the Clinical SYNTAX score in a population of patients with complex coronary artery disease demonstrated its superior discriminatory ability for endpoints such as mortality, and major adverse cardiovascular and cerebrovascular events when compared to the SYNTAX score alone. Similarly, in a population of patients with unprotected left main disease, the Global Risk Classification was also shown to be superior to using the SYNTAX score alone. All-in-all these series of studies provide evidence to support the use of combination risk models, as opposed to models assessing only clinical or angiographic characteristics.

Influence of clinical factors on clinical outcomes

Part 5 reported that patients presenting for PCI in contemporary practice continue to have a high prevalence of risk factors, some of which are uncontrolled, and consequently these patients represent a sizable population in whom secondary preventative therapy should be aimed and/or optimized. Further to that, although patient age is included as a variable in the euroSCORE and ACEF

score, in the complex patients enrolled in the ARTS-II study, age was only shown to influence outcomes in patients treated by CABG, and not PCI. In contrast, body mass index was shown to be an independent risk factor for major adverse cardiovascular events amongst the patients enrolled in the LEADERS study.

Influence of coronary anatomy on clinical outcomes

Part 6 comprised a number studies which for the most part assessed the impact of coronary artery complexity, as quantified using the SYNTAX score, on clinical outcomes at 1- and 5-year follow-up. As reported in Chapters 6.1-6.6, the use of the SYNTAX score enables the identification of those patients treated with PCI who are at highest risk of mortality and/or major adverse cardiovascular events during follow-up. Two additional applications of the SYNTAX score are explored in Chapters 6.5 and 6.7. Specifically in Chapter 6.5 the SYNTAX score was shown to have a potential role in the assessment of stent performance, whilst in Chapter 6.7 it was shown to be useful in assisting in the selection of patients with complex disease who did not require complete revascularization. Overall this series of studies indicate that the complexity of coronary anatomy has a major influencing role on the outcomes of patients having PCI. Although this is perhaps obvious, there has not been any previous method of accurately quantifying the complexity of coronary disease, stressing the need for the SYNTAX score, and reaffirming its role in the risk stratification of patients having PCI.

Influence of stent type on clinical outcomes

The earlier discussion on coronary stents highlighted the important differences between different DES. Furthermore, as previously discussed in Part 2, it was the safety concerns with first generation DES that prompted the development of newer coronary stents. In Chapter 7 early and late outcome data from randomised studies which have assessed the performance of these newer DESs are presented, demonstrating that overall stent type does have an impact on clinical outcomes. Currently there are only limited long-term data from randomised trials comparing first and second generation DES. This deficiency reiterates the significance of the first two chapters of Part 7, which confirmed the favourable outcomes, at 3- and 4-year follow-up, following use of the second generation everolimus-eluting stent. There are several second generation DES, and Chapter 7.3 provided important data from the first randomised comparison of two second generation DES, with results demonstrating non-inferiority of the RESOLUTE zotarolimus-eluting stent compared to the everolimus-eluting stent. Likewise, similar outcomes were also demonstrated in Chapters 7.5 and 7.6, in the comparison between the first generation sirolimus-eluting stent, and the newer biodegradable polymer biolimus-eluting stent. In contrast, in Chapter 7.4, the novolimus-eluting stent was shown to be superior to the second-generation zotarolimus-eluting stent. Overall these studies provide important data on the performance of these newer stents, and notably the RESOLUTE (Chapter 7.3) and LEADERS (Chapter 7.5) studies enrolled 'all-comers' patient populations, which facilitates extrapolation of these results to everyday clinical practice, whilst also overcoming some of the deficiencies of earlier DES studies which recruited selective less-representative patient populations. Unfortunately however, none of these studies were adequately powered to detect differences in stent thrombosis, and therefore the question as to whether these newer DESs really lower rates of stent thrombosis remains unanswered.

Percutaneous revascularization of complex disease

The lower threshold to investigate patients with symptoms of angina has inevitably lead to increasing numbers of patients with complex coronary artery disease presenting in need of definitive revascularization. Historically these patients would have received surgical revascularization; however in contemporary practice the availability of DES has ensured that the modality of revascularization is not as clear cut as before. Therefore Chapter 8, which reports the long-term safety and efficacy of using DES in patients with a spectrum of conditions, which all fit under the umbrella of 'complex patients and/or disease' provides important data that are relevant to everyday practice. Chapters 8.1 to 8.3 report data from the ARTS-II registry which compared DES use with historical patients enrolled in the ARTS-I study who were randomised to treatment with bare-metal stents or CABG. These three studies demonstrate that use of DES is feasible in these complex patients, with no significant difference seen when compared with CABG, in rates of death or the composite of death/myocardial infarction/stroke. The rates of repeat revascularization were consistently lower in surgically revascularized patients, which remains an important consideration when deciding, and counselling patients, with respect to the mode of revascularization. The final two analyses in this Chapter utilise data from the RESEARCH and T-SEARCH registries, both of which were unrestricted DES registries. Importantly the studies fail to demonstrate any superiority at long-term follow-up of using a DES compared to a bare metal stent for patients with unprotected left main lesions or chronically occluded arteries.

CONCLUSIONS

This thesis has several main findings. Firstly, since its inception in the late 1970s there have been significant improvements in outcomes following percutaneous revascularization, which in part can be attributable to the introduction and development of coronary stents. Nevertheless, stent thrombosis remains a valid concern following PCI, and attempts to minimise this continue through the development of newer stents, physician and patient education, and on-going research. The second major finding is that these advances in PCI have ensured that percutaneous revascularization is technically feasible for the majority of coronary lesions; however this may not be the most appropriate treatment for the patient in question. Therefore in those patients in need of revascularization, and most notably in those with the most complex disease, a through and individualised assessment, which includes consideration of clinical co-morbidities, the complexity and extent of coronary artery disease and a patient's preferences, is mandatory before a final decision is made on the optimal method of treatment.

Samenvatting en conclusies

De revascularisatie van patiënten met toenemende comorbiditeiten en complexe aandoeningen van de coronairvaten benadrukt nogmaals het belang van passende risicostratificatie. Dienovereenkomstig werden in deze thesis, na het vaststellen van welke patiënten gerevasculariseerd zouden moeten worden en het bespreken van de huidige en toekomstige coronaire stents, de huidige en nieuw te ontwikkelen beschikbare instrumenten bestudeerd voor het stratificeren van het risico bij patiënten die percutane coronaire interventie (PCI) ondergaan. Tenslotte sluit deze thesis na de beoordeling van de impact van klinische factoren, coronaire anatomie en coronaire stents op klinische resultaten af met een rapportage van de langetermijnresultaten van patiënten met complexe aandoeningen die werden behandeld met PCI met gebruik van drug-eluting stents (DES).

De noodzaak voor revascularisatie

In het recente verleden hebben verbeteringen plaatsgevonden in de klinische resultaten na percutane of chirurgische revascularisatie. Gekoppeld aan het toenemende aantal instituten dat revascularisatieprocedures uitvoert, heeft dit geleid tot een overall lagere drempel voor het doorverwijzen van stabiele patiënten voor mechanische revascularisatie. Het gevolg hiervan is echter dat patiënten vaak een suboptimale medische behandeling krijgen, of onvoldoende tijd krijgen om te stabiliseren op de voorgeschreven medicatie voordat zij worden doorverwezen voor revascularisatie. Revascularisatieprocedures brengen een eigen procedureel risico met zich mee en zouden uiteindelijk alleen uitgevoerd moeten worden bij patiënten bij wie het de symptomen en/of de prognose zou verbeteren. Hoofdstuk 1 van deze thesis bevat een hoofddiscussie waarin de drie beschikbare behandelingen voor patiënten met stabiele angina pectoris worden vergeleken: medische behandeling, PCI en coronaire bypassoperatie (CABG). Van belang is dat in 2007 de COURAGE trial gegevens leverde met betrekking tot de voordelen van een optimale medische behandeling bij patiënten met stabiele angina pectoris, waarbij het concept dat alle patiënten met obstructieve coronaire laesies revascularisatie behoeven in twijfel wordt getrokken. Zoals in dit hoofdstuk echter ook wordt benadrukt, was er een duidelijke ondergroep patiënten (patiënten met feitelijke sporen van ischemie), die niet profiteerde van mechanische revascularisatie. Uiteindelijk duurt bij patiënten die revascularisatie behoeven, de eeuwenoude discussie of patiënten behandeld moeten worden met PCI of met CAGB, nog steeds voort. Gelukkig hebben de ontwikkelingen en vooruitgang in percutane technieken, die uitgebreid worden besproken in deel 2, ertoe bijgedragen dat een groot deel van dit vraagstuk inmiddels geschiedenis is. De discussie is nu alleen nog van toepassing op patiënten met de ernstigste vorm, zoals uiteengezet in deel 2, 3 en 8.

Coronaire stents

Deel 2 van deze thesis toont een uitgebreid overzicht van huidige en toekomstige coronaire stents, waarmee wordt aangegeven dat hoewel er duidelijke voordelen zijn aan het gebruik van DES in vergelijking met historische metalen stents, hun gebruik niet zonder enig risico is. De eerste en tweede generatie DES werden allemaal onderzocht in gerandomiseerde onderzoeken, die nu langetermijngegevens hebben opgeleverd. De meeste van deze onderzoeken maakten echter gebruik van beperkte inclusiecriteria, waardoor de extrapolatie van de resultaten naar routinepraktijk gehinderd

wordt. Er bestond twijfel over de veiligheid na het wijdverspreide gebruik van de vroegere DES. Hierdoor werd de ontwikkeling van nieuwere stentplatformen, polymeer technologieën en antiproliferatieve middelen bespoedigd. Veel van deze nieuwere stents bevinden zich nog in de eerste beoordelingsfase, maar de resultaten zien er tot dusver veelbelovend uit. Van belang is dat, en dit wordt ook later in hoofdstuk 7 uiteengezet, sommige nieuwere stents worden beoordeeld bij een onbeperkte patiëntpopulatie, waardoor de onderzoeksresultaten een beter beeld geven van de prestatie van de stent dan wanneer gebruikt in de praktijk van alle dag. Helaas blijven nog veel vragen onbeantwoord als het gaat om een van de grote risico's van stentimplantatie, namelijk stenttrombose. Hoofdstuk 2.3 bevat een diepgaande discussie over de belangrijkste problemen met betrekking tot deze ongewenste en vaak fatale complicatie. Het is te hopen dat een beter begrip van deze factoren uiteindelijk de identificatie van optimale preventieve strategieën mogelijk zal maken.

