Percutaneous treatment of complex lesions and complex patients

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Percutane behandeling van complexe laesies en complexe patienten

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To my parents

INTRODUCTION

Chapter 1

Stable coronary artery disease: medical therapy versus percutaneous coronary intervention versus surgery

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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.

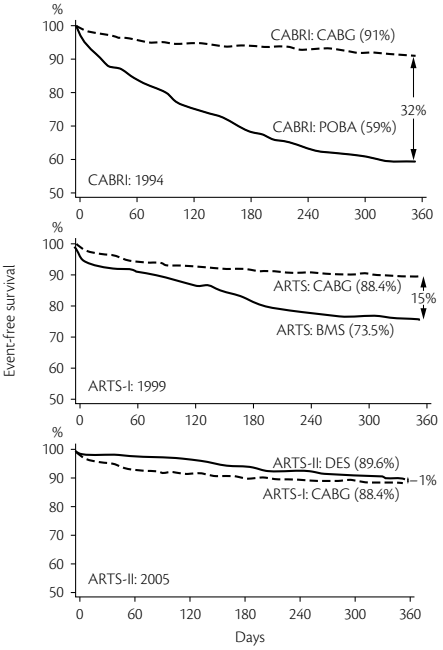

Fig. 14.1 Event-free survival at 1 year follow-up in the CABRI, ARTS-I, and ARTS-II studies showing a reduction in the difference in outcomes between CABG compared with balloon angioplasty, bare-metal stenting, and drug-eluting stents. Reproduced from Serruys, PW, ARTS I – the rapamycin eluting stent; 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).

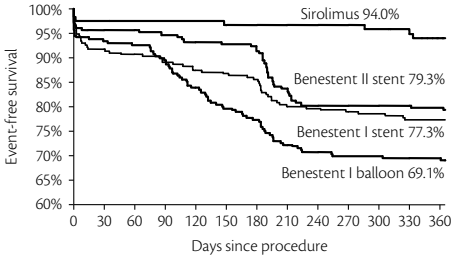

Fig. 14.2 The improved event-free survival in the Benestent I and II trials with the use of a bare-metal stent (Benestent I stent) or a heparin-coated stent (Benestent II) compared to only balloon angioplasty (Benestent balloon). The event-free survival, however, is much greater with a sirolimus-eluting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

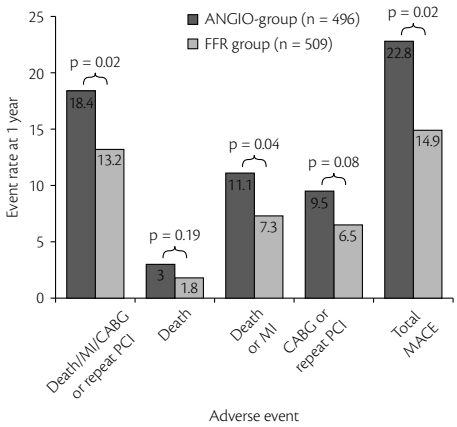

Fig. 14.3 The adverse event rates at one year from the 1005 patients in the FAME study showing improved outcomes with the use of an FFR-guided strategy[35].

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

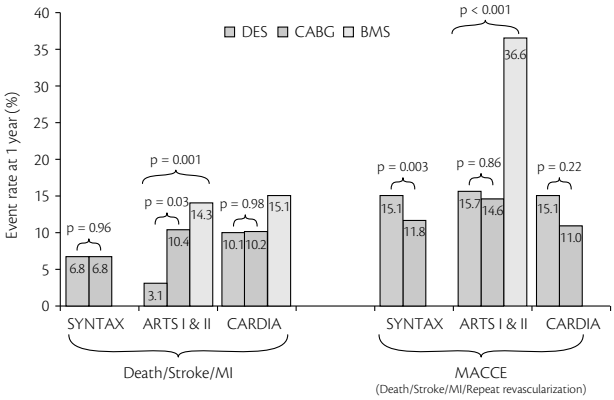

Fig. 14.4 The combined rates of death, stroke, and MI, and MACCE (death, stroke, MI, and repeat revascularization with either PCI or CABG) at 1 year amongst diabetic patients from ARTS-I, ARTS-II, CARDIA, and SYNTAX studies. From the limited data available there is an improvement in events with the use 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.

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Part I

Chapter 2

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

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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 $\leq$8 (SXlow) ($n = 464$), SXscore $>$8 and $\leq$16 (SXmid) ($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)

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.

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

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.

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

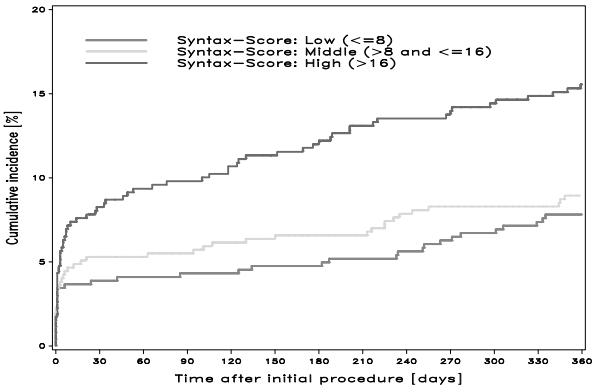

Figure 1 Kaplan-Meier Curves for MACE at 360 Days According to the SYNTAX Tertiles

Patients in the highest tertile of the SYNTAX score have an increased major adverse cardiac events (MACE) event rate (p = 0.0002).

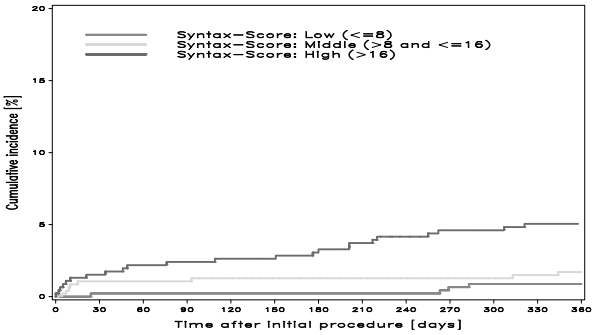

Figure 2 **Kaplan-Meier Curves for Cardiac Death at 360 Days According to the SYNTAX Score Tertiles**

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.

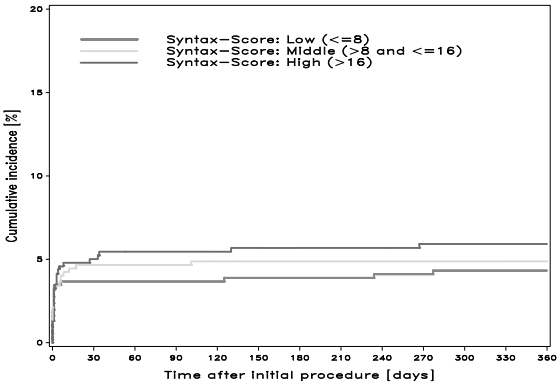

Figure 3 **Kaplan-Meier Curves for All Myocardial Infarctions at 360 Days According to the SYNTAX Score Tertiles**

There is no difference in the rate of overall myocardial infarctions across the tertiles of SYNTAX score ($p = 0.548$ [NS]).

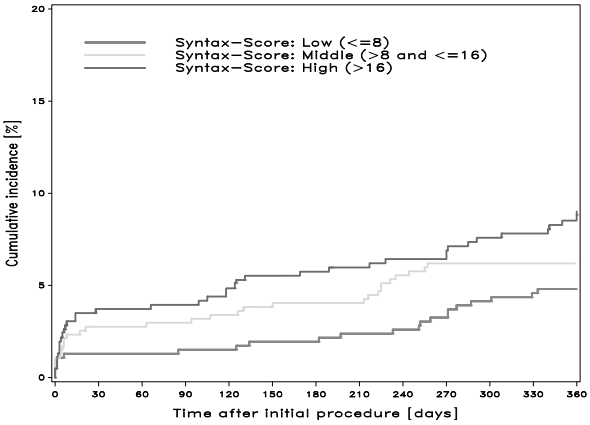

Figure 4 **Kaplan-Meier Curves for Target Lesion Revascularization at 360 Days According to the SYNTAX Score Tertiles**

Patients in the highest tertile of the SYNTAX score have an increased risk of target lesion revascularization (p = 0.036).

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Key Words: biodegradable polymer ■ biolimus-eluting stent ■ major adverse cardiac event ■ prognostic value ■ sirolimus-eluting stent ■ target vessel revascularization ■ SYNTAX score.

Chapter 3

Value of Age, Creatinine, and Ejection Fraction (ACEF Score) in Assessing Risk in Patients Undergoing Percutaneous Coronary Interventions in the 'All-Comers' LEADERS Trial

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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;CV-4:00-00.)

Key Words: ACEF score ■ SYNTAX score ■ biolimus-eluting stent ■ sirolimus-eluting stent ■ biodegradable polymer ■ cardiac death ■ major adverse cardiac event

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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 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 ●●●

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.

AQ: 4

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.

AQ:5, T1–4

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%;

T5–6,F1–4

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.

$P=0.0218$). 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% of patients with high ACEF scores (HR=2.22, $P=0.002$). The rate of MI was significantly higher in patients with

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 2b3a	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.

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). 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

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 2b3a	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)

sirolimus-eluting stents had equivalent event rates across all 3 ACEF tertiles.

Multivariate Model

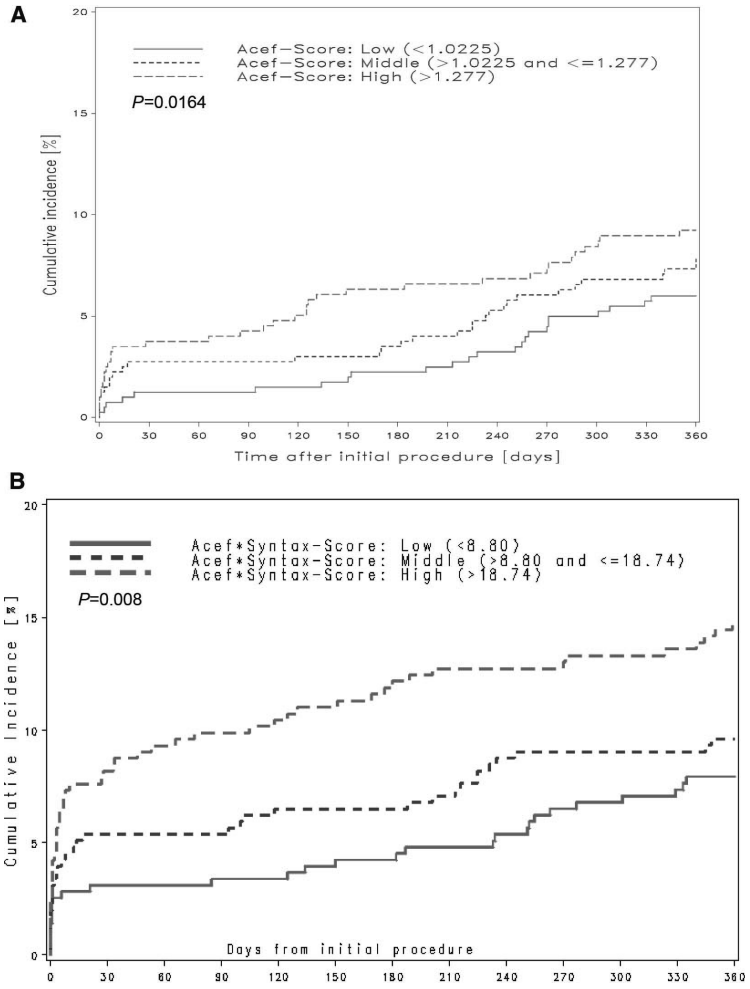
In a multivariate model, the ACEF score remained a significant predictor of MACEs and mortality (Tables 5 and 6; note that the HRs are adjusted for the following variables: ACEF score, diabetes, β-blocker use, stent type, and presence of ST-segment elevation MI/acute coronary syndrome, the same variables 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, 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). T7
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

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)



AQ: 7 **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.

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.

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

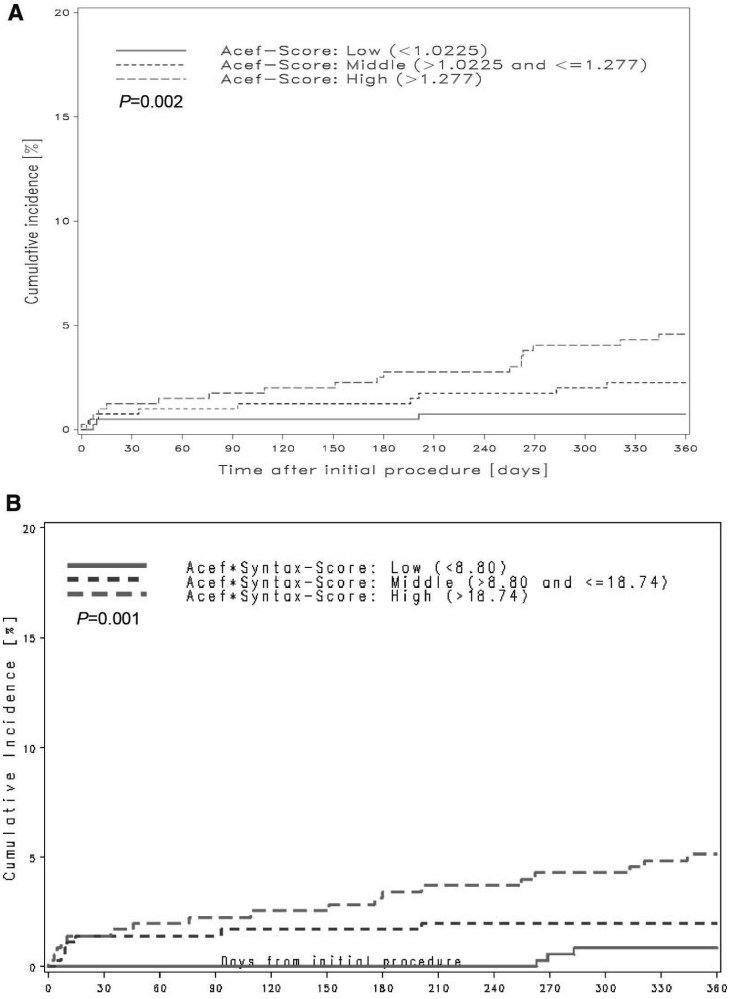


Figure 2. A, Kaplan-Meier score for cardiac death at 360 days according to ACEF score tertiles. B, Kaplan-Meier score for cardiac death at 360 days according to ACEF*SYNTAX score tertiles.

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 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

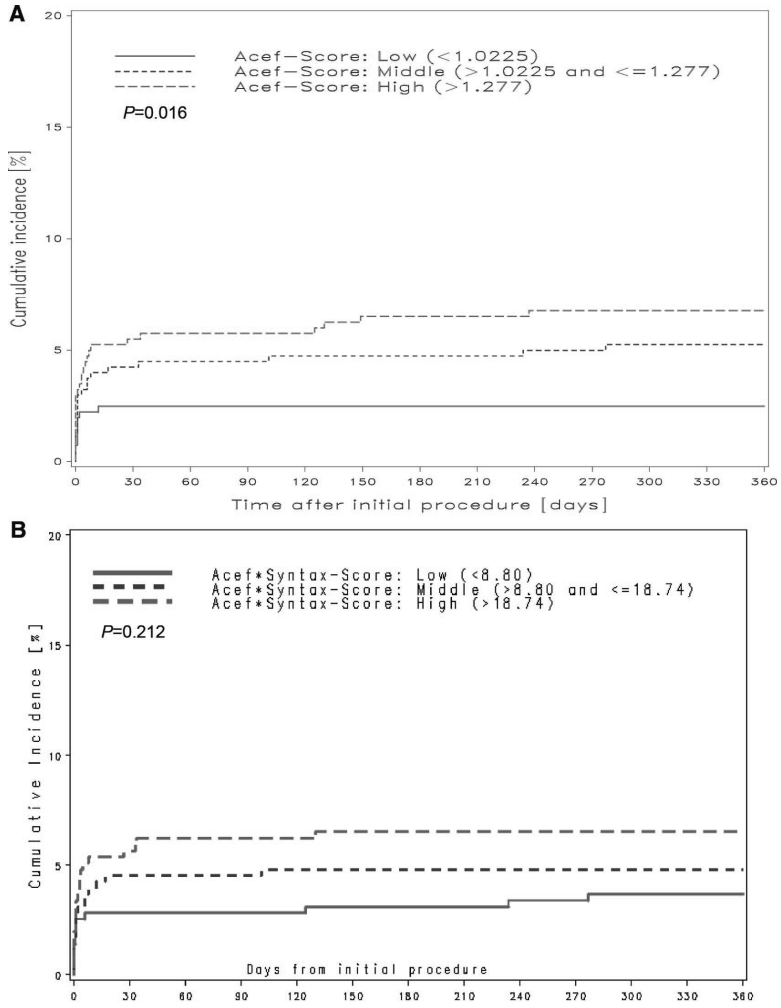


Figure 3. A, Kaplan-Meier curve for MI at 360 days according to ACEF tertiles. B, Kaplan-Meier curve for MI at 360 days according to ACEF*SYNTAX score tertiles.