Individuele beoordeling voor mechanische revascularisatie

Deel 3 toont een overzicht van de risicomodellen die artsen tot hun beschikking staan ter ondersteuning van de beoordeling van patiënten die mechanische revascularisatie behoeven. Zoals reeds besproken, zijn de huidige risicomodellen gebaseerd op de beoordeling van klinische factoren, of de complexiteit van de aandoening van de coronairvaten, terwijl de recentere modellen, die worden onderzocht in deel 4, zich baseren op een combinatie van deze twee typen variabelen. Tenslotte herhaalt dit hoofdstuk dat patiënten die revascularisatie behoeven, individueel beoordeeld moeten worden en daarnaast moet de modaliteit van revascularisatie passend worden gemaakt, waarbij de comorbiditeiten van de patiënt, de complexiteit van de aandoening en persoonlijke voorkeuren in overweging worden genomen, terwijl er ook rekening wordt gehouden met de expertise van de artsen/chirurgen die de procedure uitvoeren.

Tools voor de risicobeoordeling van patiënten die behandeld worden met PCI

Voortbordurend op de algemene discussie over risicomodellen, onderzocht deel 4 gedetailleerder de modellen die geschikt zijn voor patiënten met PCI. Met name de voordelen van het gebruik van de euroSCORE en de SYNTAX-score, in combinatie met een beoordeling van de reproduceerbaarheid van de SYNTAX-score worden bestudeerd in hoofdstuk 4.1 tot 4.3. Hierna volgde een aantal studies waarin het nut van het gebruik van nieuwere risicomodellen werd beoordeeld in een reeks verschillende patiëntpopulaties. De ACEF-score, die een eenvoudige klinische score vertegenwoordigt die alleen eerder werd gevalideerd bij patiënten die CABG ondergingen, liet zien effectief te zijn in de risicostratificatie van patiënten die PCI ondergingen die deelnamen aan het voor iedereen toegankelijke LEADERS onderzoek. Intuïtief zou een complete risicobeoordeling zowel klinische als angiografische kenmerken in overweging moeten nemen. Derhalve werden de gecombineerde scores, de klinische SYNTAX-score en de globale risicoclassificatie, verder ontwikkeld. Beide maken gebruik van een klinische score als de ACEF-score of de euroSCORE, in combinatie met de SYNTAX-score. Zoals eerder vermeld in hoofdstuk 4.5, toonde de eerste beoordeling van de klinische SYNTAX-score bij een populatie van patiënten met een complexe aandoening aan de coronairvaten, het superieure opmerkzame vermogen voor eindpunten aan, zoals mortaliteit en ernstige cardiovasculaire en cerebrovasculaire bijwerkingen, in vergelijking met alleen de SYNTAX-score. Op een vergelijkbare manier werd bij een populatie van patiënten met onbeschermde linker coronairvataandoening ook

aangetoond dat de globale risicoclassificatie superieur was in het gebruik van alleen de SYNTAX-score. Al met al leveren deze onderzoeken het bewijs voor ondersteuning van het gebruik van een combinatie van risicomodellen, in tegenstelling tot modellen die alleen klinische of angiografische kenmerken beoordelen.

Invloed van klinische factoren op klinische eindresultaten

Deel 5 liet zien dat patiënten die voor PCI kwamen nog steeds een hoge prevalentie van risicofactoren hebben, waarvan sommige niet gereguleerd zijn. Derhalve vertegenwoordigen deze patiënten een aanzienlijke populatie waarbij een secundaire preventieve behandeling het doel moet zijn en/of geoptimaliseerd moet worden. Daarnaast werd, hoewel de leeftijd van de patiënt als variabele wordt toegevoegd aan de euroSCORE en ACEF-score, bij de complexe patiënten die deelnamen aan het ARTS-II onderzoek, de leeftijd alleen getoond om de resultaten te beïnvloeden van patiënten die werden behandeld met CABG, en niet met PCI. Daar tegenover werd aangetoond dat de body mass index een onafhankelijke risicofactor was voor ernstige cardiovasculaire bijwerkingen onder de patiënten die deelnamen aan het LEADERS onderzoek.

Invloed van coronaire anatomie op klinische eindresultaten

Deel 6 bestond uit een aantal studies die voor het grootste gedeelte de impact beoordeelden van coronairvatcomplexiteit, uitgedrukt met gebruik van de SYNTAX-score, op klinische eindresultaten na 1 jaar en 5 jaar follow-up. Zoals vermeld in hoofdstuk 6.1-6.6, maakt het gebruik van de SYNTAX-score de identificatie mogelijk van patiënten die werden behandeld met PCI en die het hoogste risico lopen op mortaliteit en/of ernstige cardiovasculaire bijwerkingen tijdens de follow-up. Twee extra toepassingen van de SYNTAX-score worden uiteengezet in hoofdstuk 6.5 en 6.7. Voornamelijk in hoofdstuk 6.5 liet de SYNTAX-score zien dat het een belangrijke rol speelt bij de beoordeling van stentprestatie. In hoofdstuk 6.7 liet het juist zien nuttig te zijn ter ondersteuning van de keuze van patiënten met een complexe aandoening die geen complete revascularisatie behoefden. Over het geheel genomen tonen deze onderzoeken aan dat de complexiteit van de coronaire anatomie van zeer grote invloed is op de eindresultaten van patiënten die PCI ondergaan. Hoewel dit misschien voor de hand liggend is, is er nog geen eerdere methode geweest voor het nauwkeurig kwantificeren van de complexiteit van coronaire aandoeningen, waarmee de noodzaak voor de SYNTAX-score wordt benadrukt en de rol in de risicostratificatie van patiënten die PCI ondergaan, nogmaals wordt bevestigd.

Invloed van stenttype op klinische eindresultaten

De eerdere discussie over coronaire stents benadrukte de belangrijke verschillen tussen verschillende DES. Bovendien, zoals eerder besproken in deel 2, waren het de twijfels over de veiligheid van de eerste generatie DES die de ontwikkeling van nieuwe coronaire stents in een stroomversnelling brachten. In hoofdstuk 7 worden vroege en late resultaatgegevens van gerandomiseerde onderzoeken die de prestatie van deze nieuwere DESsen onderzochten, gepresenteerd, waarmee wordt aangetoond dat het overall stenttype wel degelijk van invloed is op klinische eindresultaten. Er zijn op dit moment niet veel langetermijngegevens van gerandomiseerde trials waarin de eerste en tweede generatie DES worden vergeleken. Dit gebrek aan gegevens benadrukt nogmaals het belang van de

eerste twee hoofdstukken van deel 7, waarin de gunstige resultaten na 3 en 4 jaar follow-up worden bevestigd, na gebruik van de tweede generatie everolimus- eluting stent. Er zijn verschillende tweede generatie DES, en in hoofdstuk 7.3 staan belangrijke gegevens van de eerste gerandomiseerde vergelijking van twee tweede generatie DES, met resultaten die non-inferioriteit aantonen van de RESOLUTE zotarolimus-eluting stent in vergelijking met de everolimus-eluting stent. Bovendien werden dezelfde resultaten ook aangetoond in hoofdstuk 7.5 en 7.6, bij de vergelijking tussen de eerste generatie sirolimus-eluting stent en de nieuwe, biologisch afbreekbare polymeer biolimus-eluting stent. In hoofdstuk 7.4 daarentegen toonde de novolimus-eluting stent zich superieur aan de tweede generatie zotarolimus-eluting stent. Over het geheel genomen leveren deze onderzoeken belangrijke gegevens over de prestaties van de nieuwere stents, en met name de RESOLUTE- (hoofdstuk 7.3) en LEADERS- (hoofdstuk 7.5) onderzoeken waaraan allerlei patiëntpopulaties deelnamen. Dit maakt de extrapolatie van deze resultaten mogelijk naar de dagelijkse klinische praktijk, terwijl het ook een aantal gebreken ondervangt van eerdere DES-onderzoeken die selectieve, minder representatieve patiëntpopulaties rekruteerden. Helaas waren deze onderzoeken echter niet voldoende krachtig om de verschillen op te sporen in stenttrombose. Daarom blijft de vraag of deze nieuwere DESsen daadwerkelijk het aantal gevallen van stenttrombose verlagen, onbeantwoord.

Percutane revascularisatie van complexe aandoening

De lagere drempel om patiënten met symptomen van angina pectoris te onderzoeken, heeft onvermijdelijk geleid tot een toenemend aantal patiënten met complexe aandoeningen van de coronairvaten, die definitieve revascularisatie behoeven. Historisch gezien zouden deze patiënten operatieve revascularisatie hebben ondergaan. In de hedendaagse praktijk echter heeft de beschikbaarheid van DES ervoor gezorgd dat de modaliteit van revascularisatie niet zo vanzelfsprekend is als dat eerder het geval was. Daarom staan er in hoofdstuk 8, met vermeldingen van de veiligheid en werkzaamheid op de lange termijn van het gebruik van DES bij patiënten met een spectrum van aandoeningen, die allemaal passen onder de noemer van 'complexe patiënten en/of aandoeningen', belangrijke gegevens die relevant zijn voor de dagelijkse praktijk. Hoofdstuk 8.1 tot 8.3 leveren gegevens van het ARTS-II-register, dat het DES-gebruik vergeleek met historische patiënten die deelnamen aan het ARTS-I onderzoek die werden gerandomiseerd naar een behandeling met metalen stents of CABG. Deze drie studies tonen aan dat het gebruik van DES uitvoerbaar is bij deze complexe patiënten, zonder dat er een significant verschil is te zien in vergelijking met CABG, voor wat betreft percentages van overlijden of de composiet overlijden/myocardinfarct/beroerte. De percentages van herhaalde revascularisatie waren consequent lager bij operatief gerevasculariseerde patiënten, wat een belangrijke overweging blijft bij de besluitvorming en bij het adviseren van patiënten, voor wat betreft de manier van revascularisatie. De laatste twee analyses in dit hoofdstuk gebruiken gegevens van het RESEARCH- en T-RESEARCH-register, beide onbeperkte DES-registers. Van belang is dat de onderzoeken er niet in slagen eventuele superioriteit bij de langetermijn follow-up aan te tonen van het gebruik van DES in vergelijking met een metalen stent bij patiënten met linker coronairvatlaesie of chronisch afgesloten arteriën.