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] 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

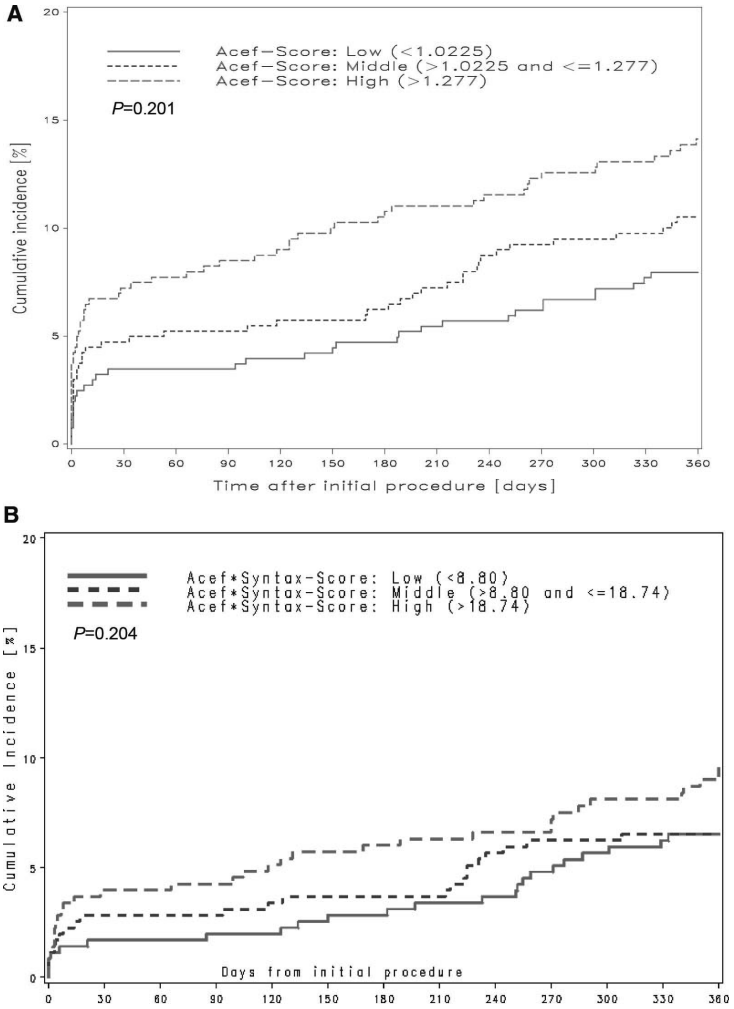


Figure 4. A, Kaplan-Meier curve for TLR at 360 days according to ACEF score tertiles. B, Kaplan-Meier curve for TLR at 360 days according to ACEF*SYNTAX score tertiles.

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 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]

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

Limitations

We acknowledge that this substudy suffers from the limitations of post hoc analysis. In addition, the ACEF score has not been 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. Last, 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).

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Disclosures

Stephan Windecker is a consultant to Biosensors, Cordis, Boston Scientific, Medtronic, and Abbott. All other authors report no conflicts of interest.

AQ: 6

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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

A New Tool for the Risk Stratification of Patients With Complex Coronary Artery Disease : The Clinical SYNTAX Score

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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

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 $CSS_{LOW} \leq 15.6$ (n=170), $15.6 \leq CSS_{MID} < 27.5$ (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-

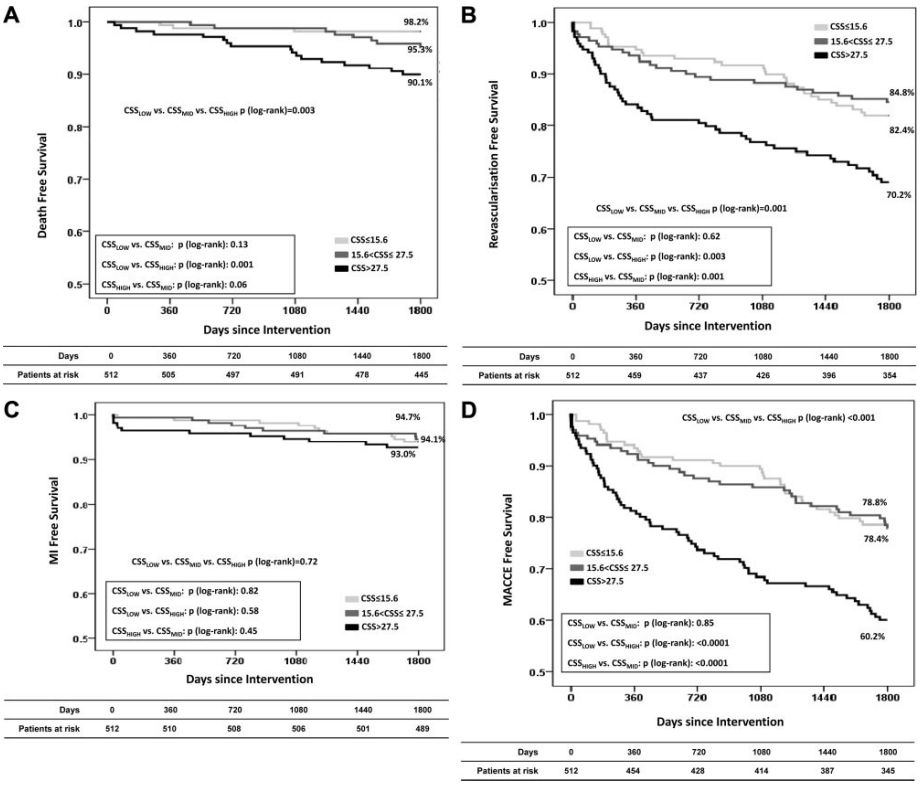

Figure 1. Kaplan Meier curves for death (A), repeat revascularization (B), myocardial infarction (MI) (C), and major adverse cardiovascular and cerebrovascular events (MACCE) (D) at 1800-day follow-up stratified accord to CSS tertile.

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.

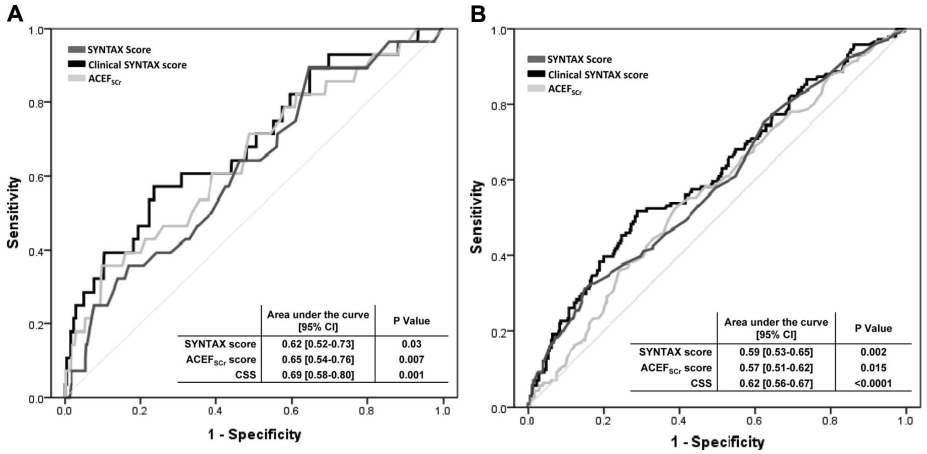

Figure 2. ROC curve for the SYNTAX score, ACEF$_{SCr}$, and CSS for mortality (A) and MACCE (B). The use of the CSS leads to an improvement in the C-statistic for both outcomes.

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).

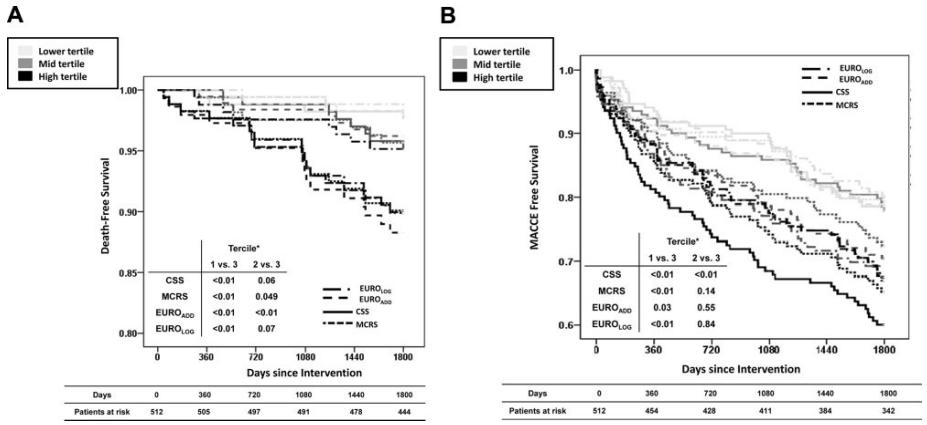

Figure 3. Kaplan-Meier curve showing the 5-year mortality (A) and MACCE-free survival (B) stratified according to tertiles of the CSS, Mayo Clinic Risk Score (MCRS), Additive euroSCORE (EURO$_{ADD}$) and Logistic euroSCORE (EURO$_{LOG}$). No significant difference was observed between outcomes in Tertiles 1 and 2 (probability values not shown). **P* (log-rank) values.

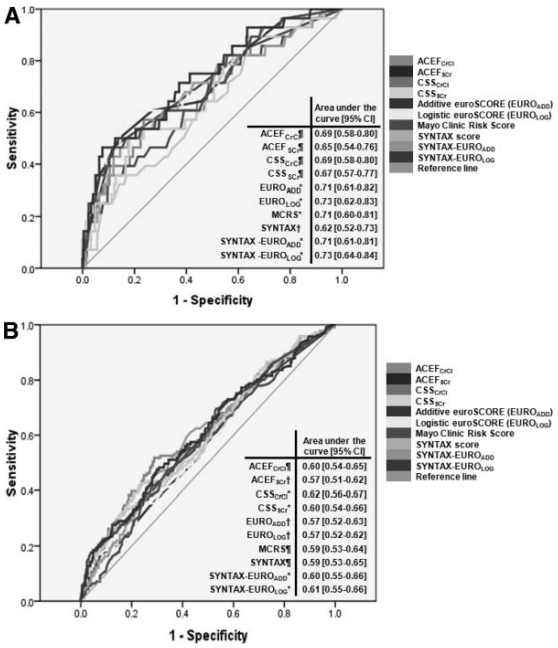

Figure 4. ROC curve for mortality (A) and MACCE (B) at 5-year follow-up for different risk scores. *$P<0.001$, †$P<0.05$, ¶$P<0.01$.

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.

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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).

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 cerebro-vascular 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.

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.

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 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 $\pm$ SD of 24.9$\pm$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: $CSS_{LOW} \leq 16$ (n=83), $16 < CSS_{MID} \leq 26$ (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, 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 univariate 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 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 for 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, atmosphere; SD, standard deviation; CSS, clinical SYNTAX Score; No., number; RVD, reference vessel diameter

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, percutaneous coronary intervention

CABG, coronary artery bypass grafting

CSS, Clinical SYNTAX Score

MACCE, major adverse cardiovascular and cerebrovascular events

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, confidence interval

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 for 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, atmosphere; SD, standard deviation; CSS, clinical SYNTAX score; No., number; RVD, reference vessel diameter

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, percutaneous coronary intervention

CABG, coronary artery bypass grafting

CSS, Clinical SYNTAX score

MACCE, major adverse cardiovascular and cerebrovascular events

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	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, confidence interval

Supplementary Figure Legends

Supplementary Figure 1: Logarithmic distribution of the Clinical SYNTAX score (CSS). The CSS is normally distributed after logarithm transformation.

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: 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: Kaplan Meier curve showing the 5-year MACCE-free survival stratified according to tertiles of the CSS, and the MCRS.

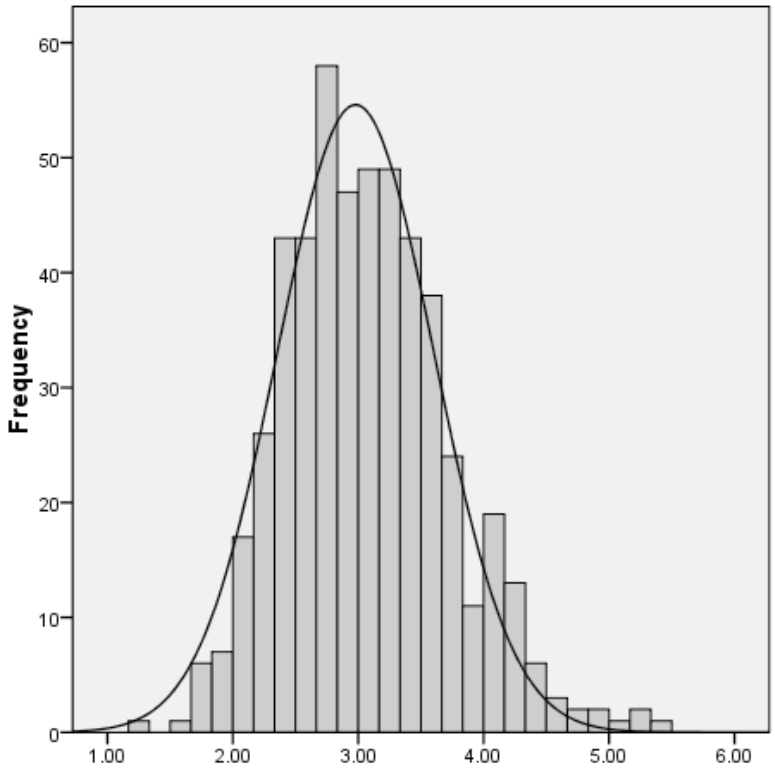
Supplementary Figure 5: Kaplan Meier curves for (A) death, (B) myocardial infarction, (C) repeat revascularisation and (D) MACCE at 5-years follow-up amongst 239 patients with three vessel disease in the ARTS-II study with a Clinical SYNTAX score.

Supplementary 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.

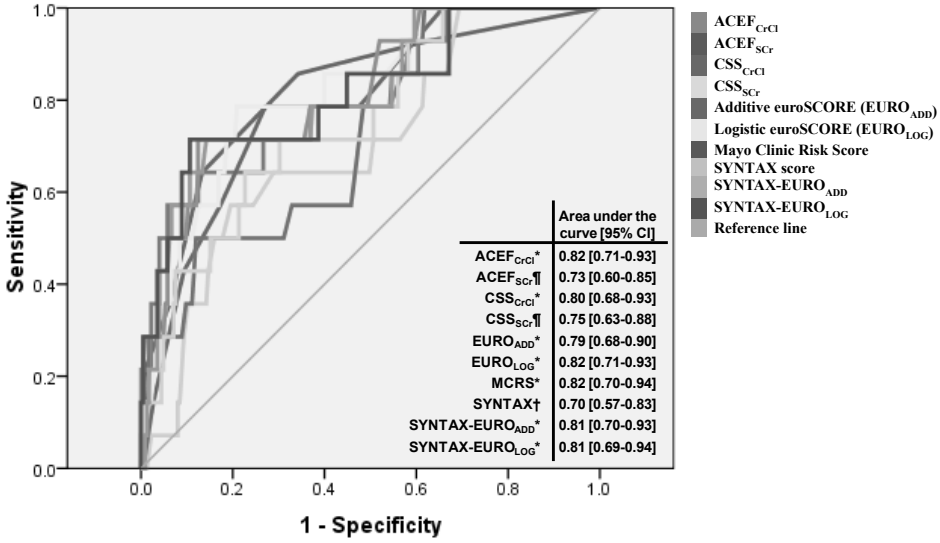
Supplementary Figure 7: Kaplan Meier curves for (A) death, (B) myocardial infarction, (C) repeat revascularisation and (D) MACCE at 5-years follow-up amongst all 251 patients in the ARTS-II study with a Clinical SYNTAX score calculated using the serum creatinine.

Supplementary Figure 8: ROC 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 Figure 1.

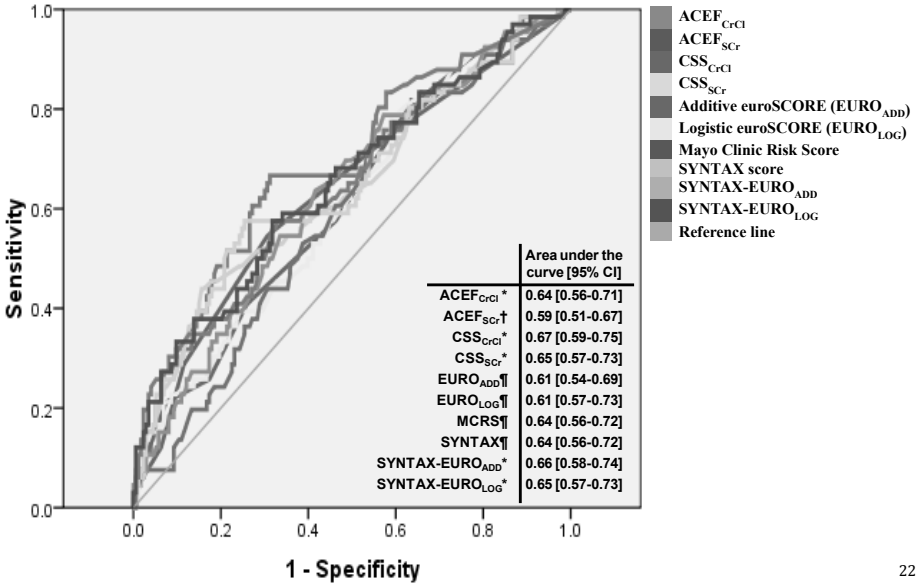


Supplementary Figure 2A:



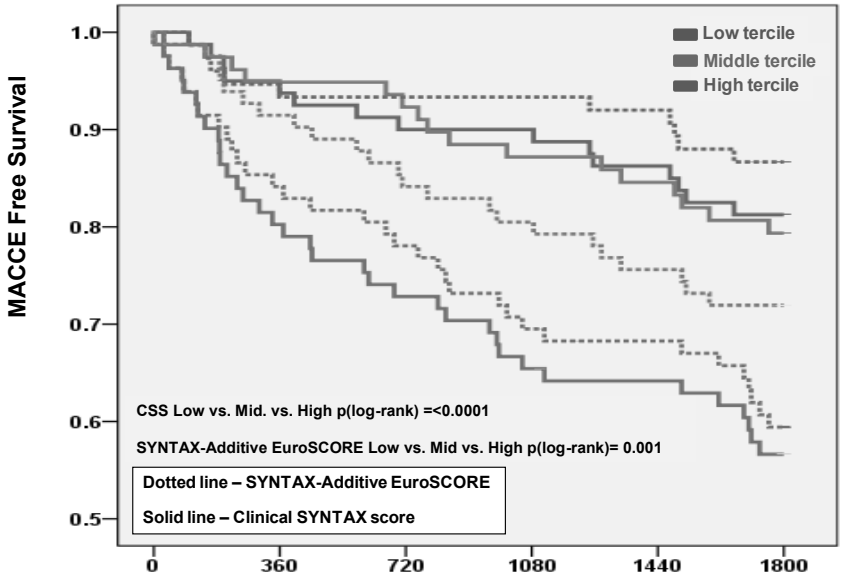
	Area under the curve [95% CI]
ACEF$_{CrCl}$*	0.82 [0.71-0.93]
ACEF$_{SCr}$¶	0.73 [0.60-0.85]
CSS$_{CrCl}$*	0.80 [0.68-0.93]
CSS$_{SCr}$¶	0.75 [0.63-0.88]
EURO$_{ADD}$*	0.79 [0.68-0.90]
EURO$_{LOG}$*	0.82 [0.71-0.93]
MCRS*	0.82 [0.70-0.94]
SYNTAX†	0.70 [0.57-0.83]
SYNTAX-EURO$_{ADD}$*	0.81 [0.70-0.93]
SYNTAX-EURO$_{LOG}$*	0.81 [0.69-0.94]

Supplementary Figure 2B:



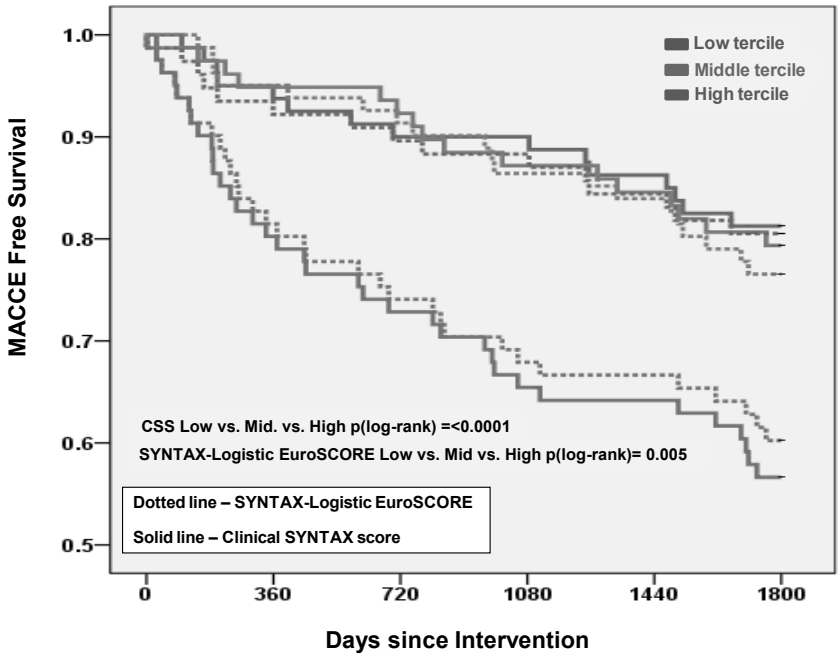
	Area under the curve [95% CI]
ACEF$_{CrCl}$*	0.64 [0.56-0.71]
ACEF$_{SCr}$†	0.59 [0.51-0.67]
CSS$_{CrCl}$*	0.67 [0.59-0.75]
CSS$_{SCr}$*	0.65 [0.57-0.73]
EURO$_{ADD}$¶	0.61 [0.54-0.69]
EURO$_{LOG}$¶	0.61 [0.57-0.73]
MCRS¶	0.64 [0.56-0.72]
SYNTAX¶	0.64 [0.56-0.72]
SYNTAX-EURO$_{ADD}$*	0.66 [0.58-0.74]
SYNTAX-EURO$_{LOG}$*	0.65 [0.57-0.73]

Supplementary Figure 3A



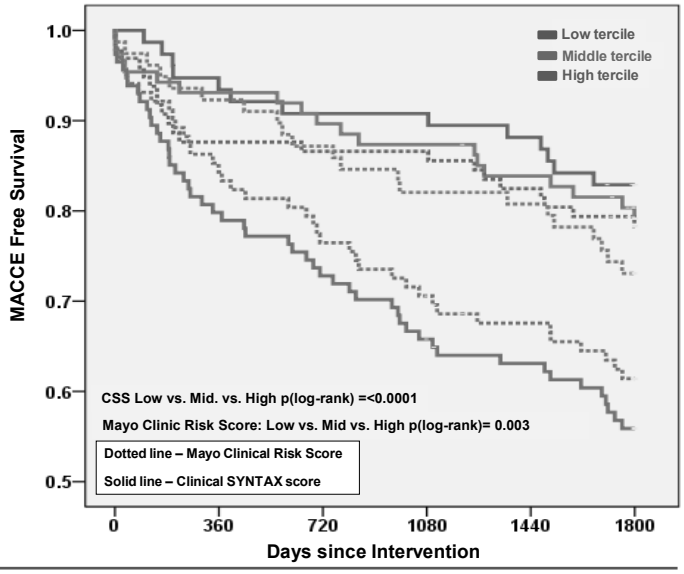
Days	0	360	720	1080	1440	1800
Patients at risk	239	214	203	193	185	162

Supplementary Figure 3B



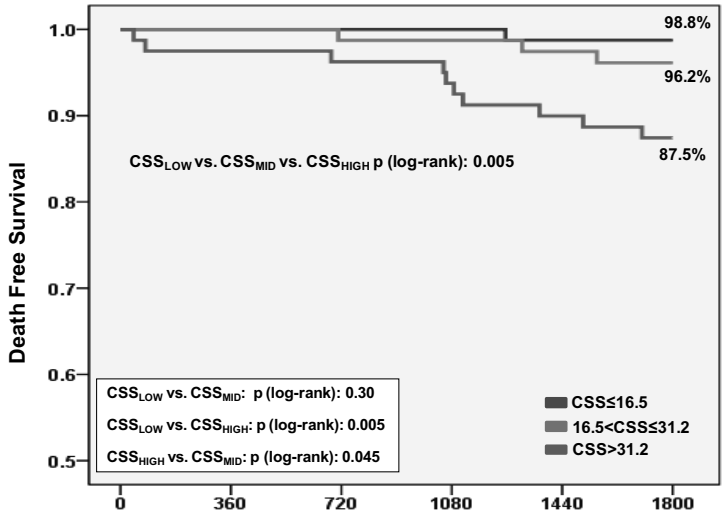
Days	0	360	720	1080	1440	1800
Patients at risk	239	214	203	193	185	162

Supplementary Figure 4



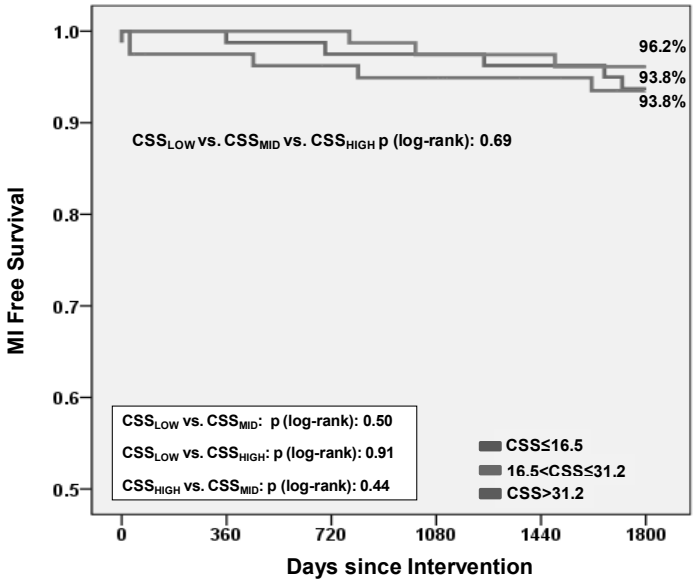
Days	0	360	720	1080	1440	1800
Patients at risk	239	214	203	193	185	162

Supplementary Figure 5A.



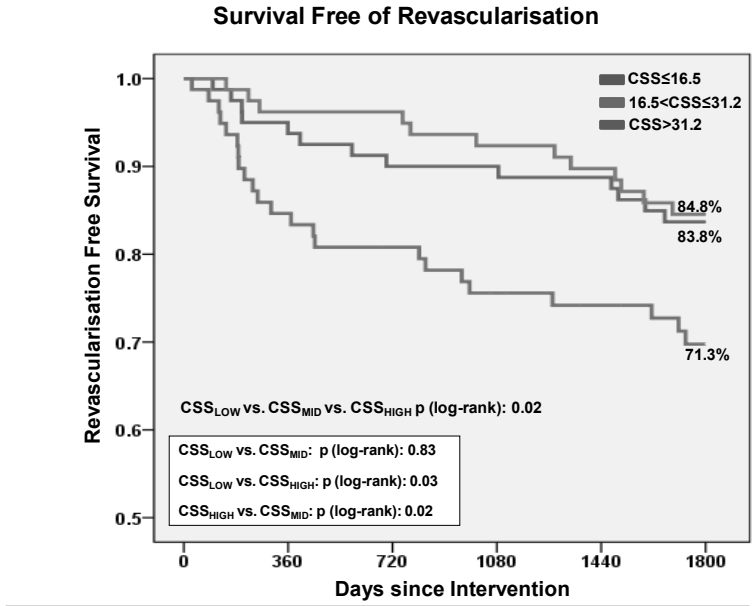
Days	0	360	720	1080	1440	1800
Patients at risk	239	237	235	233	225	207

Supplementary Figure 5B.



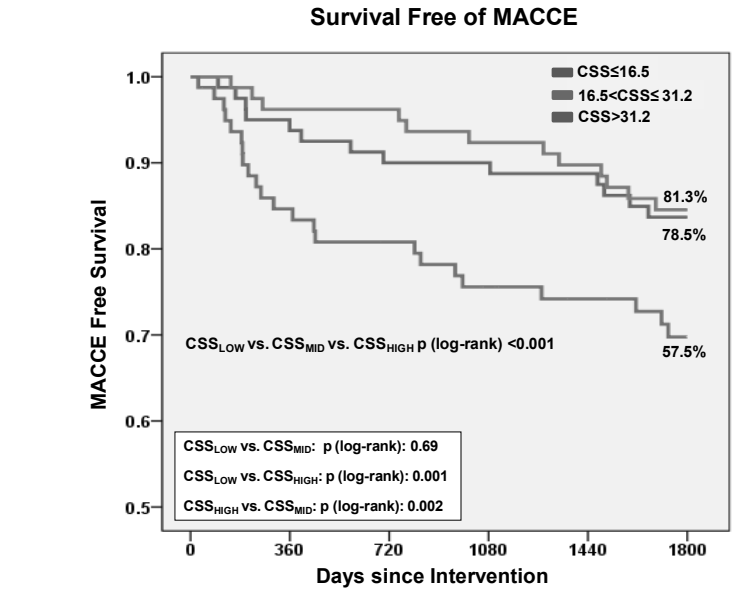
Days	0	360	720	1080	1440	1800
Patients at risk	239	234	230	226	218	198

Supplementary Figure 5C.



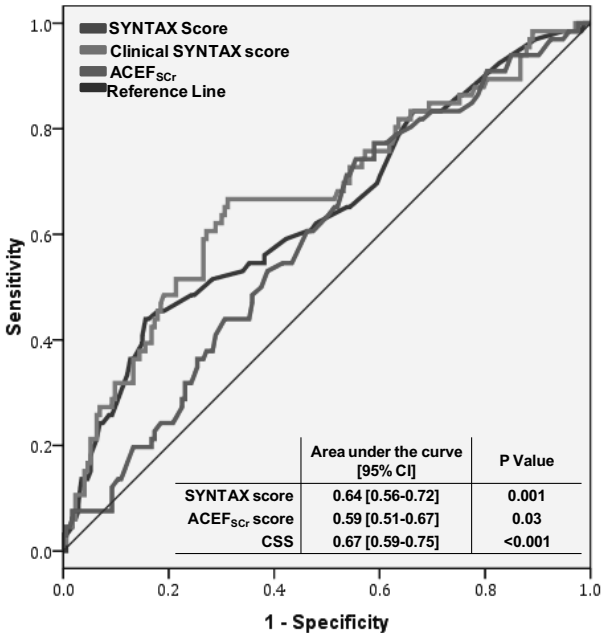
Days	0	360	720	1080	1440	1800
Patients at risk	239	217	209	200	191	167

Supplementary Figure 5D.



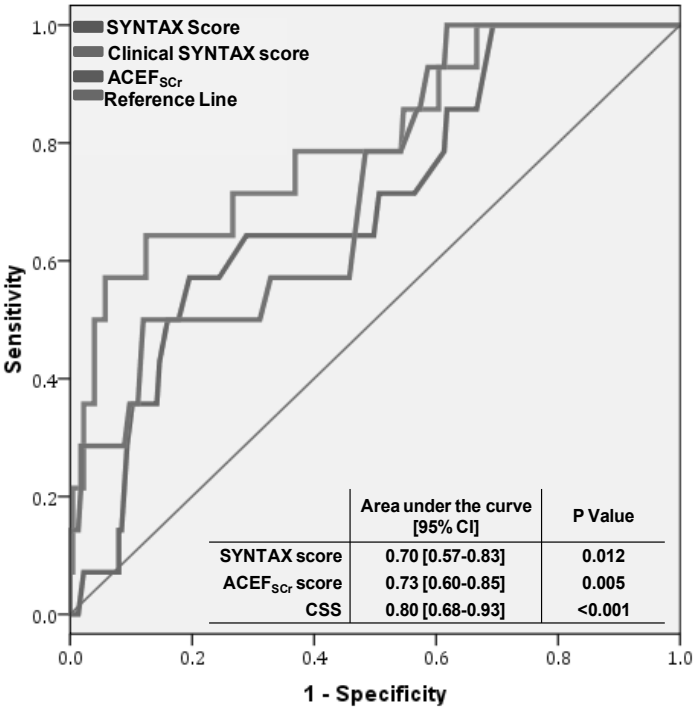
Days	0	360	720	1080	1440	1800
Patients at risk	239	214	203	193	185	162

Supplementary Figure 6A.