CONCLUSIES

Deze thesis laat verschillende hoofdbevindingen zien. In de eerste plaats zijn er sinds de aanvang zo rond 1970 significante verbeteringen waargenomen in de resultaten na percutane revascularisatie. Dit kan deels worden toegewezen aan de introductie en ontwikkeling van coronaire stents. Toch blijft stenttrombose een grote zorg na PCI en pogingen om dit te minimaliseren zetten zich voort door middel van de ontwikkeling van nieuwere stents, scholing van artsen en patiënten en voortdurend onderzoek. De tweede grote bevinding is dat deze stappen voorwaarts in PCI ervoor hebben gezorgd dat percutane revascularisatie technisch haalbaar is voor de meerderheid van coronaire laesies. Dit is wellicht niet de meest geschikte behandeling voor de patiënt in kwestie. Daarom is bij die patiënten die revascularisatie behoeven, en vooral patiënten met de meest complexe aandoeningen, een grondige en individuele beoordeling noodzakelijk, waarbij klinische comorbiditeiten, de complexiteit en de omvang van de aandoening aan de coronairvaten en de voorkeur van de patiënt mede worden meegewogen voordat een uiteindelijke beslissing wordt genomen over de optimale behandelingsmethode.

Acknowledgements

I have thought long and hard about the acknowledgement section of my thesis, most notably because this is probably the only section which will be read by everybody, and for some, it will be the only part of this thesis that they read– so I will try my best to make it memorable.

My time at the Thoraxcenter was short, and I calculate it to have been my home for 591 days – 591 eventful days which will live long in my memory.

So firstly, how did I end up in Rotterdam working for Patrick W.J.C. Serruys? Well as I was coming to end of my specialist training in interventional cardiology in the UK I was told by my supervisors that my CV was lacking any research papers, and that my chances of further employment were slim. Possibly, harsh; but it was enough of a push, and on one cold January night in 2008 I sent an email to Prof Serruys enquiring about the possibility of a research post. I did not hear anything for several weeks, (after starting, and viewing Prof's daily mountain of correspondence – the delay was perfectly understandable), but thankfully I was called for an interview, and six months later on a wet, cold, overcast November morning I arrived for my first day at the Thoraxcenter. I came with no real plans, other than a desire to write some papers, and if possible gain a PhD thesis.

The first 4-6 weeks in Rotterdam were thoroughly miserable, as every fellow will no doubt remember. I had no office, and worst of all, had nothing much to do. I spent my first few weeks watching PCI cases or in the Erasmus MC library. I later found out that this was, as elegantly described by Prof, the period when the fellow is, "marinating in the Thoraxcenter." I was also told at the time that when the work starts you will be asking for it to stop. I am glad to say after this period I became involved in some wonderful projects, which most importantly allowed me to meet, and work with marvellous determined individuals from all around the world.

Fellows

My fellow colleagues were a wonderful group of individuals from all corners of the globe, who all came to Rotterdam away from their families and friends to work with Prof. On the next page is a picture of all of us, which was taken on Valentine's Day 2009, such that we can all uniquely claim to have had our picture in Circulation (2010; 121:f1-f6). Every so often we would have to say good-bye to a colleague who would be returning home – resulting in a fellow's leaving dinner, and the buying of leaving present which usually (and consistently) amounted to a book on the sights of Rotterdam. Such creativity!

So what can I say of my fellow colleagues – they have been plenty of them and I pleased to say I have worked with all of them on one thing or another. It has been a pleasure, and without you, my time in Rotterdam would have been all that much harder. It is only fitting to thank each of you individually:

Hector – my first Mexican friend, and certainly the first Dutch speaking Mexican that I have ever met, definitely an endangered species in The Netherlands. You were the longest-serving fellow when I

A picture of all (well most) of us, taken on 14th February 2009. Left to right: Me, Apostolos Tzikas, Joanna Wykrzykowska, Zhu Jun Shen, Hector M. Garcia-Gracia, Nicolo Piazza, Nieves Gonzalo, Prof, Yoshinobu Onuma, Giovanna Sarno, Chrysafios Girasis, Takayuki Okamura, Carl Schultz, and Eun-Seok Shin.

arrived, and I am pleased you have now transcending into a more permanent position in Rotterdam. You tried for my entire time in Rotterdam to introduce me to different colourful imaging techniques. We first worked together when you introduced me to the red and yellow colours (and occasionally black) produced by the Lipiscan. I worked hard on getting that catheter into the lab, but I think you knew my heart was not in it. Next you tried to convert me with the four colours of your beloved virtual-histology (?virtual luck), and although we wrote several papers on this, I didn't hide my scepticism. I remember your punctual desire for lunch just after noon each day, and the wide variety of eateries that you would take us to within a short distance from Cardialysis. You acted as the go between for the fellows and the management of Cardialysis, and for that we have to thank you. I also had the opportunity to meet your wonderful wife Lulú, and the youngest member of the Garcia-Garcia household, Andreas.

Giovanna – from my first Mexican friend to my first Italian friend. Giovanna, it was pleasure working with you in your equally brief time in Rotterdam. We started within a month of each other, and slowly worked together on numerous projects, but this was not before you had had your bicycle stolen three times. We first worked together on the SYNTAX score website, and then we spent many months reviewing angiograms for the SYNTAX score studies, many of which are contained in this thesis. Thank you. I remember how you used to enter your references in manually, and how pleased you were when you were introduced to Endnote. In between, you like my aforementioned Mexican friend had a strong attraction to the colours of VH, and I remember the hours you spent analysing images from the AtheroRemo study. I remember the story about your sofa, and how you managed to persuade two strangers to carry it up four flights of stairs to your flat, and who could forget the time you were apparently stuck in a train station in Sheffield with no money or mobile phone. I think you

had offers of help from all over, including Gerrit-Anne whilst he was on holiday in the US, but alas it was just a spam email that probably circulated to everybody in this room, and also many eminent Cardiologists around the globe. Fun-times. It was a sad when you departed back to your native Italy, but I am glad that we have stayed in touch, and now I wish you all the best on your further travels across Europe.

Josep – you arrived after I had been in Rotterdam for approximately 10 months. At first I thought of you as another Mediterranean, and another Spaniard, however it quickly emerged you were from Cataluña and not Spain, and you loved FC Barcelona. I remember your first month here, which was spent drawing the infamous circles on VH images, hour after hour. This process of drawing circles was flavoured by the release of several firstly Spanish and then quickly Korean swear words, and interrupted only by your cigarette breaks. You were soon given the project on the stent curvature, and I admire how you tackled that daunting project, and glad it was successful; the accolades you received for it were entirely deserved. Away from Cardialysis, it was fun watching our respective teams play in the Champions League...over a beer in the Irish or Mexican bar. I left before the World Cup reached its final stages, and I still wonder whether you were happy or sad at the final result. I wish you and Marcel all the best in Barcelona.

Juan-Luis – aka Chico, you started a few weeks after me and shared Z-120 with me, although we spent the majority of our time at Cardialysis. A man of many talents, you never ceased to amaze. Be it with your knowledge of history, the arts, your opera singing, your linguistic expertise which extends to speaking nearly all European languages, and being able to imitate the voices of well-known members of the EAPCI. You are a whizz with statistics, and I have to thank you for helping me out with some papers as a result. Needless to say you were always willing to help. Funnily I remember your love for tee-shirts whatever the weather, and how you took the *Szabo* technique with you to EuroPCR, the ESC and TCT all within 3 months, and all sponsored. Well done! I know you will continue your success when you return back in Spain.

Joanna – you are certainly one of the hardest working people I have ever met. I am pleased to say we worked together on the AtheroRemo project, and numerous manuscripts, many of which are included in this thesis. You were never far away from your Blackberry, and an email to you was also answered prompted whatever time it was sent. I am sure you will enjoy an equally successfully time, and overcome any challenges in your path in your new post at the AMC.

Chrysafios – aka 'Chris', we worked together on number of SYNTAX manuscripts, and spent the best part of 6-months together calculating the SYNTAX scores from SIRTAX. Due to your clinical commitments and your QCA work, we didn't see much of you at Cardialysis, but when we did, you certainly made yourself heard. I value your straight talking, and am sure a successful career is in the making.

Taka – we shared Z-120, and I thank you for lending me your key when I first started, whilst I was waiting 6 weeks for my key to be cut. You introduced me to the world of new OCT machines, and who can forget the Taka-ograms which were so impressive, and ground-breaking. We sometimes had to

communicate using your pocket translator, but this owed more to my ignorance of Japanese than anything. I am pleased to say we worked together closely on some papers, and I wish you all the best now that you are back in Japan.

Apostolos – if things have gone to plan you should be defending your thesis today. I didn't see much of you during the working day as you spent your time in the Fellow's office in the Thoraxcenter. Nevertheless I am glad we had the opportunity to meet when the fellows went out for dinner. It was always a pleasure meeting Katrina, and Zoi was always at hand to entertain. You were always down to earth, and very pleasant company. You left Rotterdam a short time after me, and I am sure you are enjoying your time in Montreal. I wish you and your family all the best.

Michael – I didn't see much of you at Cardialysis until my final few months in Rotterdam. Nevertheless I am glad that we managed to work together before I left, and I have to thank you for helping me out with those final papers.

Shin – we shared the fellows' room for the best a year, and your passion was always VH. You were incredibility hard working, arriving before, and leaving after most of the other fellows, including me. Most remarkable was that you were also looking after your son. Through your work on VH, you invented the Shin's method, and I wish you all the success with it. I enjoyed working together, and am pleased we wrote some papers together. Language was occasionally a barrier, but we overcame it one way or the other. I fondly remember the time when I asked Giovanna to translate what I wanted to say into Italo-English before you could understand what I was going on about! You are well on the way to being a Prof in South Korea...don't forget us.

Shen – our time together was short, but I am glad you gained what you wanted out of your time in Rotterdam. Before you left I am glad to say we completed a paper together. I have to thank you for passing on your bicycle when you left, it really allowed me to experience the true Dutch way of life.

Salvatore – my Sicilian colleague, you arrived a few months before I left, but we still managed to work together on a few manuscripts. I enjoyed savouring your cooking at Giovanna's leaving party, and your dislike of Inter Milano. Enjoy the rest of your time in Rotterdam.

Roberto – you arrived a similar time to Salvatore, and took over the Lipiscan from me. I wish you all the best with your projects. Unfortunately I had to watch your team in the Champions League, and worst of all they won.

Yoshi – you have been in Rotterdam longer than any of the other fellows, and will no doubt be there for many years to come. You work incredibility hard, and I am not sure what Prof would do without you. I am glad we managed to work together on some projects together, and I wish you all the best for your future in The Netherlands.