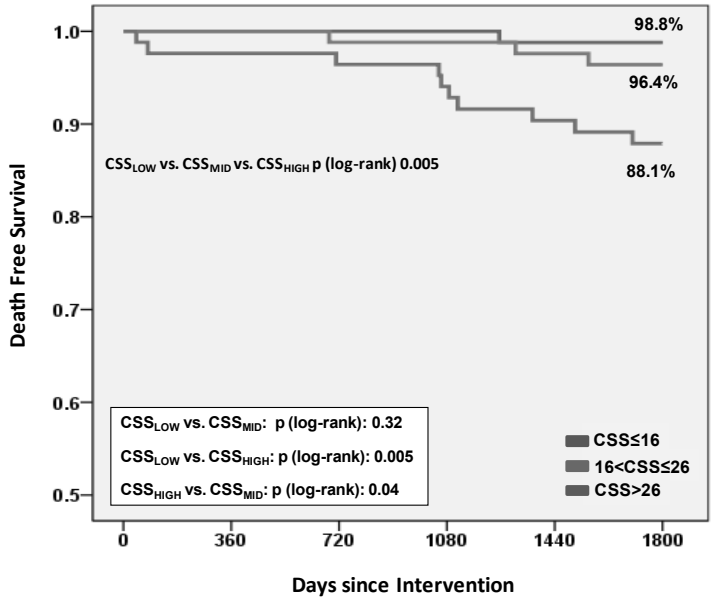
	Area under the curve [95% CI]	P Value
SYNTAX score	0.64 [0.56-0.72]	0.001
ACEF$_{SCr}$ score	0.59 [0.51-0.67]	0.03
CSS	0.67 [0.59-0.75]	<0.001

Supplementary Figure 6B.



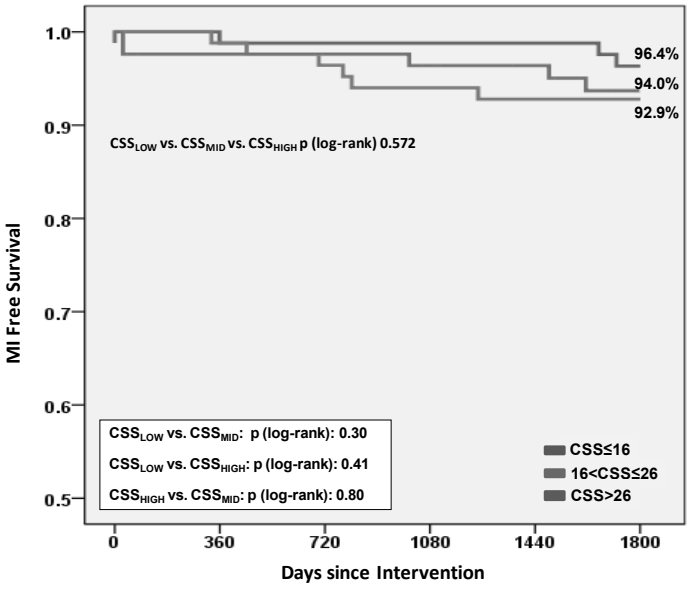
	Area under the curve [95% CI]	P Value
SYNTAX score	0.70 [0.57-0.83]	0.012
ACEF$_{SCr}$ score	0.73 [0.60-0.85]	0.005
CSS	0.80 [0.68-0.93]	<0.001

Supplementary Figure 7A.



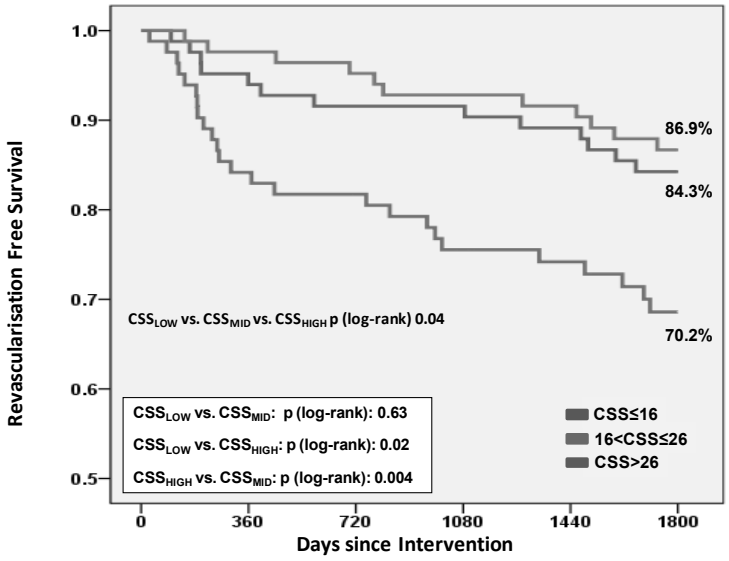
Days	0	360	720	1080	1440	1800
Patients at risk	251	249	247	246	235	217

Supplementary Figure 7B.



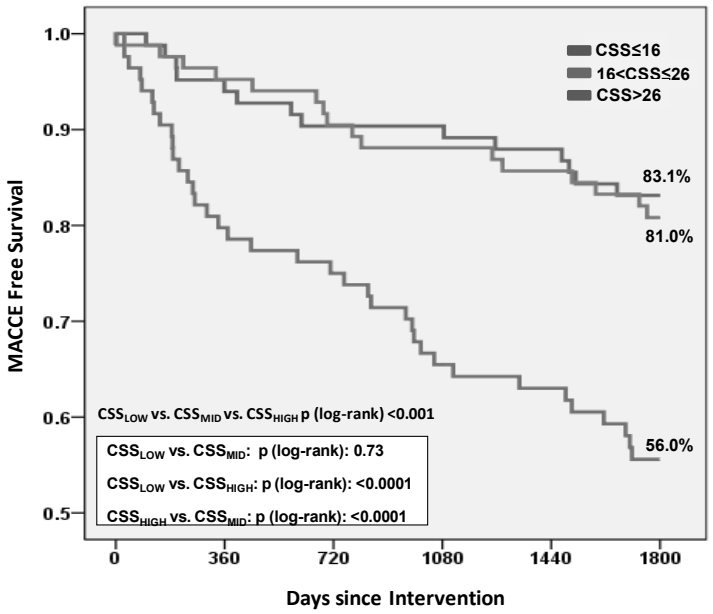
Days	0	360	720	1080	1440	1800
Patients at risk	251	245	241	237	228	208

Supplementary Figure 7C



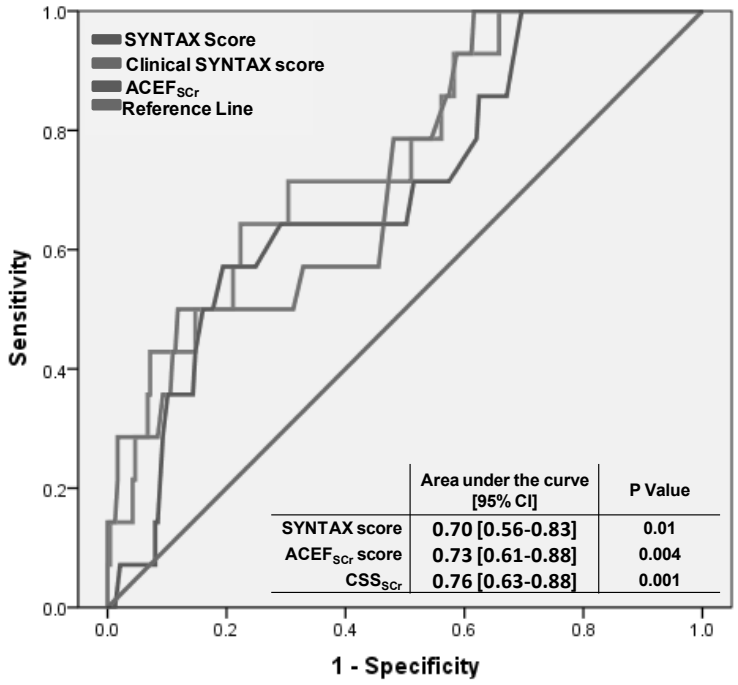
Days	0	360	720	1080	1440	1800
Patients at risk	251	229	221	212	202	177

Supplementary Figure 7D

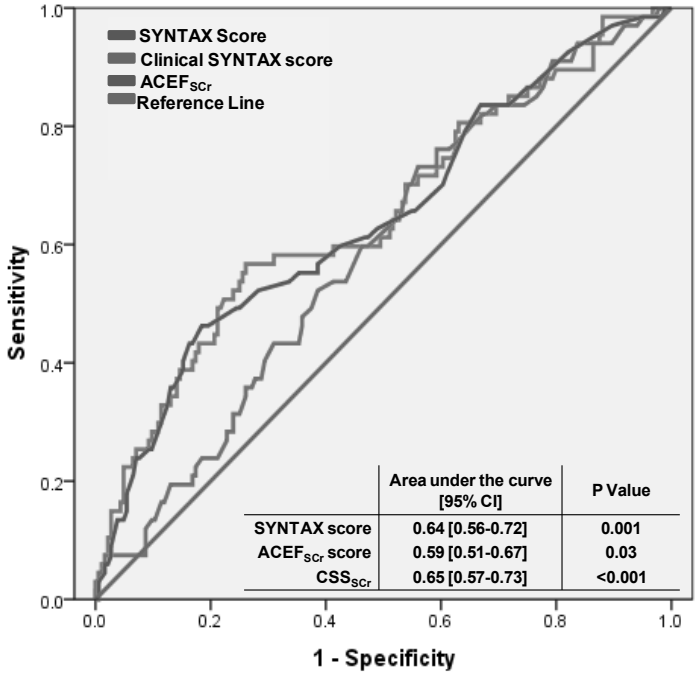


Days	0	360	720	1080	1440	1800
Patients at risk	251	234	230	222	218	210

Supplementary Figure 8A



Supplementary Figure 8B



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Chapter 5

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.

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Keywords*: SYNTAX score, prognostic value, biolimus-eluting stent, sirolimus-eluting stent, biodegradable polymer, target vessel revascularization, cardiac mortality*

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 in the "all-comers" LEADERS trial (patients after 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.

Results: 1,397 patients were divided into tertiles based on the SXscore in the following fashion: SXlow ≤8 (n=464), 8 <SXmid ≤16 (n=472) and SXhigh >16 (n=461). At 2 year follow-up the rate of major adverse cardiovascular events was 18.4%, 12.0% and 9.4% in the SXhigh, SXmid, and SXlow 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% SXhigh versus 2.4% SXmid versus 1.8% SXlow; HR 2.22 (CI 1.5-3.27); p<0.001). Within the SXhigh tertile the rate of cardiac death was significantly lower in patients treated with Biolimus Eluting Stent (4.7%) compared with Sirolimus Eluting Stent (9.6%) (HR 0.48; CI 0.23-0.99; p=0.046).

Conclusions: The SXscore when applied to an "all-comers" patient population allows for prospective risk stratification of patients undergoing PCI up to two years follow-up. In addition, the SXscore appears 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 revascularization 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 four-fold 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 evaluated as a predictor of peri-procedural myocardial infarction in a 100 patients undergoing an elective procedures for long lesions and bifurcation stenting.[9] 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.[10] In the current sub-study 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 myocardial infarction 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 percutaneous coronary intervention 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 SXscore is not currently validated in patients with acute myocardial infarction or previous PCI, and no scoring algorithm has been devised for these groups of patients at present. Core lab analysts were blinded to all clinical data and therefore patients with occluded infarct related arteries were scored as occlusions of unknown duration in the same manner as 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.

Limitations: The methods employed for scoring acutely occluded arteries and 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 at least 75 mg of acetylsalicylic acid, 300-600 mg loading dose of clopidogrel, and unfractionated heparin at a dose at least 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.[11]

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.[11] The primary endpoint of this sub-study was MACE, defined as the composite of cardiac death, myocardial infarction (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, myocardial infarction, stent thrombosis (defined according to the Academic Research Council[12]), device success (defined as achievement of a final residual diameter stenosis of less than 50% during the initial procedure), and lesion success (achievement of less than 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% or greater 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.*[10] 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 SYNTAX score. 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: SXlow ≤8 (n=467), 8<SXmid ≤16 (n=472) and SXhigh >16 (n=461).

The baseline clinical and angiographic data according to the three SXscore tertiles has been previously reported and is included in Table 1 and 2.[10] Briefly, the SXscore ranged from 1 to 49, with a mean ± SD of 13.5±8.7, and a median of 12 (inter-quartile range of 12; 7 to 19). Overall, at 1-year patients in the highest SXscore tertile had a significantly higher rate of death, TVR, MACE and a trend for high rates of MI.

Table 1. Baseline clinical characteristics based on SYNTAX tertiles

Baseline clinical variables, (%)	SX score <8 N=464	SX score 8-16 N=472	SX score >16 N=461	p-value on Trend (2-sided)
Age >65	45	48	52	0.048
Male	75	73	74	0.79
Diabetes	20	25	24	0.15
Current smoking	29	26	27	0.61
Hypertension	76	75	70	0.048
Hypercholesterolemia	68	67	62	0.06
Family history	43	40	36	0.034
Renal insufficiency	4	5	6	0.09
Previous MI	29	31	30	0.69
Previous PCI	39	35	32	0.036
Clinical presentation:				
Stable	32	33	23	0.008
Unstable	27	33	19	0.002
STEMI	10	19	28	<0.0001

Table 2. Baseline angiographic characteristics by SYNTAX tertiles

Angiographic variable	SX score <8	SX score 8-16	SX score >16	p-value
No. of diseased lesions per patient (based on SYNTAX application)	1.5	2.4	3.5	<0.001
No. of treated lesions per patient (as defined by Corelab)	1.2	1.5	1.7	<0.001
Coronary artery treated				
LAD	35%	51%	64%	<0.001
LCX	30%	31%	36%	0.079
RCA	47%	44%	38%	0.007
2-vessel disease	11%	22%	30%	<0.001
3-vessel disease	1%	3 %	5%	<0.001
Stent type				
Biolimus	49%	50%	52%	NS
Sirolimus	51%	50%	48%	NS
Number of implanted stents	1.5	1.9	2.3	<0.001
Total stent length/patient (mm)	26	34	43	<0.001
Chronic total occlusion	1%	2%	4%	0.006
Moderate to severe calcification	5%	20%	40%	<0.001
Bifurcation lesion	12%	34%	40%	<0.001
Use of 2b3a	17%	24%	33%	<0.001

Two-year clinical outcomes for the overall study population:

At 2 year follow-up the MACE rate was 18.4% in the SXhigh tertile, 12.0% in the SXmid and 9.4% in the SXlow tertile (HR 1.45; CI 1.21-1.74; p<0.01) (Figure 1A). In addition, there was a significantly higher rate of cardiac death in patients in the highest SXscore tertile (SXhigh 7.0% versus SXmid 2.4% versus SXlow 1.8%; HR 2.22 [CI 1.5-3.27]; p<0.001) (Figure 1B). Myocardial infarction was higher in patients in the SXhigh and SXmid groups (6.2%) than in patients with SXlow group (4.3%) but this difference was not statistically significant (HR 1.18; CI 0.89-1.56; p=0.24) (Figure 1C). Clinically driven TVR was 10.2% in the Sxhigh group versus 6.9% and 5.17% in the SXmid and SXlow groups (HR 1.45; CI 1.14-1.85; p=0.003).

(Figure 1D). Secondary end-point of clinically driven TLR was 10.6% in the SXhigh group versus 7.5% and 5.7% in the SXmid and SXlow groups, respectively (HR 1.38; CI 1.09-1.76; p=0.007) (Figure 1 E).

Differential performance of the BES and SES in the SXhigh group:

The analysis of outcomes in patients treated with BES versus SES has been performed in all three tertiles of the SXscore, however, differences between the two devices were only apparent in the SXhigh group (highest risk) and are reported here (Figure 2). Baseline clinical and angiographic characteristics, and angiographic outcomes for the SXhigh group treated with BES versus SES are reported in Tables 3-5. There were no significant differences between 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 1 A. SYNTAX SCORE IN LEADERS: MACE RATE

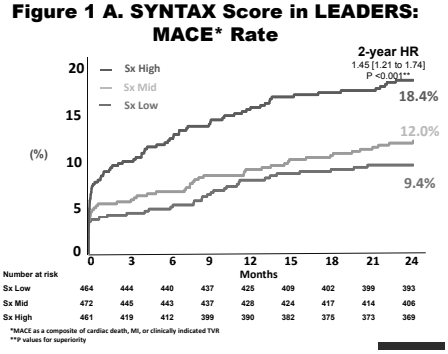


Figure 1 B. SYNTAX SCORE IN LEADERS: CARDIAC DEATH RATE

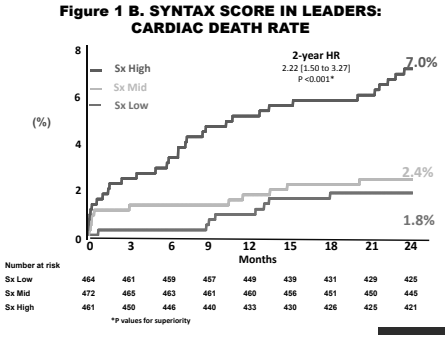


Figure 1 C. SYNATX SCORE in LEADERS: clinically indicated TVR RATE

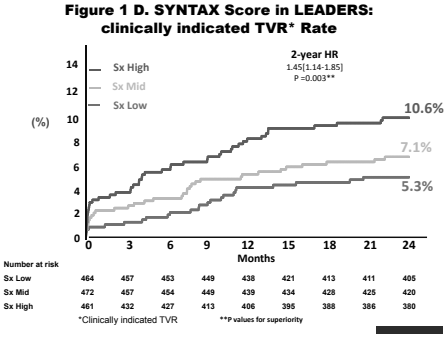


Figure 1 D. SYNTAX SCORE IN LEADERS: TLR RATE

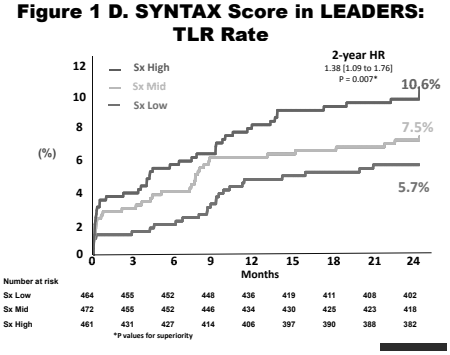
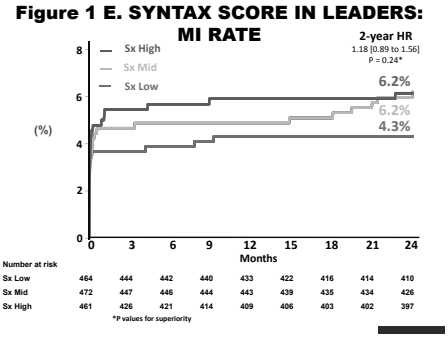


Figure 1 E. SYNTAX SCORE IN LEADERS: MI RATE



Overall MACE rate was 15.3% in SXhigh group treated with BES versus 21.8% in SXhigh group treated with SES (HR 0.68; CI 0.44-1.04; p=0.08) (Figure 2A). Within the SXhigh tertile the rate of cardiac death was significantly lower in patients treated with BES (4.7%) than SES (9.6%) (HR 0.48; CI 0.23-0.99; p=0.046) (Figure 2B). TLR and TVR rates also tended to be lower in the BES treated group (8.7% versus 12.7% for clinically driven TVR; HR=0.65 CI = 0.36-1.15; p=0.14; 8.3% versus 13.1% for TLR; HR 0.59; CI 0.33-1.05; p=0.07) (Figure 2 C and D). The rate of myocardial infarction 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 myocardial infarctions with BES between 1- and 2-year follow-up compared 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 SXhigh group at two year follow-up:

Definite stent thrombosis rates was 2.6% in the BES treated group and 5.1% in the SES treated group within the SXhigh tertile at two years (HR 0.5; CI 0.18-1.34; p=0.17) (Figure 3 A). 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; CI 0.29-1.62; p=0.39) (Figure 3 B and Figure 3B'). Most of the events occurred early after stent implantation (Figure 3B'). Possible stent thrombosis was 2.6% in the BES group versus 4.8% in the SES group (HR 0.54; CI 0.2-1.49; p=0.23) (Figure 3 C). The rate of overall stent thrombosis in the SXhigh group was 6.0% (n=14) in patients treated with BES and 9.8% (n=21) in patients treated with SES (HR 0.6; CI 0.31-1.18; p=0.14) (Figure 3 D). The increase in stent thrombosis in SXhigh 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 superimposed, most of the cardiac death events could be accounted for by stent thrombosis events, implying that reduced thrombosis rate may be the mechanism responsible for the reduced cardiac mortality rate in patients treated with BES in the SXhigh tertile (Figure 3 E), 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.[10] 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

Figure 2 A. MACE Rate in High SYNTAX Score (>16) patients treated with BES versus SES

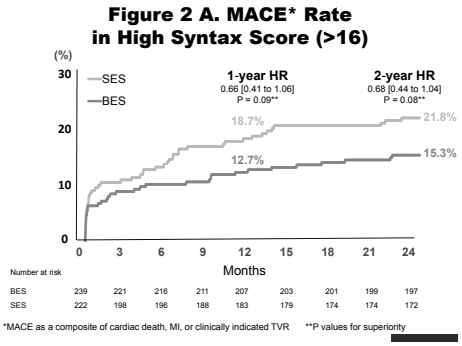


Figure 2 B. Cardiac Death rate in High SYNTAX Score (>16) patients treated with BES versus SES

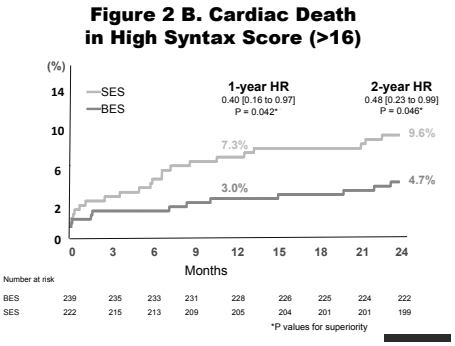


Figure 2 C. TLR rate in High SYNTAX Score (>16) patients treated with BES versus SES

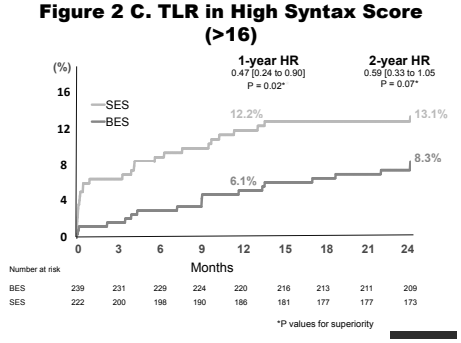


Figure 2 D. TVR rate in High SYNTAX Score (>16) patients treated with BES versus SES

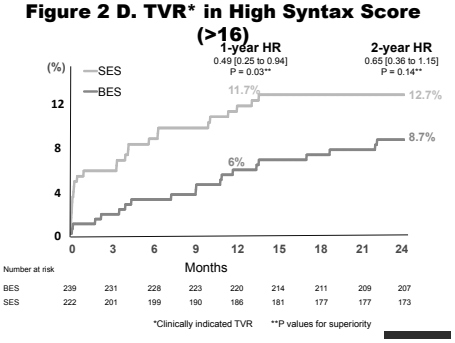


Figure 2 E. MI rate in High SYNTAX Score (>16) patients treated with BES versus SES

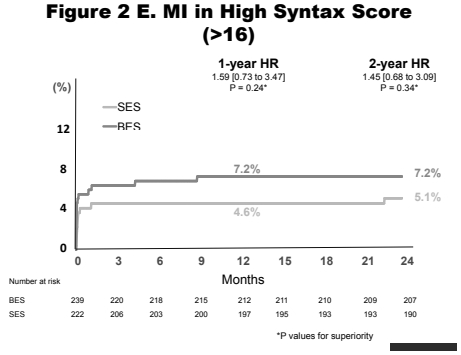


Table 3. Baseline Clinical SXhigh Patient Characteristics

	BioMatrix Flex™ 239 Patients	Cypher® Select™ 222 Patients
Age in years	65.8	65.2
Male gender	73.2%	74.3%
Arterial hypertension	69.5%	72.2%
Diabetes mellitus	27.2%	20.7%
- insulin-dependent	11.7%	9.5%
Hypercholesterolemia	58.2%	65.8%
Family history	36.0%	36.9%
Smoking	25.5%	29.3%
Previous MI	29.3%	30.2%
Previous PCI	32.6%	31.1%
- with drug-eluting stent	10%	9.9%
Previous CABG	1.8%	1.7%
Chronic stable angina	21.8%	25.2%

Table 4. Baseline SXhigh Clinical and Angiographic Patient Characteristics

	BioMatrix Flex™ 239 Patients	Cypher®Select™ 222 Patients
Acute coronary syndrome	66.1%	69.8%
- Unstable angina	20.1%	18%
- Non-ST-elevation MI	20.9%	21.2%
- ST-elevation MI	25.1%	30.6%
Left ventricular ejection fraction	54.5 %	52.8 %
Number of lesions treated with stent per patient	1.9	2.0
Number of study stent implanted per patient	2.3	2.4
Diameter of study stent (mm)	3.0	2.9

Table 5. Angiographic Follow-up Results of SXhigh patients

	Biolimus Stent 75 lesions	Sirolimus Stent 73 lesions	*P*
MLD			
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,95% CI. Based on t-test

Figure 3 A. Definite Stent Thrombosis in High SYNTAX Score (>16) patients treated with BES versus SES

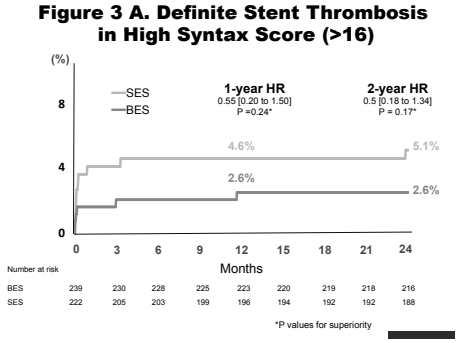


Figure 3 B. Definite and Probable Stent Thrombosis in High SYNTAX Score (>16) patients treated with BES versus SES

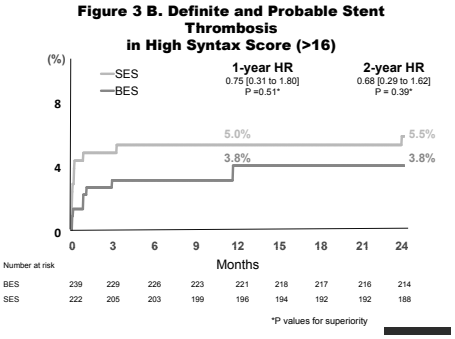


Figure 3 B'. Definite and Probable Stent Thrombosis in High SYNTAX Score (>16) patients treated with BES versus SES (with event type superimposed).

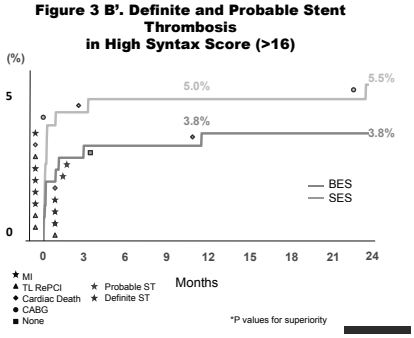
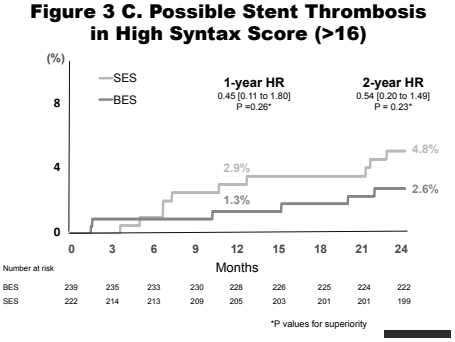


Figure 3 C. Possible Stent Thrombosis in High SYNTAX Score (>16) patients treated with BES versus SES

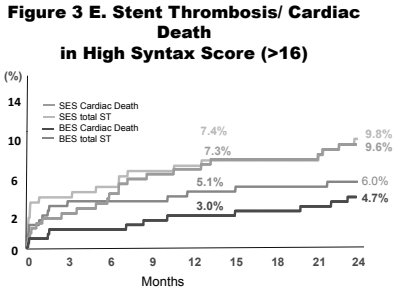


a 2.5 fold increase in cardiac death, which remained true even after adjustment for other risk factors for cardiac death such as diabetes, presentation with acute coronary syndrome, beta-blocker use and stent type. Here we report that the predictive value of SXscore remains robust at 2 year follow-up 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

Figure 3 D. All Stent Thrombosis in High SYNTAX Score (>16) patients treated with BES versus SES

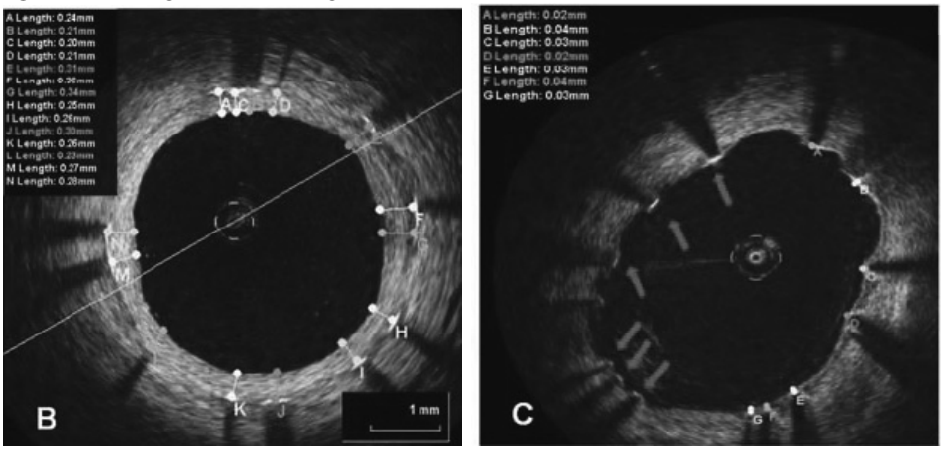
Figure 3 E. Stent Thrombosis/ Cardiac Death in High SYNTAX Score (>16) patients treated with BES versus SES



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[13] (Figure 4), suggest that the reduction in

Figure 4. OCT images of strut coverage (from Barlis et al., 2010)



BES SES

Adapted from Peter Barlis, et al., European Heart Journal (2010) 31, 165–176

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.[14] 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 SXscore has not been validated in patients post-PCI and with acute myocardial infarction, 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-generationstents in high risk lesions in future clinical trials.

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Chapter 6

THE PROGNOSTIC UTILITY OF THE SYNTAX SCORE ON 1-YEAR OUTCOMES FOLLOWING REVASCULARIZATION WITH ZOTAROLIMUS- AND EVEROLIMUSELUTING STENTS: A SUB-STUDY OF THE RESOLUTE ALL-COMERS TRIAL

Brief title: SYNTAX Score the in RESOLUTE All Comers
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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 and treated with 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.

CONDENSED ABSTRACT

We assessed the ability of the SYNTAX Score (SXscore) to stratify risk in patients enrolled in the randomized RESOLUTE All-Comers trial treated with zotarolimus-eluting or everolimus-eluting stents. Clinical outcomes were stratified according to SXscore tertiles, and at 1 year follow-up, rates of all clinical outcomes were higher in patients in the highest tertile. After multivariate analysis, the SXscore was also identified as an independent predictor of adverse outcomes.This study confirms the ability of the SXscore to stratify risk amongst an all-comers population using second generation drug-eluting stents.

ABBREVIATIONS AND ACRONYMS

ARC = Academic Research Consortium

CAD = coronary artery disease

CSS=Clinical SYNTAX score

DES = drug-eluting stent

LVEF=left ventricular ejection fraction

MI = myocardial infarction

PCI = percutaneous coronary intervention

POCE=patient orientated composite endpoint

SXscore = SYNTAX Score

TLF = target lesion failure

TLR = target lesion revascularization

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).

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.

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.

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.

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.

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 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 the 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 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.

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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

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.

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.

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 2.

MI, myocardial infarction

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

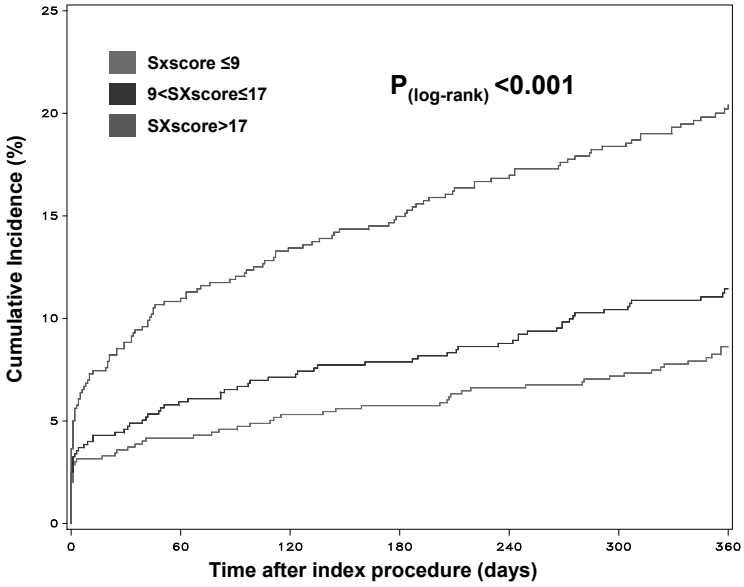
SXscore, SYNTAX score; CSS, Clinical SYNTAX score; TLR, target lesion revascularization

†, ‡, § defined as in Table 2.