Carl – a fellow Brit in part, I have to thank you for all your help in putting me touch with my landlord before I even came to Rotterdam. We worked together on a few projects; however we had different interests. I was happy when you got married, and more so when your son Zachery arrived. I wish you all the best for your future in The Netherlands.

Cardialysis

Cardialysis is an amazing place, filled with very hard working individuals who I cannot thank enough for their help during my time in Rotterdam. Through all my projects I got to know many of the staff members very well and I will try and thank as many of them as I can.

Statisticians – Ton, Marco, Tessa, Michael, Pierre, Eric and Dick- you all had to put up with me pestering you for data or analyses, and being bombarded by my emails. You made allowances for my statistical naivety and without you all many of the manuscripts in this thesis would not have made it into print. Thank you very much. Ton the analysis for the bifurcation paper from LEADERS seemed to take an eternity, and I am glad you didn't kill me with all my requests. Pierre, Tessa and Marco, I am sure you do not need reminding of those three intensive days during the Resolute writing session, when things were changing by the minute.

Study Co-ordinators – Bianca, Monique, Anne-Marie den Drijver, Yvonne, and Jacintha – you also had to put with me pestering you for requests, study protocols, CRFs etc. Thank you. You were always helpful, and accommodating. Anne-Marie we worked together on the EXCELLA project, and that had a successful ending. Yvonne and Jacintha, we worked together on Resolute All-Comers, and I'm pleased that things worked out well. Yvonne, you also had to work with me on LEADERS, and I'm pleased that that was also very productive.

Peter-Paul – a gentleman – our paths crossed on several projects, not least Resolute All-Comers. It was a pleasure working with you.

Marie-Angèle – you were the first to arrive, and the last to leave Cardialysis. You were always full of energy, and willing to help. I am glad that I was able to help, when you were tirelessly working on the SYNTAX score website. You know everybody, and everybody knows you, in the world of Cardiology. We share a passion for football, although our support extends to different teams. It was wonderful watching your Orange transformation during the World Cup. I must also thank you and Ravindra for buying my son his Dutch football shirt, which he wore whilst he watched his first World Cup final, aged 21 days.

Gerrit-Anne – a statistician and part of the board of directors at Cardialysis. I have to thank you for allowing me to be part of the Cardialysis team. We worked together on several projects, and your input was always invaluable.

Paul Cummins – a Scouse loving Irishman. I have to admit I am glad you supported Liverpool; it always gave me something to laugh at, and also helped me remember the similar conversations I

week-in-week-out back home with similarly deluded Scousers. You are the lynchpin of EuroIntervention, and your door was always open for a chat about anything. In my time in Rotterdam, it has been a pleasure to watch EuroIntervention grow and grow, and you certainly deserve a lot of credit for all your behind the scenes work.

Pascal – a weekly visitor to Cardialysis, I am pleased that we got to work on some manuscripts together...although it is a pity there weren't more.

Thoraxcenter

I did not spend any time in the cath labs of the Thoraxcenter but on occasion when I have needed help, John de Vries, Elco, Anne-Marie, Sander, and Marjo de Ronde were always helpful. I reserve special words for Jurgen, a mastermind of intra-vascular ultrasound and with whom I worked with closely when the Lipiscan was being introduced. He was always encouraging, and enthusiastic, and I enjoyed listening to his interesting tales from when he travelled around Europe in his younger days.

My supervisor was Prof and I was mainly based at Cardialysis, however through the weekly filmbespreking, EuroIntervention board meetings, and the annual preparations for EuroPCR I am pleased to say I got to work with, and got to know many of the staff members who each had their area of expertise and knowledge to part. Thank you.

Hull

I am indebted to the help given to me by the many different people I worked and became friends with during my 5 years of specialist training in Hull, East Yorkshire. In particular:

Ann – my training supervisor, you were always only a phone call away; and always ready to listen. I continue to value your well-directed and thoughtful advice. Before I left for Rotterdam, you helped me get my OOPE application approved by the post-graduate dean, which ultimately allowed me to go. Moreover, whilst I was there, you were still very supportive. Thank you very much.

Farqad – besides thanking you for my clinical training, I have to thank you for first putting the idea of going to Rotterdam in my mind.

Brags – we left Hull at a similar time, and although you moved to west coast of America, we stayed in touch. I have to thank you for your support, and advice, which really helped me during my time in Rotterdam. I am glad that you are now back in the UK and that we are still close friends.

Christos – we worked together in Hull for a short time before you moved back to Greece, but I am glad we stayed in touch. You came to visit me in Rotterdam, when you were in Brussels on a conference, but it was only recently that you told me how you ended up spending the night at Paris-Nord station, when you didn't get off the train in Brussels! Your experiencing of the UK rail system is similarly colourful. I am glad that we managed to work together on a few papers, even whilst I was in Rotterdam, and now we are back in the UK I hope we will work together again.

Huan & Shani – I am glad that we stayed in touch; it was always great to see you again when I went back to Hull, or when we met at conferences elsewhere. I have fond memories of our dinner in Barcelona during the ESC 2009. I wish you well on your new adventures abroad.

Maria, Angie, Becks, Janine, Kim and Liam -- I was sad when I left the cath lab in Hull, but I always looked forward to our regular meetings at AAI and PCR. Maria, I have to thank you for always sorting me out a place, when needed. It was always great catching up, and I have to thank you all for your support whilst I was in Rotterdam. It *really* did help. When we did we meet up, I don't think we ever had a dull moment together, whether it was drinking canned beers on the beach in Barcelona, or savouring wine in the Hilton Metropole. Long may it continue. Keith Edwards lives on in our thoughts.

Industry

Cardiology is unique amongst medical specialities through the close interaction between physicians and industry. Much of the work contained in this thesis would not have been possible without this close interaction, and I would like to thank those people who I have liaised with closely over the past few years, enabling me to complete my work in a timely fashion.

Keith Dawkins–Some of the work contained in this thesis centres on the SYNTAX trial, and I have to thank you for taking time out of your busy schedule to respond to my requests for data, which ultimately allowed me to complete my work.

Janine, Jason, Frank and Manuela – I enjoyed working with all of you on Resolute All-Comers. The week of the writing session in Rotterdam, and the following weeks were intensive to say the least, but I am glad that we were able to successfully work together. Frank, I have to thank you for always picking the best restaurant for us to eat, even when you couldn't join us. Special thanks are reserved for you J9, for all your additional help, the purple scribed emails, and your 'advertising' at EuroPCR.

Susanne – it has been a pleasure working with you over the past few years. Our paths first crossed in preparation for EuroPCR 2009, and I remember our first meeting; you came to Cardialysis to review some LEADER's data that I had been working on, and we met for over 2-hours, and I didn't even get round to offering you a coffee! After that start, I am pleased to say subsequent meetings were a considerable improvement.

Claudia – I am pleased that we had the opportunity to work together on a number of projects. I am still waiting however for the masterpiece that you promised for my wall...

Moira – I reserve a special thanks to you Moira. You didn't know me, but you agreed to help me out before I came to Rotterdam. I am glad that we have stayed in touch, and now you work just down the road in Belgium. Thank you.

Prof

My time in Rotterdam will live long in the memory, and one of the primary reasons for that is Prof Serruys. Prior to coming to the Thoraxcenter, I had heard about the unique work that went on, but had heard little about Prof himself. The review of his achievements in *Circulation* last year was simply an introduction, and by no means the full story. Prof, I think it is impossible for me to accurately and completely describe your achievements, your thirst for research, your innovative thinking and your drive to take our speciality forward for the best of our patients, to those who have not experienced this first hand – seeing really is believing. Thankfully after witnessing these in the flesh, I could not help introducing them into my own work.

It has been a privilege to work for you, and I am eternally grateful for all the opportunities you gave me whilst I was in Rotterdam. The list is endless, but three stick out in my mind. Firstly you asked the Chairs of the ESC Guidelines committee for myocardial revascularization to allow me to join the Task force, and consequently I attended writing sessions in Barcelona and Bruges. Secondly, you nominated me to give a key-note talk on the SYNTAX Trial on your behalf at the Japanese Circulation Society in Kyoto. You told me it was on the condition that I took my wife Shruti; not that she needed asking! Nevertheless it gave my wife and me the chance to visit Japan for the first time, which was an amazing experience. I remember how before I left you spent 30 minutes on the phone to KLM, and tried (unsuccessfully) to get my wife upgraded into Business class. At the time you said your efforts should at the very least get a mention in my thesis! Thirdly, you got me involved in working on the Resolute All-Comers study, which besides being hard-work, was very educational, and very rewarding.

Despite the number of fellows, and the amount of work that you have on, I find it amazing how you are still able to remember everything you asked us to do, even when we thought (even hoped) you'd forgotten. Usually you would make these enquires first thing in the morning as you were driving to work, and none of us were exempt. Similarly amazing is the active interest you took in each of our journeys through the Thoraxcenter, and the interest you had in 'our other lives' back in our native countries. In my last year in Rotterdam, when Shruti was pregnant, you would always ask how she was. When she developed problems, you were the first to tell me to go leave asap, and I remember how you rang me on a daily basis until our son was born. When I think of the workload that you had on, this is made all the more astonishing. The words Thank You don't really cover the facts. I must also thank Danielle. She was always welcoming at the door when I would come on the weekend, whatever the time. Thank you for sending Aarav a present, it was most thoughtful.

Family

Whilst I lived away in Rotterdam, and was meeting new people, and experiencing new things, Shruti, was still back in the UK working. I would not have been able to come to Rotterdam, had it not been for her support, and her green light. She realised the opportunity I had, and encouraged me to take it. The days I was away were hard for both of us, and I am pleased that we got through it. Thank you for allowing me to follow my dreams. Our son, Aarav, was the timely cue for me to return back to the UK. My mum was an immense help to Shruti and I during my time away, and I don't think we could

have got through things without her contribution. Amongst many other things, she stored all our furniture in her house, and made endless trips back and forth from the airport. She also came to Rotterdam on several occasions, and helped, along with Shruti, to keep my fridge well stocked. Thanks! I must also give thanks to my other close family, many of whom also came to visit me in Rotterdam, in particular my mother- and father-in-law, Smisha, Saurabh, and Aanchal.