Figure 1. Kaplan Meier curves

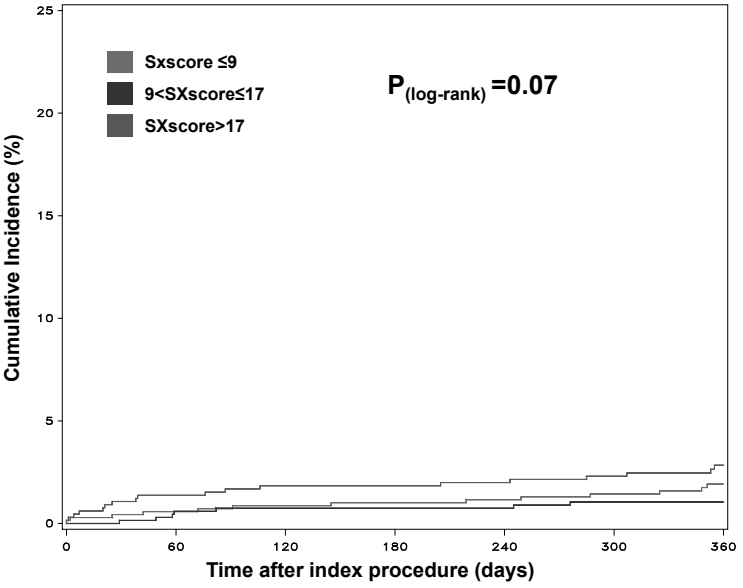
Kaplan Meier survival curves for (A) the patient oriented composite endpoint (a composite of all-cause death, any myocardial infarction and any repeat revascularization; (B) Any death; (C) Any myocardial infarction; (D) Any repeat revascularization out to 12-months follow-up.

A



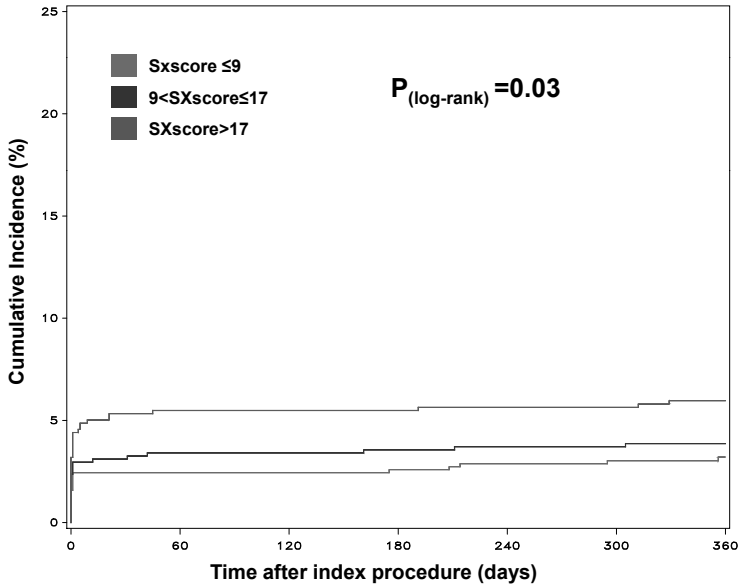
Days	0	60	120	180	240	300	360
Sxscore ≤9	698	666	658	653	646	642	476
9<SXscore≤17	676	630	622	616	607	595	433
SXscore>17	659	580	564	554	534	524	378

B



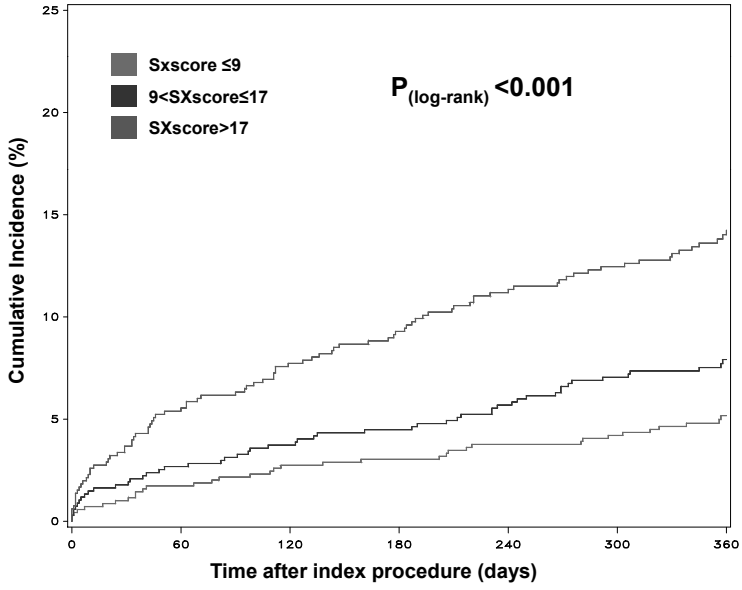
Days	0	60	120	180	240	300	360
Sxscore ≤9	698	691	689	686	683	680	508
9<SXscore≤17	676	666	665	663	659	656	486
SXscore>17	659	643	639	639	630	626	460

C



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

D



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

Part II

Chapter 7

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
The LEADERS Trial Substudy

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Objectives We assessed the impact of vessel size on outcomes of stenting with biolimus-eluting degradable polymer stent (BES) and sirolimus-eluting permanent polymer stent (SES) within a randomized multicenter trial (LEADERS).

Background Stenting of small vessels might be associated with higher rates of adverse events.

Methods "All-comer" patients (n = 1,707) were randomized to BES and SES. Post-hoc–stratified analysis of angiographic and clinical outcomes at 9 months and 1 year, respectively, was performed for vessels with reference diameter ≤2.75 mm versus >2.75 mm.

Results Of 1,707 patients, 429 patients in the BES group with 576 lesions and 434 patients in the SES group with 557 lesions had only small vessels treated (50.6% of the patient cohort). In patients with small vessels there was no significant difference in overall major adverse cardiac events (MACE) rate (12.1% vs. 11.8%; p = 0.89) or target lesion revascularization (TLR) rate (9.6% vs. 7.4%; p = 0.26) between BES and SES. The MACE and TLR rates in the small-vessel patient population were higher than in the large-vessel population. The TLR rate was 9.6% versus 2.6%, and MACE rate was 12.1% versus 7.1% for small versus large vessels in the BES arm (TLR: hazard ratio [HR] = 3.724, p = 0.0013; MACE: HR = 1.720, p = 0.0412). In the SES arm, TLR was 7.4% versus 5.1%, and MACE was 11.8% versus 10.3% in small versus large vessels (TLR: HR = 1.435, p = 0.2594; MACE: HR = 1.149, p = 0.5546).

Conclusions Prevalence of small vessel disease is high in an "all-comer" population with higher TLR and MACE rates. The BES and SES seem equivalent in treatment outcomes of small vessels in this "all-comer" patient population. (J Am Coll Cardiol Intv 2009;2:861–70) © 2009 by the American College of Cardiology Foundation

The recently published "all-comers" European LEADERS (Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularization) trial showed that the biolimus-eluting biodegradable polymer stent (BES) represents a safe and noninferior alternative to sirolimus-eluting durable polymer stent (SES) in the treatment of coronary artery disease (1). Biolimus is a highly lipophilic sirolimus analogue (2). It inhibits the mammalian target of rapamycin and cell-cycle transition in smooth muscle cells with similar potency as sirolimus. It is eluted from a polylactic acid biodegradable polymer solely applied on the abluminal surface. Unlike paclitaxel-eluting stents (PES), BES has similar potency as SES in the suppression of neoinitmal hyperplasia and therefore late luminal loss (0.13 vs. 0.19 mm; $p = 0.34$ at 9 months). The amount of late luminal loss is usually independent of vessel size (3–8), and therefore a greater degree of restenosis is observed in smaller vessels owing to a reduced ability to accommodate neointimal growth without causing hemodynamically significant flow compromise (9,10). In the RAVEL (Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent) study it was first demonstrated that SES perform well in small vessels with low restenosis rates (11). At 6-month follow-up, the restenosis rate in the SES group was 0% versus 20% to 35% in the different vessel-size strata of the bare-metal stents group. We hypothesized that, given the non-inferior rate of late loss in the BES arm of the LEADERS trial, BES will perform equivalently in small vessels to SES, unlike PES.

Abbreviations and Acronyms

BES = **biolimus-eluting stent(s)**

MACE = **major adverse cardiac events**

MI = **myocardial infarction**

MLD = **minimal lumen diameter**

PES = **paclitaxel-eluting stent(s)**

RVD = **reference vessel diameter**

SES = **sirolimus eluting stent(s)**

TLR = **target lesion revascularization**

TVR = **target vessel revascularization**

Methods

Device description. The BES, as used in this study and already described in the preceding text, elutes a highly lipophilic sirolimus analogue (2) (Fig. 1), which inhibits the mammalian target of rapamycin and cell-cycle transition in smooth muscle cells with similar potency as sirolimus. It is eluted from a polylactic acid biodegradable polymer applied to the abluminal surface (Fig. 1). This fully biodegradable polymer polylactic acid is metabolized to water and carbon dioxide and promises to cause less long-term inflammatory reaction. Full resorption occurs within 6 months. In the LEADERS trial the BES was found noninferior to the SES in terms of major adverse cardiac events (MACE) at 9 months as well as in-stent percent diameter stenosis (p = NS) (1).

Study population. The LEADERS trial was a multicenter European non-inferiority trial comparing the safety and efficacy of BES with SES in 1,707 "all-comers" patients. Patients over the age of 18 with chronic stable coronary artery disease or acute coronary syndromes including ST-segment elevation myocardial infarction (MI) were eligible if they had at least 1 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 percutaneous coronary intervention unless the dual anti-platelet therapy could be maintained throughout the perisurgical period; pregnancy or 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.

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, Rotterdam, the Netherlands). The allocation sequence was computer-generated, stratified according to center, and blocked with block sizes of 8 and 16, which varied randomly. We randomly allocated patients on a 1:1 basis to treatment with a BES (Biomatrix Flex, Biosensors, Inc., Newport Beach, California) or an SES (Cypher Select, Cordis, Miami Lakes, Florida) and to active angiographic follow-up at 9 months or clinical follow-up only on a 1:3 basis with a factorial design.

The 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. The 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. We performed balloon angioplasty and stent implantation 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 at least 75 mg of acetylsalicylic acid, 300 to 600 mg loading dose of clopidogrel, and unfractionated heparin at a dose at least 70 IU/kg. After the procedure, all patients were advised to take aspirin indefinitely and clopidogrel for at least 12 months. In case of intercurrent revascularization procedures requiring stent implantation, treating cardiologists were encour-

- Biolimus is a semi-synthetic sirolimus analogue with 10x higher lipophilicity and similar potency as sirolimus.
- Biolimus is immersed at a concentration of 15.6 μg/mm into a biodegradable polymer, polylactic acid, and applied solely to the abluminal stent surface by a fully automated process.
- Polylactic acid is co-released with biolimus and completely desolves into carbon dioxide and water during a 6-9 months period.
- The stainless steel stent platform has a strut thickness of 112 μm with a quadrature link design.

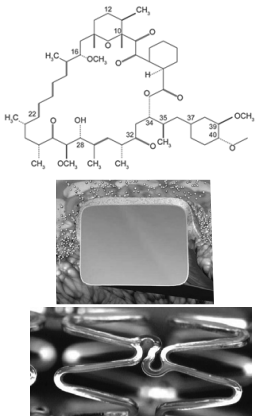

Figure 1. Structure of Biolimus and Scanning Electron Micrograph of the Biolimus Biodegradable Polymer Stent

aged to use the study stent. For other details we refer to the primary end point article (1).

Study end points. Adverse events were assessed in the hospital and at 1, 6, 9, and 12 months. An independent clinical events committee unaware of the patient's treatment assignments adjudicated all end points. One in four patients was asked to return for angiographic follow-up at 9 months. Definitions of all end points are provided elsewhere (1). Briefly, the pre-specified primary end point was the composite of cardiac death, MI, and clinically indicated target vessel revascularization (TVR) within 9 months. Secondary end points were any target lesion revascularization (TLR) (both clinically and nonclinically 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 Consortium) (12); device success (defined as achievement of a final residual diameter stenosis of <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 substudy was in-stent percent diameter stenosis. Secondary angiographic outcomes were in-segment percent diameter stenosis, minimal lumen diameter (MLD), late lumen loss, and binary restenosis. We obtained angiographic measurements within the stented segment (in-stent) and over the entire segment consisting of the stent and 5-mm proximal and distal margins (in-segment). We defined percent diameter stenosis as: ([reference vessel diameter − MLD]/reference vessel diameter) × 100%; late lumen loss as the difference between MLD after the procedure and MLD at follow-up; and binary restenosis as percentage diameter stenosis of 50% or greater in the target lesion.

Independent study monitors (D-Target, Montagny-pres-Yverdon, Switzerland) verified all case reports from data on-site. Data were stored in a database (KIKA Medical, Paris, France), which was maintained by a contract research organization (Cardialysis, Rotterdam, the Netherlands) in collaboration with an academic clinical trials unit (CTU Bern, Bern University Hospital, Bern, Switzerland). Clinical follow-up was done at 1, 6, 9, and 12 months. 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. Angiographies were centrally assessed at 1 angiographic core laboratory (Cardialysis) 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 vessel size. Methodology similar to the previously published SIRTAX (Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization) trial was used (9). Quantitative coronary angiography served to determine the reference vessel diameter (RVD). Patients who underwent stent implantation in lesions with an RVD ≤2.75 mm were categorized as having undergone treatment of small vessels. Conversely, patients who underwent stent implantation in lesions with RVD >2.75 mm were classified as having had treatment of large vessels. Patients with stent implantations in both small and large vessels were classified as "mixed". All

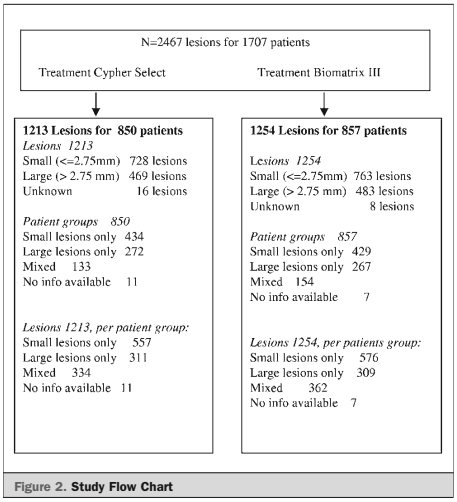

Figure 2. Study Flow Chart

randomized patients were included in the analysis of primary and secondary clinical end points in the groups that they were originally assigned to (intention-to-treat analysis). Analyses of the angiographic substudy were restricted to lesions from patients who attended follow-up angiography. Angiographic outcomes were analyzed with SAS version 8 Proc Mixed (SAS Institute, Cary, North Carolina) 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 with SAS version 8.02 by a dedicated statistician. All p values and confidence intervals were 2-sided.

Results

Baseline clinical, angiographic, and procedural data. A total of 1,707 patients with 2,467 lesions were randomly assigned to treatment with either BES (857 patients, 1,254 lesions) or SES (850 patients, 1,213 lesions). Four hundred twenty-nine patients in the BES group with 576 lesions and 434 patients in the SES group with 557 lesions had only small vessels treated (863 of 1,707 [50.6%] of the entire patient population); 267 patients in the BES arm with 309 lesions and 272 patients in the SES arm with 311 lesions had only large vessels treated (RVD >2.75); and 154 patients in the BES group with 362 lesions and 133 patients with 334 lesions in the SES group had "mixed" disease (Fig. 2).

Baseline clinical and angiographic characteristics are summarized in Tables 1 and 2. There were no significant differences in the numbers of patients with diabetes, hypertension, hypercholesterolemia, smoking history, prior history of MI, stroke, or peripheral vascular disease between the SES and BES groups. These patient characteristics differed, however, when compared for vessel size. There was a higher proportion of women with small vessels (29% vs. 25% overall; $p < 0.001$), whereas no significant difference in the numbers of diabetic patients across vessel sizes was found. Smokers were more frequently found in the large vessel group ($p < 0.001$), whereas patients with small vessel disease had a higher frequency of previous MIs ($p = 0.007$) and past history of PCI ($p < 0.001$). A high proportion of patients in the entire cohort had presented with acute coronary syndromes (between 51% and 61%) and 13% to 21% of the cases were ST-segment elevation MIs. Lastly, patients with mixed vessel disease had a higher proportion of multivessel disease ($p < 0.001$).

Mean reference vessel diameters in the BES and SES group were 2.21 ± 0.34 mm and 2.24 ± 0.33 mm for small vessels, respectively, 3.21 ± 0.47 mm and 3.18 ± 0.37 mm for large vessels, and 2.69 ± 0.57 mm and 2.66 ± 0.59 mm for mixed lesions (Table 1). The lesion length did not differ between the 2 treatment groups but differed slightly over the range of 12 to 16 mm between vessel sizes. Percent diameter stenosis was 63 ± 18% in small vessels in both treatment arms, 66 ± 18% in large vessels treated with BES, 69 ± 18% in large vessels treated with SES, 62 ± 18% in the mixed vessels treated with BES, and 61 ± 18% in the mixed vessels treated with SES. The MLD amounted to 0.80 and 0.84 mm in small vessels treated with BES and SES and 1.01 and 1.07 mm in large vessels treated with BES and SES, respectively.