Sept 2010

Curriculum Vitae

Personal Details

Name:	Scot Anil Garg
Address:	16 Thornway, Worsley, Manchester, UK, M28 1YS
Email Address:	scotgarg@hotmail.com
Contact Telephone:	+44-797-740-8384
Date of Birth:	17th June 1976
Nationality:	British

Professional Qualifications

2010	**CCT (Certificate of Completion of Training)**
	Cardiology
	Joint Royal Colleges of Physicians Training Board
	6th September 2010
2002	**MRCP (UK)**
	Royal College of Physicians (London)
	November 2002
1999	**MB ChB**
	University of Manchester
	September 1994 – July 1999

Current Position

May 11— to date	Consultant Interventional Cardiologist
	Royal Blackburn Hospital, Blackburn, Lancashire

Higher Specialist Training

Sept 10—April 11	Interventional Fellow
	University Hospitals of North Staffordshire, Stoke-on-Trent, Staffs
Sep 03—June 10	Specialist Registrar Cardiology & General (internal) medicine
	Yorkshire Deanery
Nov 08—Jun 10	Research Fellow
	Erasmus Medical Center, Rotterdam, The Netherlands
Mar 05—Nov 08	Specialist Registrar Cardiology & General (internal) medicine
	Hull Royal Infirmary and Castle Hill Hospital, Hull, East Yorkshire
Mar 04—Mar 05	Specialist Registrar Cardiology & General (internal) medicine
	Diana Princess of Wales Hospital, Grimsby, NE Lincolnshire
Sep 03—Mar 04	Specialist Registrar Cardiology & General (internal) medicine
	Hull Royal Infirmary and Castle Hill Hospital, Hull, East Yorkshire

Previous Appointments

Feb 03—Sep 03	Cardiology Registrar
	Queen Elizabeth II Hospital, Welwyn Garden City, Hertfordshire
Aug 00—Feb 03	Senior House Officer (medical rotation)
	Blackpool Victoria Hospital, Blackpool, Lancashire
Feb 00—Aug 00	Surgical House Officer
	Royal Blackburn Infirmary, Blackburn, Lancashire
Aug 99—Feb 00	Medical House Officer
	Burnley General Hospital, Burnley, Lancashire

List of publications

Original Studies

1. **Garg S**, Sarno G, Serruys PW, Rodriguez A, Bolognese L, Anselmi M, De Cesare N, Colangelo S, Moreno R, Gambetti S, Monti M, Bristot L, Bressers M, García-García HM, Parrinello G, Campo G, Valgimigli M. Prediction of 1-year clinical outcomes using the SYNTAX score in patients with acute ST-elevation myocardial infarction undergoing primary PCI: A sub-study of the STRATEGY and MULTI-STRATEGY trials. *J Am Coll Cardiol Intv.* 2011; 4(1):66-75

2. **Garg S**, Sarno G, García-García HM, Girasis C, Wykrzykowska J, Dawkins KD, Serruys PW. A new tool for the risk stratification of patients with complex coronary artery disease: The Clinical SYNTAX score. *Circ Cardiovasc Interv.* 2010; 3(4):317-326

3. Serruys PW, Silber S, **Garg S**, van Geuns RJ, Richardt G, Buszman PE, Kelbæk H, van Boven AJ, Hofma SH, Linke A, Klauss V, Wijns W, Macaya C, Garot P, Dimario C, Manoharan G, Kornowski R, Ischinger T, Bartorelli A, Ronden J, Bressers M, Gobbens P, Negoita M, van Leeuwen F, Windecker S. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *N Eng J Med.* 2010; 363(2):123-35

4. **Garg S**, Sarno G, Serruys PW, de Vries T, Buszman P, Linke A, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, Di Mario C, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Jüni P, Windecker S. The twelve month outcomes of a biolimus eluting stent with a biodegradable polymer compared with a sirolimus eluting stent with a durable polymer. *EuroIntervention.* 2010; 6(2): 233-239

5. **Garg S**, Girasis C, Sarno G, Goedhart D, Morel MA, Bressers M, García-García HM, van Es GA, Serruys PW. The SYNTAX score revisited: a new assessment of the SYNTAX score reproducibility. *Catheter Cardiovasc Interv.* 2010; 75(6):946-52.

6. **Garg S**, Serruys PW, Miquel- Hébert K. Four year clinical follow up of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo coronary artery lesions: The SPIRIT II Trial. *Catheter Cardiovasc Interv.* 2010 Sep 7. [Epub ahead of print]

7. **Garg S**, Serruys PW, Onuma Y, Dorange C, Veldhof S, Miquel-Hébert K, Sudhir K, Boland J, Huber K, Garcia E, te Riele JA on behalf of the SPIRIT II Investigators. Three year clinical follow up of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo coronary artery lesions. The SPIRIT II Trial. *J Am Coll Cardiol Intv.* 2009; 2(12):1190-1198

8. **Garg S**, Wykrzykowska JJ, Serruys PW, de Vries T, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Tyczynski P, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Juni P, Windecker S. The outcome of bifurcation lesion stenting using a biolimus-eluting stent with a bio-degradable polymer compared to a sirolimus-eluting stent with a durable polymer. *EuroIntervention* 2011;6(8):928-35

9. **Garg S**, Sarno G, Gutiérrez-Chico JL, García-García HM, Gomez-Lara J, Serruys PW. Five year outcomes of percutaneous coronary intervention compared to bypass surgery in patients with multi-vessel disease involving the proximal left anterior descending artery: an ARTS-II sub-study. *EuroIntervention*. In press.

10. **Garg S**, Serruys PW, Holmes DR Jr, Kappetein AP, van den Brand M, Mack M, Feldman T, Morice MC, Ståhle E, Colombo A, van Dyck N, Leadley K, Morel MA, van Es GA, Mohr FW, Dawkins KD. Combined clinical and angiographic risk assessment in patients with left main stem disease treated with percutaneous coronary intervention: A sub-study of the SYNTAX trial. *EuroIntervention*. In press.

11. **Garg S**, Serruys PW, Silber S, Wykrzykowska J, van Geuns R-J, Richardt G, Buszman P, Kelbæk H, van Boven AJ, Hofma SH, Linke A, Klauss V, Wijns W, Macaya C, Garot P, DiMario C, Manoharan G, Kornowski R, Ischinger T, Bartorelli A, Bressers M, van Remortel E, Ronden J, Windecker S. The prognostic utility of the SYNTAX score for risk assessment in patients undergoing coronary revascularization with second generation drug eluting stents: A sub-study of the randomized RESOLUTE All Comers trial. *J Am Coll Cardiol Intv*. In press.

12. **Garg S**, Sarno G, Girasis C, Vranckx P, de Vries T, Swart M, Bressers M, García-García HM, van Es GA, Räber L, Campo G, Valgimigli M, Dawkins KD, Windecker S, Serruys PW. A patient level pooled analysis assessing the impact of the SYNTAX score on 1-year clinical outcomes in 6,508 patients enrolled in contemporary coronary stent trials. *J Am Coll Cardiol Intv*. In press.

13. **Garg S**, Saha A, Clark A. Is sensible use being made of an inpatient Holter monitoring and transthoracic echocardiogram service within acute medicine? *Clin Med* 2006; 6(6):586-91

14. Wykrzykowska JJ, **Garg S**, Onuma Y, de Vries T, Goedhart D, Morel, van Es GA, Buszman P, Linke A, Ischinger T, Klauss V, Corti R, Eberli F, Wijns W, Morice MC, di Mario C, van Geuns RJ, Juni P, Windecker S, Serruys PW. Value of Age, Creatinine and Ejection Fraction (ACEF score) in assessing risk in patients undergoing percutaneous coronary interventions in an "all-comers" LEADERS trial. *Circ Cardiovasc Interv.* 2011; 4(1):47-56

15. Legrand VM, **Garg S**, Serruys PW, Virtanen K, Szurawitzki G, Voudris V, Fontanelli A, Endersen K, Kranjec I, Rademaker T, Stefanadis C, Wittebols K. Influence of age on the clinical outcomes of coronary revascularization for the treatment of patients with multivessel de novo coronary artery lesions. Sirolimus-eluting stent vs. coronary artery bypass surgery and bare metal stent: Insight from the multicenter randomized Arterial Revascularization Therapy Study Part I (ARTS-I) and Part II (ARTS-II). *EuroIntervention*. 2011; 6(7):838-845

16. Bourantas CV, **Garg S**, Naka KK, Thury A, Hoye A, Michalis LK. Focus on the research utility of intravascular ultrasound - comparison with other invasive modalities. *Cardiovasc Ultrasound*. 2011; 9(1): 2

17. Wykrzykowska JJ, **Garg S**, Girasis C, de Vries T, Morel, van Es GA, Buszman P, Linke A, Ischinger T, Klauss V, Corti R, Eberli F, Wijns W, Morice MC, di Mario C, van Geuns RJ, Juni P, Windecker S, Serruys PW. Value of the SYNTAX score (SX) for risk assessment in the "all-comers" population of the randomized multicenter LEADERS trial. *J Am Coll Cardiol*. 2010; 56(4): 272-277

18. Okamura T, **Garg S**, Gutierrez-Chico JL, Shin ES, Onuma Y, García-García HM, Rapoza RJ, Sudhir K, Regar E, Serruys PW. In-vivo evaluation of stent strut distribution patterns in the bioabsorbable everolimus-eluting device: An OCT ad hoc analysis of the Revision 1.0 and Revision 1.1 stent design in the ABSORB clinical trial. *EuroIntervention*. 2010; 5(8):932-938

19. Serruys PW, **Garg S**, Abizaid A Ormiston J, Windecker S, Verheye S, Dubois C, Stewart J, Hauptmann KE, Schofer J, Stangl K, Witzenbichler B, Wiemer M, Barbato E, de Vries T, den Drijver AM, Otake H, Meredith L, Toyloy S, Fitzgerald P. A randomised comparison of novolimus-eluting and zotarolimus-eluting coronary stents: 9-month follow-up results of the EXCELLA II study. *EuroIntervention*. 2010; 6(2): 195-205

20. Sarno G, **Garg S**, Onuma Y, Buszman P, Linke A, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, van Geuns RJ, Eerdmans P, García-García HM, van Es GA, Goedhart D, de Vries T, Jüni P, Meier B, Windecker S, Serruys P. The impact of body mass index on the one year outcomes of patients treated by PCI with biolimus- and sirolimus- eluting stents in the LEADERS trial. Does the obesity paradox exist? *Am J Cardiol.* 2010;105(4):475-479