Procedural results are shown in Table 2. Post-stenting MLD in small vessels treated with BES and SES was 2.09 ± 0.35 mm and 2.13 ± 0.35 mm, respectively ($p = NS$); it was 2.76 ± 0.41 mm and 2.67 ± 0.38 mm in large vessels treated with BES and SES, respectively. There were no significant differences in acute gain after stenting with BES or SES, the acute gain being 1.29 ± 0.45 mm for small vessels, 1.74 ± 0.62 mm for large vessels treated with BES, and 1.59 ± 0.59 mm for large vessels treated with SES. This translated also in equivalent diameter stenosis after PCI in both stent groups.

Angiographic results. Angiographic follow-up at 9 months were obtained in 168 patient in the BES group and 167 patients in the SES group (Table 2). One hundred nine small vessel lesions, 62 large vessel lesions, and 82 mixed vessel lesions were evaluated angiographically at 9 months in the group treated with BES. One hundred fourteen small vessel lesions, 58 large vessel lesions, and 59 mixed lesions were evaluated angiographically in the SES group. In small, large, and mixed vessels there was no significant difference

Table 1. Baseline Clinical and Angiographic Characteristics for Small, Large, and "Mixed" Vessel Groups

	BES, Small	SES, Small	BES, Large	SES, Large	BES, Mixed	SES, Mixed	p Value*
Patient demographic data							
Number of patients	429	434	267	272	154	133	†
Age >65 yrs	225 (52)	209 (48)	125 (47)	134 (49)	78 (51)	73 (55)	0.44
Male	295 (69)	314 (72)	217 (81)	207 (76)	125 (81)	105 (79)	<0.001
Diabetes	104 (24)	105 (24)	63 (24)	56 (21)	51 (33)	29 (22)	0.18
Hypertension	315 (73)	319 (74)	193 (72)	205 (75)	117 (76)	88 (66)	0.74
Hyperlipidemia	291 (68)	299 (69)	170 (64)	177 (65)	95 (62)	101 (76)	0.27
Current smoking	85 (20)	96 (22)	76 (29)	82 (30)	41 (27)	33 (25)	0.002
Previous MI	151 (35)	146 (34)	64 (24)	84 (31)	59 (38)	46 (35)	0.007
Previous PCI	184 (43)	180 (42)	77 (29)	88 (32)	48 (31)	44 (33)	<0.001
Previous stroke	24 (6)	16 (4)	7 (3)	6 (2)	9 (6)	6 (4.5)	0.06
Previous PVD	39 (9)	35 (8)	13 (5)	19 (7)	18 (12)	9 (7)	0.12
Multivessel disease	83 (19)	58 (13)	22 (8)	22 (8)	103 (67)	96 (72)	<0.001
Clinical presentation							
Stable angina	160 (37)	156 (36)	79 (30)	78 (29)	55 (36)	53 (40)	0.03
Acute coronary syndromes	224 (52)	233 (54)	156 (58)	166 (61)	87 (56.5)	68 (51)	0.042
Unstable angina	99 (23)	92 (21)	58 (22)	61 (22)	33 (21)	27 (20)	
STEMI	54 (13)	61 (14)	56 (21)	56 (21)	22 (14)	18 (13.5)	
Non-STEMI	71 (17)	80 (18)	42 (16)	49 (18)	32 (21)	23 (17)	
Angiographic parameters							
Number of lesions	576	557	309	311	363	334	‡
Lesion length	15 ± 13	14 ± 11	17 ± 11	16 ± 12	14 ± 10	13 ± 9	<0.001
Reference vessel diameter	2.21 ± 0.34	2.24 ± 0.33	3.21 ± 0.47	3.18 ± 0.37	2.69 ± 0.57	2.66 ± 0.59	<0.001
MLD	0.80 ± 0.40	0.84 ± 0.43	1.01 ± 0.63	1.08 ± 0.58	1.02 ± 0.48	1.05 ± 0.53	<0.001
% diameter stenosis	63 ± 18	63 ± 18	69 ± 18	66 ± 18	62 ± 17	61 ± 17	<0.001

Values are n, n (%), and mean ± SD. *The p value is given for the difference among the 3 groups (small, large, and mixed) rather than biolimus-eluting degradable polymer stent (BES) versus sirolimus-eluting permanent polymer stent (SES). †Tested: equal distribution in the 3 groups. ‡Tested: equal mean in the 3 groups.
MI = myocardial infarction; MLD = minimal lumen diameter; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; STEMI = ST-segment elevation myocardial infarction.

in late luminal loss, MLD, percent diameter stenosis, or binary restenosis between BES and SES groups. In small vessels late loss was 0.17 ± 0.47 mm in the BES group and 0.22 ± 0.51 mm in the SES group (p = NS). Corresponding percent diameter stenosis was 24.9 ± 20.7% and 23.8 ± 21.3% in the BES and SES stent groups, respectively. In the large lesion population, in-stent late luminal loss was 0.14 ± 0.51 in the BES arm and 0.05 ± 0.37 in the SES group (p = NS). The percent diameter stenosis in the large vessel group was 18.2 ± 14.6% in the BES group and 19.2 ± 14.5% in the SES group (p = NS). Late loss, percent diameter stenosis, and binary in-stent restenosis were lower in the "mixed" lesion group treated with BES compared with SES.

Clinical outcomes. Clinical events at 1-year follow-up stratified by vessel size are listed in Table 3 and summarized in Figures 3 and 4. Vessel size seemed to influence the TLR rates in both SES and BES groups. Within the BES treatment arm TLR rate was 9.6% in the small vessel group (41 events) versus 2.6% in the large vessel group (7 events). Within the SES treatment arm TLR rate was 7.4% in the small vessel group (32 events) versus 5.1% in the large vessel group (14 events). There were no differences in the overall rate of MACE or TLR/TVR in patients with small vessels and large vessels treated with BES versus SES stents. There was no significant difference in overall MACE rate between BES- and SES-treated patients with "mixed" vessel disease, although rates of overall percutaneous TLR (7 [4.5%] patients vs. 15 [11.3%] patients; p = 0.037) were lower. Tests for interaction between treatment and vessel size reached statistical significance for TLR and TVR rates in the mixed disease group.

There were 13 definite stent thrombosis events in small vessels in the BES arm (3.0%) and 9 definite stent thrombosis events in the SES arm (2.1%) (p = 0.38).

Discussion

We present here a novel stent technology now commercially available in Europe that combines the biodegradable polymer technology with solely abluminal elution of biolimus and performs well in complex lesions such as small vessels in an "all-comer" patient population. The main finding of this substudy of the LEADERS multicenter randomized trial focusing on the effect of vessel size on angiographic and clinical outcomes is that BES seems noninferior to the

Table 2. Baseline Angiographic Characteristics, Procedural Outcomes, and Angiographic Follow-Up Results at 9 Months

	BES, Small	SES, Small	BES, Large	SES, Large	BES, Mixed	SES, Mixed	p Value Interaction
Number at initial procedure (at 9-month follow-up)	561 (105)	539 (114)	308 (62)	309 (58)	360 (82)	326 (59)	
In-stent							
Reference vessel diameter							
After procedure	2.46 (0.36)	2.48 (0.35)	3.24 (0.42)	3.16 (0.40)	2.79 (0.52)	2.79 (0.52)	0.0192
9-month follow-up	2.55 (0.37)	2.45 (0.39)	3.25 (0.33)	3.21 (0.44)	2.84 (0.49)	2.81 (0.51)	0.7792
MLD							
After procedure	2.09 (0.35)	2.13 (0.35)	2.76 (0.41)	2.67 (0.38)	2.36 (0.51)	2.38 (0.50	0.0033
9-month follow-up	1.91 (0.59)	1.87 (0.62)	2.65 (0.53)	2.60 (0.59)	2.08 (0.51)	1.83 (0.62)	0.209
Acute gain	1.29 (0.46)	1.30 (0.45)	1,74 (0.62)	1.60 (0.59)	1.34 (0.55)	1.32 (0.53)	0.0169
Late loss	0.17 (0.47)	0.22 (0.51)	0.14 (0.51)	0.05 (0.37)	0.06 (0.40)	0.25 (0.56)	0.047
% diameter stenosis							
After procedure	14.8 (8.4)	14.1 (7.6)	14.6 (7.5)	15.2 (7.0)	15.0 (9.7)	14.7 (9.1)	0.3955
9-month follow-up	24.9 (20.7)	23.8 (21.3)	18.2 (14.6)	19.2 (14.5)	17.8 (13.7)	26.4 (20.0)	0.0236
Binary restenosis rate (%)	10.1	7.9	3.2	3.4	1.2	15.3	0.0144
In-segment							
Reference vessel diameter							
After procedure	2.37 (0.38)	2.39 (0.38)	3.14 (0.45)	3.06 (0.46)	2.69 (0.55)	2.71 (0.56)	0.0723
9-month follow-up	2.50 (0.38)	2.37 (0.40)	3.16 (0.36)	3.13 (0.46)	2.78 (0.52)	2.76 (0.52)	0.4379
MLD							
After procedure	1.78 (0.36)	1.84 (0.37)	2.48 (0.46)	2.44 (0.43)	2.07 (0.52)	2.07 (0.52)	0.0845
9-month follow-up	1.73 (0.55)	1.65 (0.56)	2.42 (0.50)	2.35 (0.56)	2.08 (0.51)	1.83 (0.62)	0.1293
Acute gain	0.99 (0.48)	1.00 (0.47)	1.45 (0.66)	1.36 (0.63)	1.04 (0.56)	1.02 (0.53)	0.2238
Late loss	0.09 (0.44)	0.19 (0.48)	0.10 (0.49)	0.04 (0.33)	0.04 (0.42)	0.19 (0.51)	0.079
% diameter stenosis							
After procedure	24.4 (10.1)	23.3 (9.3)	21.0 (8.6)	20.2 (8.8)	22.8 (10.6)	23.3 (10.5)	0.236
9-month follow-up	30.6 (19.2)	30.6 (19.7)	23.3 (14.0)	24.8 (14.7)	25.2 (12.7)	33.3 (18.7)	0.1105
Binary restenosis rate (%)	12.8	9.7	3.2	5.2	1.2	18.6	0.0052

Values are mean (SD), unless otherwise indicated.
Abbreviations as in Table 1.

"gold standard" SES in small vessels. To our knowledge this is the first report of another drug-eluting stent being noninferior to SES in the setting of small vessel disease. Angiographic outcomes at 9-month follow-up in a subset of patients show equivalent late luminal loss, percent diameter stenosis, and binary restenosis rates, which translate into similar rates of MACE and TLR at 1 year in both stent treatment groups in small vessel disease. This equivalent performance is achieved in a complex "all-comer" patient population that reflects "real world" clinical practice. These results in small vessel disease are unlike those reported in trials to date comparing SES and PES, where SES has shown a consistent advantage over PES in both angiographic and clinical outcomes (13–16).

Another important finding of our study is that the prevalence of small vessel lesions (defined as reference diameter <2.75 mm) is high (50.6%) in real world clinical practice, and the overall rate of MACE and TLR in small vessel lesions across stent types are higher than for large vessel lesions (Online Figures). This latter finding is at variance with recent findings of the BASKET (Basel Stent Cost-Effectiveness Trial) 3-year follow-up, where within the drug-eluting stent-treated group there seemed to be no difference in the MACE and TLR rates between small and large vessels (17). The increased event rate in the large stent group seemed to be a late rather than early phenomenon, with the curve diverging after 6 to 9 months, a phenomenon that might have been missed in the present study with only 1-year clinical follow-up. Conversely, failure to detect earlier higher event rates in the small vessel group in the BASKET study might have been due to the lower number of patients (187 patients with small vessels treated with DES compared with 863 patients in the present study).

The SES (Cypher Select) uses a poly-n-butyl methacrylate durable polymer technology for drug elution that has been shown to cause inflammation and fibrin deposition as well as endothelial dysfunction and delayed endothelialization (18). Poly-n-butyl methacrylate is hydrophobic and causes monocytes to adhere to its surface and

Table 3. Clinical Outcomes at 1-Year Follow-Up

	BES, Small (n = 429)	SES, Small (n = 434)	HR (95% CI)	p Value	BES, Large (n = 267)	SES, Large (n = 272)	HR (95% CI)	p Value	BES, Mixed (n = 154)	SES, Mixed (n = 133)	HR (95% CI)	p Value	p Value Interaction
Death	12 (2.8)	10 (2.3)	1.21 (0.52–2.8)	0.65	10 (3.7)	12 (4.4)	0.85 (0.37–1.97)	0.71	4 (2.6)	5 (3.8)	0.68 (0.18–2.55)	0.57	0.73
Cardiac death	10 (2.3)	8 (1.8)	1.26 (0.50–3.20)	0.62	6 (2.2)	9 (3.3)	0.68 (0.24–1.91)	0.47	1 (0.6)	5 (3.8)	0.17 (0.02–1.47)	0.11	0.16
MI	24 (5.6)	20 (4.6)	1.21 (0.67–2.19)	0.52	10 (3.7)	11 (4.0)	0.92 (0.39–2.17)	0.85	16 (10.4)	7 (5.3)	2.02 (0.83–4.92)	0.12	0.43
All TLR	41 (9.6)	32 (7.4)	1.31 (0.82–2.08)	0.26	7 (2.6)	14 (5.1)	0.50 (0.20–1.25)	0.14	8 (5.2)	15 (11.3)	0.44 (0.19–1.04)	0.06	0.03
TLR percutaneous	40 (9.3)	31 (7.1)	1.32 (0.83–2.11)	0.25	5 (1.9)	12 (4.4)	0.42 (0.15–1.20)	0.10	7 (4.5)	15 (11.3)	0.39 (0.16–0.95)	0.037	0.014
TLR surgical	5 (1.2)	4 (0.9)	1.26 (0.34–4.68)	0.73	2 (0.7)	2 (0.7)	1.02 (0.14–7.23)	0.99	1 (0.6)	1 (0.8)	0.84 (0.05–13.46)	0.90	0.96
Clinically justified TLR	34 (7.9)	26 (6.0)	1.33 (0.80–2.21)	0.28	5 (1.9)	11 (4.0)	0.46 (0.16–1.32)	0.15	5 (3.2)	10 (97.5)	0.42 (0.14–1.23)	0.11	0.05
Cliniinally justified TLR percutaneous	33 (7.7)	25 (5.8)	1.34 (0.80–2.26)	0.27	4 (1.5)	10 (3.7)	0.40 (0.13–1.29)	0.13	5 (3.2)	10.75	0.42 (0.14–1.23)	0.11	0.041
Cliniinally justified TLR surgical	4 (0.9)	3 (0.7)	1.34 (0.30–6.00)	0.70	1 (0.4)	1 (0.4)	1.02 (0.06–16.33)	0.99	—	—			0.99
All TVR	46 (10.7)	43 (9.9)	1.08 (0.72–1.64)	0.7	10 (3.7)	21 (7.7)	0.48 (0.22–1.01)	0.054	10 (6.5)	18 (13.5)	0.45 (0.21–0.99)	0.046	0.048
TVR percutaneous	44 (10.3)	39 (9.0)	1.15 (0.75–1.77)	0.53	6 (2.2)	17 (6.3)	0.35 (0.14–0.90)	0.029	9 (5.8)	18 (13.5)	0.41 (0.18–0.91)	0.029	0.012
TVR surgical	6 (1.4)	7 (1.6)	0.86 (0.29–2.56)	0.79	4 (1.5)	4 (1.5)	1.02 (0.25–4.07)	0.98	1 (0.6)	1 (0.8)	0.84 (0.05–13.46)	0.90	0.98
Cliniinally justified TVR	36 (8.4)	32 (7.4)	1.14 (0.71–1.83)	0.59	7 (2.6)	14 (5.1)	0.50 (0.20–1.25)	0.14	6 (3.9)	12 (9.0)	0.42 (0.16–1.11)	0.08	0.08
Cliniinally justified TVR percutaneous	35 (8.2)	31 (7.1)	1.15 (0.71–1.86)	0.58	5 (1.9)	12 (4.4)	0.42 (0.15–1.19)	0.10	6 (3.9)	12 (9.0)	0.42 (0.16–1.11)	0.08	0.06
Cliniinally justified TVR surgical	4 (0.9)	3 (0.7)	1.34 (0.30–6.00)	0.70	2 (0.7)	2 (0.7)	1.02 (0.14–7.22)	0.99	—	1 (0.8)			0.42
Stent thrombosis	19 (4.4)	12 (2.8)	1.61 (0.78–3.32)	0.20	6 (2.2)	8 (2.9)	0.76 (0.26–2.19)	0.61	5 (3.2)	6 (4.5)	0.72 (0.22–2.34)	0.58	0.36
Definite stent thrombosis	13 (3.0)	9 (2.1)	1.47 (0.63–3.43)	0.38	1 (0.4)	4 (1.5)	0.25 (0.03–2.27)	0.22	3 (1.9)	4 (3.0)	0.65 (0.14–2.88)	0.57	0.22
Possible stent thrombosis	2 (0.5)	3 (0.7)	0.67 (0.11–4.02)	0.66	4 (1.5)	3 (1.1)	1.36 (0.30–6.09)	0.69	1 (0.6)	3 (2.3)	0.28 (0.03–2.73)	0.28	0.49
Probable stent thrombosis	5 (1.2)	1 (0.2)	5.05 (0.59–43.24)	0.14	1 (0.4)	1 (0.4)	1.02 (0.06–16.36)	0.99	—	1 (0.6)			0.53
MACE	52 (12.1)	51 (11.8)	1.03 (0.70–1.51)	0.89	19 (7.1)	28 (10.3)	0.68 (0.38–1.22)	0.20	18 (11.7)	19 (14.3)	0.83 (0.44–1.58)	0.57	0.50
Target vessel failure	58 (13.5)	57 (13.1)	1.03 (0.71–1.48)	0.88	17 (6.4)	30 (11.0)	0.57 (0.31–1.03)	0.06	18 (11.7)	24 (18)	0.63 (0.34–1.17)	0.14	0.16

CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac events; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table1.