21. Sarno G, **Garg S**, Onuma Y, Gutiérrez-Chico JL, van den Brand M, Rensing B, Morel MA, Serruys PW. The impact of completeness of revascularization on the five-year outcome in PCI and CABG patients (from the ARTS-II study). *Am J Cardiol*. 2010;106 (10):1369–1375

22. Sarno G, **Garg S**, Onuma Y, Girasis C, Tonino P, Morel MA, van Es GA, Pijls N, Serruys PW. Bifurcation lesions: Function assessment by fractional flow reserve vs. anatomical assessment using conventional and dedicated bifurcation quantitative coronary angiogram. *Catheter Cardiovasc Interv.* 2010; 76 (6):817-823

23. Sarno G, **Garg S**, Gomez-Lara J, García-García HM, Ligthart J, Bruining N, Onuma Y, Witberg K, van Geuns R-J, de Boer S, Wykrzykowska J, Schultz C, Duckers H, Regar E, de Jaegere P, de Feyter P, van ES G, Boersma E, van der Giessen W, Serruys PW. Intravascular ultrasound radiofrequency analysis after optimal coronary stenting with initial quantitative coronary angiography guidance (An ATHEROREMO sub-study). *EuroIntervention* 2011; 6(8):977-984

24. Wykrzykowska J, **Garg S**, Onuma Y, de Vries T, Morel MA, van Es GA, Buszman P, Linke A, Ischinger T, Klauss V, Corti R, Eberli F, Wijns W, Morice MC, DiMario C, van Geuns RJ, Juni P, Windecker S, Serruys PW. Implantation of the biodegradable polymer biolimus eluting stent in patients with high SYNTAX score is associated with decreased cardiac mortality compared to permanent

polymer sirolimus eluting stent. Two year follow-up results from the all-comers LEADERS trial. *EuroIntervention*. In press.

25. García-García HM, **Garg S**, Brugaletta S, Morocutti G, Ratner RE, Kolatkar NS, Kravitz BG, Miller DM, Huang C, Nesto RW, Serruys PW and the APPROACH study group. Evaluation of In-stent Restenosis in the APPROACH trial (Assessment on the Prevention of Progression by Rosiglitazone On Atherosclerosis in Diabetes Patients with Cardiovascular History). *Int J Cardiovasc Imaging*. In press.

26. Vranckx P, Boersma E, **Garg S**, Valgimigli M, Vans Es GA, Goedhart D, Serruys PW. Cardiovascular Risk profile of patients included in stent trials: A meta-analysis of individual patient data from randomized clinical trials. Insights from 33 prospective stent trials in Europe. *EuroIntervention*. In press.

27. Serruys PW, Onuma Y, **Garg S**, Vranckx P, De Bruyne B, Morice MC, Colombo A, Macaya C, Richardt G, Fajadet J, Hamm C, Schuijer M, Rademaker T, Wittebols K, Stoll HP; on behalf of the ARTS II Investigators. Five-year clinical outcomes of the Arterial Revascularisation Therapies (ARTS-II) study of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. *J Am Coll Cardiol.* 2010; 55(11): 1093-101

28. Serruys PW, Onuma Y, **Garg S**, Sarno G, Van den Brand M, Kappetein AP, van Dyck N, Mack MJ, Holmes Jr DR, Feldman TE, Morice MC, Colombo A, Bass EJ, Leadley K, Dawkins K, van Es GA, Morel MA, Mohr F. Assessment of the SYNTAX score in the SYNTAX study. *EuroIntervention*. 2009; 5(1):50-56.

29. Shen ZJ, García-García HM, **Garg S**, Onuma Y, Schenkeveld L, van Domburg RT, Serruys PW; on behalf of the Interventional Cardiologists at Thoraxcentre in 2000–2003. Five-year clinical outcomes after coronary stenting of chronic total occlusion using sirolimus-eluting stents: Insights from the rapamycin-eluting stent evaluated at Rotterdam Cardiology Hospital-(Research) Registry. *Catheter Cardiovasc Interv*. 2009; 74(7):979-986

30. Shin ES, García-García HM, **Garg S**, Serruys PW. A comparison between plaque-based and vessel-based measurement for plaque component using volumetric intravascular ultrasound radiofrequency data analysis. *Int J Cardiovasc Imaging.* 2010 [Epub ahead of print]

31. Brugaletta S, García-García HM, **Garg S**, Gomez-Lara J, Diletti R, Onuma Y, van Geuns RJ, McClean D, Dudek D, Thuesen L, Chevalier B, Windecker S, Whitbourn R, Dorange C, Miquel-Hebert K, Sudhir K, Ormiston JA, Serruys PW. Temporal changes of coronary artery plaque located behind the struts of the everolimus eluting bioresorbable vascular scaffold. *Int J Cardiovasc Imaging.* 2010 [Epub ahead of print]

32. Shin ES, García-García HM, **Garg S**, Park J, Kim SJ, Serruys PW. The assessment of Shin's method for the prediction of creatinine kinase-MB elevation after percutaneous coronary intervention: an intravascular ultrasound study. *Int J Cardiovasc Imaging.* 2010 [Epub ahead of print]

33. Shin ES, García-García HM, **Garg S**, Ligthart J, Thuesen L, Dudek D, Ormiston JA, Serruys PW. Assessment of the serial changes of vessel wall contents in atherosclerotic coronary lesion with bioresorbable everolimus-eluting vascular scaffolds using Shin's method: an IVUS study. *Int J Cardiovasc Imaging*. 2010 [Epub ahead of print].

34. Onuma Y, Wykrzykowska JJ, **Garg S**, Vranckx P, Serruys PW. Five-year clinical outcomes of diabetic patients in the arterial revascularisation therapies (ARTS-II) study of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. *J Am Coll Cardiol Intv.* In press

35. Gomez-Lara J, García-García HM, Onuma Y, **Garg S**, Regar E, De Bruyne B, Windecker S, McClean D, Thuesen L, Dudek D, Koolen J, Whitbourn R, Smits P, Chevalier B, Dorange C, Veldhof S , Morel MA, deVries T, Ormiston JA. A comparison of the conformability of everolimus-eluting bioresorbable vascular scaffolds to metal platform coronary stents. *J Am Coll Cardiol Intv.* 2010;3(11):1190-1198

36. Sarno G, Onuma Y, García-García HM, **Garg S**, Regar E, Thuesen L, Dudek D, Veldhof S, Dorange C, Ormiston JA, Serruys PW. IVUS radiofrequency analysis in the evaluation of the dynamic changes of the polymeric struts of the bioabsorbable everolimus-eluting device during the bioabsorption process. *Catheter Cardiovasc Interv.* 2010;75(6):946-52

37. García-García HM, Gomez-Lara J, Gonzalo N, **Garg S**, Shin E, Goedhart D, Serruys PW. A comparison of the distribution of necrotic core in bifurcation and non-bifurcation coronary lesions: an in vivo assessment using intravascular ultrasound radiofrequency data analysis. E*uroIntervention* 2010; 6(3):321-327

38. Gomez-Lara J, Diletti R, Brugalleta S, **Garg S**, Onuma Y, Gogas W, van Geuns RJ, Dorange C, Veldhof S, Whitbourn R, Windecker S, García-García HM, Regar E, Serruys PW. A comparative assessment by optical coherence tomography of the performance of the first and second generation of the everolimus-eluting bioresorbable vascular scaffolds. *Eur Heart J.* 2011; 32(3): 294-304

39. Sarno G, Bruining N, Onuma Y, **Garg S**, Brugaletta S, De Winter S, Regar E, Thuesen L, Dudek D, Veldhof S, Dorange C, García-García HM, Ormiston JA, Serruys PW. Morphological and functional evaluation of the bioresorption of the bioresorbable everolimus-eluting vascular scaffold using IVUS, echogenicity and vasomotion testing at two year follow-up: a patient level insight into the ABSORB a clinical trial. *Int J Cardiovasc Imaging.* 2011 Jan 7. [Epub ahead of print]

40. Gutiérrez-Chico J-L, Serruys PW, Girasis C, **Garg S**, Onuma Y, Brugaletta S, García-García HM, van Es GA, Regar E. Quantitative multi-modality imaging analysis of a fully bioresorbable stent: a head-to-head comparison between QCA, IVUS and OCT. *Int J Cardiovasc Imaging.* In press.

41. Onuma Y, Girasis C, Piazza N, Kukreja N, **Garg S**, Eindhoven J, Cheng JM, Valgimigli M, van Domburg R, Serruys PW; Interventional Cardiologists at Thoraxcenter 2000–2005. Long-term clinical results following stenting of the left main stem insights from RESEARCH (Rapamycin-Eluting

Stent Evaluated at Rotterdam Cardiology Hospital) and T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) Registries. *J Am Coll Cardiol Intv.* 2010;3(6):584-594

42. Magro M, Nauta S, Simsek C, Onuma Y, **Garg S**, van der Heide E, van der Giessen W, Boersma H, van Domburg RT, van Geuns RJ, Serruys PW. Value of the SYNTAX score in patients treated by primary percutaneous coronary intervention for acute ST elevation myocardial infarction - the MI SYNTAXscore study. *Am Heart J.* In press.

43. Bourantas CV, Loh HP, Bragadeesh T, Rigby AS, Lukaschuk EI, **Garg S**, Tweddel AC, Alamgir FM, Nikitin NP, Clark AL, Cleland JGF. Relationship between right ventricular volume measured by cardiac magnetic resonance imaging and prognosis in patients with chronic heart failure. *Eur J Heart Fail.* 2011;13(1) :52-60

Reviews

1. **Garg S**, Serruys PW, Coronary Stents – Current status. *J Am Coll Cardiol*. 2010;56(10): S1-S42

2. **Garg S**, Serruys PW, Coronary Stents – Looking Forward. *J Am Coll Cardiol*. 2010;56(10): S43-S78

3. **Garg S**, Stone GW, Kappetein AP, Sabik J, Simonton C, Serruys PW. Clinical and angiographic risk assessment in patients with left main stem lesions. *J Am Coll Cardiol* Intv. 2010;3(9): 891-901

4. Holmes DR, Kereiakes DJ, **Garg S**, Serruys PW, Dehmer GJ, Ellis SG, Williams DO, Kimura T, Moliterno DJ. Stent Thrombosis. *J Am Coll Cardiol*. 2010; 56(17):1357-1365

5. **Garg S**, Serruys PW. Biodegradable stents and non-biodegradable stents. *Minerva Cardioangiol*. 2009; 57(5):537-65

6. **Garg S**, Hoye A. Percutaneous Coronary Intervention for de novo Bifurcation Lesions. *Interventional Cardiology*. 2006:30-32.

7. Magro M, **Garg S**, Serruys PW. Revascularization treatment of stable coronary artery disease. *Expert Opin Pharmacother*. 2011;12(2):195-212

8. Pernicova I, **Garg S**, Bourantas CV, Alamgir F, Hoye A. Takotsubo Cardiomyopathy: a review of the literature. *Angiology*. 2010; 61(2):166-173

9. Serruys PW, **Garg S**. Clinical implications of the SYNTAX trial. *Interventional Cardiology*. 2009; (4):41-45

10. Bourantas CV, Naka KK, **Garg S**, Thackray ST, Papadopoulos D, Alamgir MF, Hoye A, Michalis LK. Clinical indications for intracoronary ultrasound Imaging. *Echocardiography*. 2010; 27(10):1282-90

11. Sarno G, Okamura T, Gomez-Lara J, **Garg S**, Girasis C, Kopia G, Pomeranz M, Easterbrook W, van Geuns R-J, van der Giessen W, Serruys PW. The coronary Stent-On-A-Wire. *EuroIntervention*. 2010; 6(3):413-417

Editorials

1. **Garg S**, Serruys PW. Drug-eluting stents: a reappraisal. *Heart*. 2010; 96(7):489-93

2. **Garg S**, Serruys PW. A review of the benefits of and safety concerns associated with drug eluting coronary stents. *Expert Rev Cardiovasc Ther*. 2010; 8(3):449-70

3. **Garg S**, Duckers HJ, Serruys PW. Endothelial progenitor cell capture stents: will this technology find its niche in contemporary practice? *Eur Heart J*. 2010;31(9):1032-5

4. **Garg S**, Serruys PW. Drug eluting stents are safe. *Clin Pharmacol Ther*. 2009; 86(2):130-2

5. **Garg S**, Serruys PW. Interventional cardiology: Coronary angioplasty: Do we need to euroSCORE? *Nat Rev Cardiol*. 2009; 6(4): 267-268.

6. **Garg S**, Serruys PW. Mediations on secondary revascularisation in the aftermath of the SYNTAX trial. *EuroIntervention*. 2009; 5 (Suppl D):D14-20

7. Serruys PW, **Garg S**. PCI for all complex coronary artery disease: triple vessel and/or left main stem disease. Yes? No? Don't know? *Rev Esp Cardiol*. 2009; 62(7):719-25

Guidelines

1. Wijns W, Kolh P, Danchin N, DiMario C, Falk V, Folliguet T, **Garg S**, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini F, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. Guidelines on myocardial revascularization: the task force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2010; 31(20):2501-2555

2. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous Cardiovascular Interventions. Guidelines on myocardial revascularization. *Eur J Cardiothorac Surg*. 2010; 38 Suppl: S1-S52

Correspondence

1. **Garg S**, Rademaker T, Serruys PW. Correspondence fractional flow reserve for guiding PCI. *N Engl J Med*. 2009; 360(19):2024-2027

Book Chapters

1. **Garg S**, Wykrzykowska J, Serruys PW (2010). Stable angina: medical therapy vs. PCI vs. CABG. In: Thomas M, Redwood SR, Curzen N (eds.) Oxford Textbook of Interventional Cardiology. Oxford: Oxford University Press. pp221-34

2. **Garg S**, Serruys PW (In press). Individualised assessment for percutaneous or surgical revascularisation. In: Topol E, Ternstein P (eds) Textbook of Interventional Cardiology, 6th Edition. Oxford: Elsevier.

3. **Garg S**, Magro M, Serruys PW (In press). Coronary stents. In: Ducheyne P, Healy K, Hutmacher D, Kirkpatrick J (eds) Comprehensive Biomaterials. Oxford: Elsevier.

4. **Garg S**, Wykrzykowska J, Serruys PW (In press). Percutaneous Coronary Intervention In: Tse HF, Lip GYH, Coats A (eds) Oxford Desk Reference--Cardiology. Oxford: Oxford University Press.

5. **Garg S**, Räber L, Serruys PW, Windecker (In press). Coronary Artery Stenting. In: Eeckhout E, Serruys PW, Wijns W, Vahanian A, van Sambeek M (eds) Percutaneous Interventional Cardiovascular Medicine. Paris: Europa Edition Publishing.

6. **Garg S**, Holmes DR Jr, Wijns W (In press). Functional evaluation and risk stratification. In: Eeckhout E, Serruys PW, Wijns W, Vahanian A, van Sambeek M (eds) Percutaneous Interventional Cardiovascular Medicine. Paris: Europa Edition Publishing.

7. García-García HM, **Garg S**, Diletti R, Brugaletta R, Shin ES, Serruys PW (In press). In: Lampros M, Fotiadis D, Naka K, Bourantas C, Tsakanikas V (eds) Intravascular Imaging - Current Applications and Research Developments. Hershey PA: IGI Global.

Case reports

1. **Garg S**, Bourantas CV, Thackray S, Alamgir MF. Echocardiographic identification of ventricular septal rupture caused by acute stent thrombosis. *J Clin Ultrasound*. 2010; 38(4): 218-221

2. **Garg S**, Schultz C, Sarno G, Serruys PW. How should I treat a tortuous calcified right coronary artery? *EuroIntervention*. 2010; 6(1):161-7

3. **Garg S**, Serruys PW, van der Ent M, Schultz C, Mastik F, van Soest G, van der Steen AF, Wilder MA, Muller JE, Regar E. First use in patients of a combined near infra-red spectroscopy and intravascular ultrasound catheter to identify composition and structure of coronary plaque. *EuroIntervention*. 2010; 5(6):755-756

4. **Garg S**, Bourantas CV, Nair R, Alamgir F. Carcinoid syndrome diagnosed by echocardiography. *Int J Cardiol*. 2009 – published online ahead of print

5. **Garg S**, Bourantas CV, Thackray S, Alamgir F. Left main occlusion diagnosed on CT chest. *Br J Cardiol*. 2008; 15: 269-70.

6. **Garg S**, Bourantas C, Thackray S. Angiographically occult coronary artery dissection post-stenting imaged using optical coherence tomography. *Heart*. 2008; 94(3):335.

7. **Garg S**, Nair R, Alamgir MF. Palliative percutaneous coronary intervention with the PRESILLION stent in an elderly patient. *Cardiac & Vascular Update*. 2008; 2:4-6.

8. **Garg S**, Perez L, Griffin S. Type A aortic dissection presenting as complete heart block. *Resuscitation*. 2007; 75(3):398-99

9. **Garg S**, Walters M, Khan A. External cardiac pacing causing Staphylococcus aureus septicaemia. *Resuscitation*. 2006; 69(2):169-70

10. Onuma Y, **Garg S**, Okamura T, Ligthart J, Van Geuns RJ, De Feyter P, Serruys PW, Tamai H. Ten-year follow-up of the IGAKI-TAMAI stent. A post-humous tribute to the scientific work of Dr. Hideo Tamai. *Eurointervention*. 2009; 5 (Suppl F) F109-F111

11. Wentzel JJ, van der Giessen AG, **Garg S**, Schultz C, Mastik F, Gijsen FJH, Serruys PW, van der Steen AFW, Regar E. 3D distribution of lipid rich plaque in human coronary artery as assessed by fusion of NIR-IVUS and MSCT. *Circ Cardiovasc Imaging.* 2010; 3(6):e6-e7

12. Sarno G, Schultz C, **Garg S**, Ligthart J, García-García HM, Serruys PW. How should I treat a complex post CABG patient? *EuroIntervention*. 2009; 5(5):627-632.

13. Schultz C, Serruys PW, van der Ent M, Ligthart J, Mastik F, **Garg S**, Muller JE, Wilder MA, van der Steen A, Regar E. First in man clinical use of a combined near infra-red spectroscopy and intravascular ultrasound - a potential key to predict distal embolization and no reflow? *J Am Coll Cardiol*. 2010; 56(4): 314

PhD Portfolio

Name:	Scot Anil Garg
Erasmus MC Department:	Interventional Cardiology
PhD period:	November 2008—June 2010
Supervisor:	Prof. dr. P.W.J.C. Serruys

PhD Training

Oral presentations

2010 *Available stents, Future trends*
ICE Meeting
Ioannina, Greece, 9th—11th December 2010

2010 *Scores in multi-vessel disease patients: important tools for decision-making or just for trial purposes?*
Session on Multivessel Disease
EuroPCR, Paris, France, 25th—28th May 2010

2010 *The SYNTAX study*
Keynote presentation
Japanese Circulation Society, Kyoto, Japan, 5th—7th March 2010

2009 *Does stent design impact the outcome in bifurcation lesions?*
Session: LEADERS symposium
EuroPCR, Barcelona, Spain, 19th—22th May 2009

2009 *Thermography, OCT, and near-infra-red spectroscopy – will they become everyday tools?*
Trans-Pennine Meeting, Manchester, UK, 30th April—1st May 2009

2008 *Holters in acute medicine*
Royal College of Physicians SpR Teaching
Wakefield, Yorkshire, UK, October 16th 2008

2006 *Is sensible use being made of an in-patient Holter service within acute medicine?*
Yorkshire Cardiac network regional audit meeting
East Yorkshire, UK, June 21st 2006

Oral abstract presentations

2010 Shin ES, Garcia-Garcia HM, **Garg S**, Thuesen L, Dudek D, Ormiston JA, Serruys PW.
Assessment of the serial changes of necrotic core and calcium content in atherosclerotic coronary lesion with bioresorbable everolimus-eluting vascular scaffolds using shin's method: An IVUS study,
American Heart Association, Chicago, USA, 13th —17th November 2010

2010 Magro M, Nauta S, Simsek C, Onuma Y, **Garg S**, van der Heide E, van der Giessen W, Boersma E, van Domburg R, van Geuns RJ, Serruys PW.
Value of the SYNTAX score in patients treated by primary percutaneous coronary intervention for acute ST-elevation myocardial infarction — the MI SYNTAX score study.
American Heart Association, Chicago, USA, 13th—17th November 2010

2010 **Garg S**, Sarno G, Gutiérrez-Chico JL, Garcia-Garcia HM, Gomez-Lara J, Serruys PW.
Five year outcomes of percutaneous coronary intervention compared to bypass surgery in patients with multi-vessel disease involving the proximal left anterior descending artery: an ARTS-II sub-study.
European Society of Cardiology, Stockholm, Sweden, 28th Aug—1st Sept 2010

2010 **Garg S**, Serruys PW, Abizaid A, Ormiston J, Windecker S, Verheye S, Dubois C, Stewart J, Hauptmann KE, Schofer J, Stangl K, Witzenbichler B, Wiemer M, Barbato E, de Vries T, den Drijver AM, Otake H, Meredith L, Toyloy S, Fitzgerald P.
A randomised comparison of novolimus-eluting and zotarolimus-eluting coronary stents: 9-month follow-up results of the EXCELLA II study.
EuroPCR, Paris, France, 25th—28th May 2010

2010 Sarno G, Okamura T, **Garg S**, Gomez-Lara J, Girasis C, Kopia G, Pomeranz M, Easterbrook W, van Geuns R-J, van der Giessen W, Serruys PW.
The coronary Stent-On-A-Wire.
EuroPCR, Paris, France, 25th—28th May 2010

2010 Serruys PW, Silber S, **Garg S**, van Geuns RJ, Richardt G, Buszman PE, Kelbæk H, van Boven AJ, Hofma SH, Linke A, Klauss V, Wijns W, Macaya C, Garot P, di Mario C, Manoharan G, Kornowski R, Ischinger T, Bartorelli A, Ronden J, Bressers M, Gobbens P, Negoita M, van Leeuwen F, Windecker S.
Comparison of zotarolimus-eluting and everolimus-eluting coronary stents.
EuroPCR, Paris, France, 25th—28th May 2010

2009 **Garg S**, Girasis C, Sarno G, Goedhart D, Morel MA, Bressers M, Garcia-Garcia HM, van Es G-A, Serruys PW.
The SYNTAX score revisited: A new assessment of the SYNTAX score reproducibility.
Transcatheter Cardiovascular Therapeutics, San Francisco, CA, USA, 21st—25th Sept 2009

2009 **Garg S**, Wykrzykowska J, Serruys PW, de Vries T, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morcie MC, di Mario C, Tyczynski P, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Juni P, Windecker S.
The outcome of bifurcation lesion stenting using a biolimus-eluting stent with a biodegradable polymer compared to a sirolimus-eluting stent with a durable polymer.
EuroPCR, Barcelona, Spain, 19th—22nd May 2009

2009 Serruys P, Onuma Y, **Garg S**, Vranckx P, De Bruyne B, Morice MC, Colombo A, Macaya C, Richardt G, Fajadet J, Hamm C, Schuijer M, Rademaker T, Wittebols K, Stoll HP; ARTS II Investigators.
Five-year clinical outcomes of the arterial revascularisation therapies (ARTS-II) study of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions.
EuroPCR, Barcelona, Spain, 19th—22nd May 2009

Poster abstract presentations

2010 Sarno G, **Garg S**, Onuma Y, Gutiérrez-Chico JL, Van den Brand M, Rensing B, Morel MA, Serruys PW.
The impact of completeness of revascularization on the five-year outcome in PCI and CABG patients (from the ARTS-II study): insights from the SYNTAX score in multivessel coronary disease.
European Society of Cardiology, Stockholm, Sweden, 28th Aug—1st Sept 2010

2010 Wykrzykowska J, **Garg S**, Onuma Y, de Vries T, Goedhart D, Morel MA, van Es GA, Buszman PE, Linke A, Ischinger T, Klauss V, Corti R, Eberli F, Wijns W, Morice MC, di Mario C, van Geuns RJ, Juni P, Windecker S, Serruys PW.
Value of Age, Creatinine, and Ejection Fraction (ACEF score) in assessing risk in patients undergoing percutaneous coronary intervention in the "all-comers" LEADERS trial.
European Society of Cardiology, Stockholm, Sweden, 28th Aug—1st Sept 2010

2010 **Garg S**, Sarno G, Gutiérrez-Chico JL, Wykrzykowska J, Girasis C, Serruys PW.
Percutaneous coronary intervention in patients post-surgical revascularisation.
American College of Cardiology Scientific Sessions, Atlanta, USA, 14th—16th March 2010

2010 **Garg S,** Sarno G, Girasis C, Garcia-Garcia HM, Wykrzykowska J, Dawkins KD, Serruys PW.
A new tool for the risk stratification of patients with complex coronary artery disease: The Clinical SYNTAX Score.
American College of Cardiology Scientific Sessions, Atlanta, USA, 14th—16th March 2010

2010 Wykrzykowska JJ, **Garg S**, Girasis C, de Vries T, Morel, van Es GA, Buszman P, Linke A, Ischinger T, Klauss V, Corti R, Eberli F, Wijns W, Morice MC, di Mario C, van Geuns RJ, Juni P, Windecker S, Serruys PW.
Value of the SYNTAX Score for risk assessment in the "All-comers" population of the randomised multi-centre LEADERS trial.
American College of Cardiology Scientific Sessions, Atlanta, USA, 14th—16th March 2010

2010 Girasis C, **Garg S**, Raber L, Sarno G, Morel MA, Garcia-Garcia HM, Serruys PW, Windecker S.
Prediction of 5-year outcomes using the SYNTAX score in patients undergoing percutaneous coronary intervention from the SIRolimus-Eluting Stent Compared with PacliTAXel-Eluting Stents for Coronary Revascularisation (SIRTAX) Trial.
American College of Cardiology Scientific Sessions, Atlanta, USA, 14th—16th March 2010

2010 Regar E, **Garg S,** van der Ent M, Schultz C, Mastik F, van Soest G, van der Steen AF, Wilder MA, Muller JE, Serruys PW.
The first in human clinical use of a combined near infrared spectroscopy and intravascular ultrasound catheter to identify and characterise intracoronary plaque (SAVOIR study).
American College of Cardiology Scientific Sessions, Atlanta, USA, 14th—16th March 2010

2010 Sarno G, **Garg S**, Onuma Y, Buszman P, Linke A, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, van Geuns RJ, Eerdmans P, Garcia-Garcia HM, van Es GA, Goedhart D, de Vries T, Jüni P, Meier B, Windecker S, Serruys PW.
The impact of body mass index on the one year outcomes of patients treated by PCI with biolimus- and sirolimus- eluting stents in the LEADERS trial. Does the obesity paradox exist?
American College of Cardiology Scientific Sessions, Atlanta, USA, 14th—16th March 2010

2006 **Garg S**, Saha A, Clark AL.
Is sensible use being made of inpatient Holter service within acute medicine?
Society of Acute Medicine, Hull, UK, March 16—17th 2006

(Inter) national Conferences

2011	Advanced Cardiovascular Interventions, London, UK, 26th—28th January 2011	3 days
2010	Interventional cardiovascular education, Ioannina, Greece, 9th—11th December 2010	3 days

2010	Transradial Masterclass, Crewe, UK, 4th—5th November 2010	2 days
2010	British Cardiac Society Annual Conference, Manchester, UK, 7th—9th June 2010	3 days
2010	EuroPCR, Paris, France, 25th—28th May 2010	4 days
2010	Japanese Circulation Society, Kyoto, Japan, 5th—7th March 2010	3 days
2010	Advanced Cardiovascular Interventions, London, UK, 27th—29th January 2010	3 days
2009	Transcatheter Cardiovascular Therapeutics, San Francisco, USA, 22nd—25th Sep 2009	4 days
2009	European Society of Cardiology, Barcelona, Spain, 29th August 2009	1 day
2009	EuroPCR, Barcelona, Spain, 19th—22nd May 2009	4 days
2009	Advanced Cardiovascular Interventions, London, UK, 29th—31th January 2009	3 days
2008	EuroPCR, Barcelona, Spain, 13th—16nd May 2008	4 days
2008	Advanced Cardiovascular Interventions, London, UK, 23rd—25th January 2008	3 days
2006	European Society of Cardiology, Barcelona, Spain, 2nd—6th Sept 2006	5 days
2005	British Cardiac Society Annual Conference, Manchester, UK, 6th—7th June 2005	2 days
2004	British Cardiac Society Annual Conference, Manchester, UK, 24th—27thMay 2004	4 days

Other Courses

2010	TransRadial Masterclass, Crewe, UK, 4th-5th Nov 2010	2 days
2009	TransPennine meeting, Manchester, UK, 30th April — 1st May 2009	2 days
2009	OSCE training update, Leeds, UK, 3rd March 2009	1 day
2008	Intra-vascular ultrasound, Rotterdam, The Netherlands, 21st—22nd Nov 2008	2 days
2008	General cardiology update, Wakefield, UK, 17th October 2008	1 day
2008	Radiation Protection course, Hull, UK, June 2008	5 days
2008	Regional cardiology training, York, UK, 18th June 2008	1 day
2008	Trans-Pennine meeting, Leeds, UK, 17th—18th April 2008	2 days
2008	Regional cardiology training, York, UK, 10th April 2008	1 day
2008	OSCE Examiners workshop, Bradford, UK, 9th April 2008	1 day
2008	Regional cardiology audit, Bradford, UK, 26th February 2008	1 day
2007	Chronic total occlusions, Brussels, Belgium, 10th—12th December 2007	3 days
2007	Communicating risk, Leeds, UK, 17th October 2007	1 day
2007	Advanced life support, Hull, UK, 8th—10th October 2007	3 days
2007	Regional cardiology audit, Barnsley, UK, 4th October 2007	1 day
2007	Management and Leadership course, Hull, UK	7 days

2007	Cardiac MRI, Hull, UK	1 day
2007	PCI in acute MI, Geneva, Switzerland, 17th—18th April 2007	2 days
2006	PCI update, Leeds, UK, 2nd—4th October 2006	3 days
2006	Regional cardiology audit, East Yorkshire, UK, 21st June 2006	1 day
2006	Society of Acute Medicine, Hull, UK, 30th-31st March 2006	2 days
2006	Troubleshooting AICD, Geneva, Switzerland, 6th—8th February 2006	3 days
2005	Nuclear cardiology, Hull, UK, 29th September 2005	1 day
2005	An introduction to AICD, Stratford, UK, 19th-20th September 2005	2 days
2005	Lipid management, London, UK, 28th January 2005	1 day
2004	Acute medical update, London, UK, 8th-10th November 2004	3 days
2003	Hands on Echo, London, UK, 07th –11th April 2003	5 days

2. Teaching

1999-2010	Medical student teaching during all hospital appointments
1999-2010	Teacher of invasive procedures to junior colleagues
2008	OSCE examiner for final year medical students at Leeds University
2003-2010	MRCP teaching to colleagues studying for MRCP