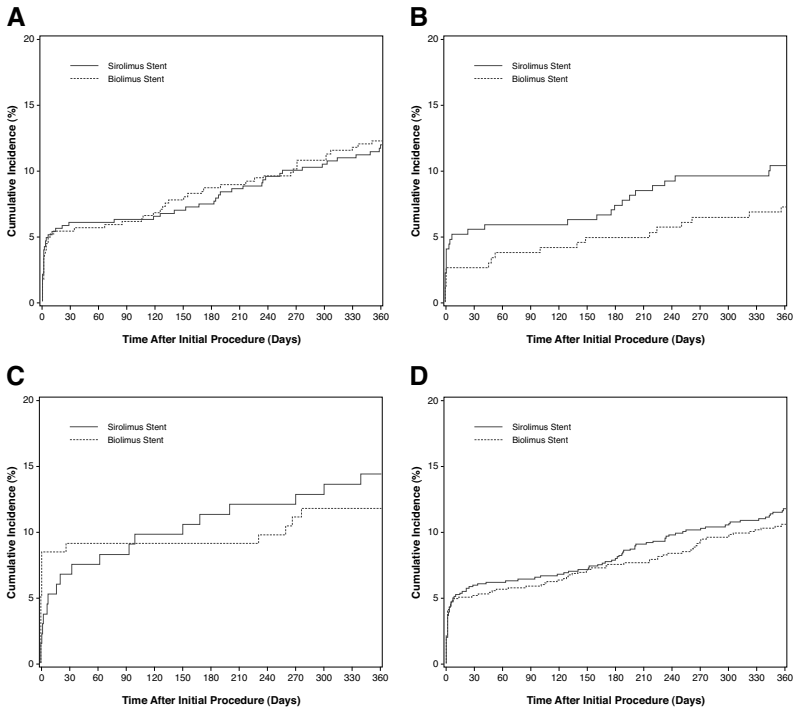

Figure 3. Kaplan-Meier Curves for Overall MACE Rate at 1 Year

Kaplan-Meier curves for overall major adverse cardiac events (MACE) rate at 1 year. **(A)** Small vessels; **(B)** large vessels; **(C)** mixed vessels; **(D)** all vessels.

produce cytokines such as monocyte chemotactic protein-1, plasminogen activator inhibitor-1, and tissue factor (19). Persistence of this pro-inflammatory polymer is hypothesized to be a potential major contributor to late stent thrombosis events. The BES in the present study uses, unlike SES, a biodegradable polymer made of polylactic acid, which completely disintegrates to water and carbon dioxide within 6 months. Therefore, it holds promise of a lower rate of late stent thrombosis or need for dual antiplatelet inhibition in the long term as well as equivalent performance in terms of efficacy in the short term. The drug is eluted on the abluminal surface and therefore might be hypothetically less likely to cause delayed endothelialization, while still preventing in-stent restenosis.

We noted a higher number of stent thrombosis cases than in on-label clinical trials, particularly in small vessels in both BES- and SES-treated groups of patients. Yet, the rate of stent thrombosis corresponds well to other all-comer trials such as SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) (20). It might also be explained by a relatively high percentage of patients with acute coronary syndromes, including up to 21% with ST-segment elevation MI, because similar rates of stent thrombosis have been reported in TRITON–TIMI 38 (A Comparison of CS-747 and Clopidogrel in Acute Coronary Syndrome Subjects who are to Undergo Percutaneous Coronary Intervention–Thrombolysis In Myocardial Infarction 38) and HORIZON-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trials (21,22). There seems to be overall similar rates of definite stent thrombosis in small, large, and "mixed" vessel groups. Longer-term follow-up will determine whether the biodegradable polymer adds any advantage over a durable polymer in terms of very late events.

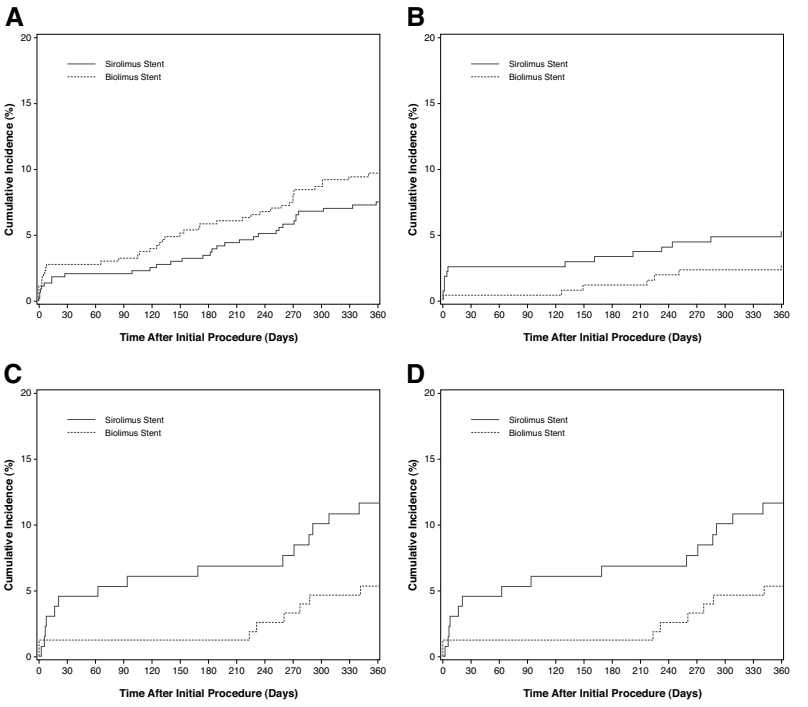

Figure 4. Kaplan-Meier Curves for TLR Rates at 1 Year

Kaplan-Meier curves for target lesion revascularization (TLR) rates at 1 year. **(A)** Small vessels; **(B)** large vessels; **(C)** mixed vessels (p = 0.05); **(D)** all vessels.

Lastly, there seems to be an advantage of treatment with BES in patients with "mixed" lesions and multivessel disease. This difference in angiographic outcomes (late loss) and trend to a significant difference in TLR and TVR in patients with "mixed" disease must be explored further. Although late loss has been established as a discriminating factor in stent performance (3–5), it remains uncertain whether this translates into differences in long-term clinical outcomes. The interpretation of this result in this complex group with "mixed" lesions is difficult; nevertheless, given the prevalence of "mixed" lesion populations in our clinical practice, it is noteworthy.

Study limitations. The study suffers from the usual limitations of post hoc analyses and, for some subgroup analyses, might lack sufficient power to detect superiority of 1 treatment over the other. Some of the key differences in outcomes such as late stent thrombosis in a degradable versus permanent polymer stent might emerge at long-term follow-up.

Conclusions

Vessel size has been an important predictor of in-stent restenosis and clinical events. The SES have been thus far superior to PES and bare-metal stents in treatment of small vessels. We demonstrate for the first time the non-inferiority of BES to SES in angiographic late loss and percutaneous TLR rates.

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Key Words: biodegradable polymer ■ biolimus-eluting stent ■ long lesions ■ sirolimus-eluting stent ■ small vessels ■ target vessel revascularization.

APPENDIX

For supplementary figures and tables, please see the online version of this article.

Chapter 8

Biolimus-eluting biodegradable polymer versus sirolimus eluting permanent polymer stent performance in long lesions: results from the LEADERS multicentre trial substudy

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KEYWORDS
Biolimus-eluting stent (BES), sirolimus-eluting stent (SES), biodegradable polymer, target vessel revascularisation, long lesions

Abstract

Aims: Lesion length remains a predictor of target lesion revascularisation and results of long lesion stenting remain poor. Sirolimus-eluting stents have been shown to perform better than paclitaxel eluting stents in long lesions. In this substudy of the LEADERS trial, we compared the performance of biolimus biodegradable polymer (BES) and sirolimus permanent polymer stents (SES) in long lesions.

Methods and results: A total of 1,707 'all-comer' patients were randomly allocated to treatment with BES and SES. A stratified analysis of angiographic and clinical outcomes at nine months and one year, respectively was performed for vessels with lesion length <20 mm versus >20 mm (as measured by quantitative angiography). Of 1,707 patients, 592 BES patients with 831 lesions and 619 SES patients with 876 lesions had only short lesions treated. One hundred and fifty-three BES patients with 166 lesions and 151 SES patients with 162 lesions had long lesions. There were no significant differences in baseline clinical characteristics, except for higher number of patients with long lesions presenting with acute myocardial infarction in both stent groups. Long lesions tended to have lower MLD and greater percent diameter stenosis at baseline than short lesions. Late loss was greater for long lesions than short lesions. There was no statistically significant difference in late loss between BES and SES stents (0.32±0.69 vs 0.24±0.57, p=0.59). Binary in-segment restenosis was present in 23.2% versus 13.1% of long lesions treated with BES and SES, respectively (p=0.042). In patients with long lesions, the overall MACE rate was similar for BES and SES (17% vs 14.6%; p=0.62). There was a trend towards higher overall TLR rate with BES (12.4 % vs 6.0%; HR=2.06; p=0.07) and clinically driven TLR (10.5% vs 5.3%: HR 1.94; p=0.13). Rates of definite stent thrombosis were 3.3% in the long lesion group and 1.3-1.7 % in the short lesion group.

Conclusions: BES and SES appear similar with respect to MACE in long lesions in this "all-comer" patient population. However, long lesions tended to have a higher rate of binary in-segment restenosis and TLR following BES than SES treatment.

Introduction

Drug eluting stents have considerably reduced restenosis and the need of repeat revascularisation compared to bare metal stents.[1,2] The ADVANCE study was the first to demonstrate that stenting in long lesions (> 40 mm) was associated with higher MACE rates.[3] Sirolimus eluting stents (SES) have been shown to yield superior results to paclitaxel eluting stents in most, but not all studies,[1,4,5] particularly in complex lesions and patient populations.[6,7] Patients with long lesions remain at increased risk for impaired long-term clinical outcome mainly related to repeat revascularisation procedures. In a study of 500 patients with long lesions, SES showed superior angiographic outcome in terms of late loss (0.09 vs 0.45 mm; p<0.001), percent diameter stenosis and binary restenosis (3.3% vs 14.6%; RR=0.23; p<0.001), as well as TLR rates (2.4% vs 7.2%; p=0.012) but not overall MACE rates.[5]

Biolimus is a highly lipophilic sirolimus analogue.[8] It inhibits the mammalian target of rapamycin (mTOR) and cell-cycle transition in smooth muscle cells with similar potency to sirolimus. In the LEADERS multicentre randomised study of biolimus-eluting biodegradable polymer stent (BES) versus sirolimus-eluting permanent polymer stent (SES), we noted that late loss in the overall patient population was similar for BES than SES (0.13 versus 0.19 mm; p=0.34 at 9 months).[9] In the present stratified analysis of lesion length, we investigated the outcome of patients with short and long lesions following treatment with BES and SES. We hypothesised that since late loss and TLR rates were non-inferior for the BES in the overall population in LEADERS, that this stent will also perform equivalently to SES in the long lesion subset.

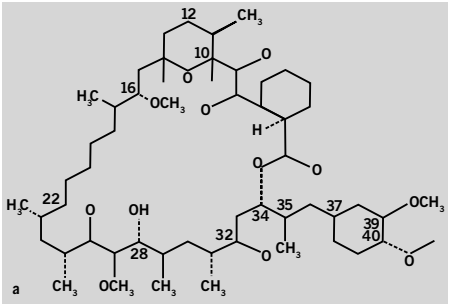
Methods

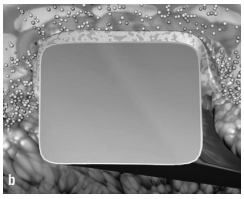
Study population

LEADERS was a multicentre European non-inferiority trial comparing safety and efficacy of BES to SES in 1,707 'all comer' patients. Patients over the age of 18 with chronic stable coronary artery disease or acute coronary syndromes including ST-elevation myocardial infarction 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 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 six months of percutaneous coronary intervention – unless the dual anti-platelet therapy could be maintained throughout the peri-surgical period, pregnancy or 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.

Randomisation and procedures

Randomisation was done centrally after diagnostic cardiac catheterisation and before PCI by use of a telephone allocation service (Limburgia Telefonische Antwoord Service BV, 3068 NP Rotterdam, The Netherlands). The allocation sequence was computer generated, stratified according to centre, and blocked with block sizes of eight and 16 which varied randomly. Randomisation was performed on a 1:1 basis to treatment with a stent eluting biolimus-A9 with a biodegradable polylactic acid polymer (Biomatrix Flex, Biosensors Inc., Newport Beach, CA, USA) (Figures 1a, b and c) or a sirolimus-eluting stent with a durable polymer (Cypher SELECT, Cordis, Miami Lakes, FL, USA)





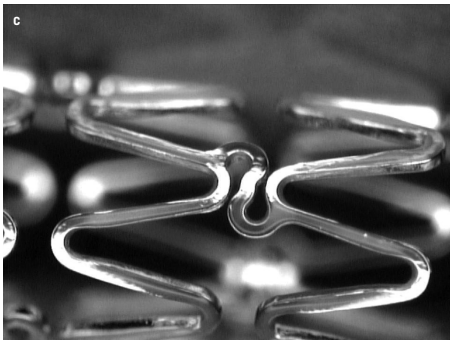


Figure 1. A9™ Eluting Stent: Structure of biolimus and scanning electron micrograph of the biolimus biodegradable polymer stent. 1a. Biolimus is a semi-synthetic sirolimus with 10x higher lipophilicity and similar potency as sirolimus. 1b. Biolimus is immersed at a concentration of 15.6 µg/mm into a biodegradable polymer, polylactic acid and applied solely to the abluminal stent surface by a fully automated process. Polylactic acid is co-released with biolimus and completely dissolves into carbon dioxide and water during a 6-9 months period. 1c. The stainless steel stent platform has a strut thickness of 112 µm with a quadrature link design.

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, 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 was performed according to standard technique and direct stenting was allowed. No mixture of drug eluting stents was allowed 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 permitted. The length of the stent was left at the discretion of the operators who followed good clinical practice guidelines which include using one stent to cover the lesion when possible. Before, or at the time of the procedure, patients were given at least 75 mg of acetylsalicylic acid, 300-600 mg loading dose of clopidogrel and unfractionated heparin in a dose at least 5,000 IU 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 revascularisation procedures needing stent implantation, treating cardiologists were encouraged to use the study stent. For other details please see the main manuscript.[9]

Study endpoints

Adverse events were assessed in the hospital and at nine and 12 months. An independent clinical events committee unaware of the patient's treatment assignments adjudicated all endpoints. One in four patients was asked to return for angiographic follow-up at nine months. Definitions of all endpoints are explained in the main manuscript.[9] Briefly, the pre-specified primary endpoint was the composite of cardiac death, myocardial infarction and clinically-indicated target vessel revascularisation (TVR) within nine and 12 months. Secondary endpoints were: any target lesion revascularisation (TLR) – both clinically and non-clinically indicated – which we defined as repeat revascularisation 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, myocardial infarction, stent thrombosis (defined according to the ARC)[10], device success (defined as achievement of a final residual diameter stenosis of less than 50% during the initial procedure), and lesion success (achievement of less than 50% stenosis with any approach for PCI). The pre-specified principal outcome for angiographic substudy was in-stent percentage diameter stenosis. Secondary angiographic outcomes were: in-segment percentage diameter stenosis, minimal lumen diameter, late lumen loss and binary restenosis. We obtained angiographic measurements within the stented segment (in-stent) and over the entire segment consisting of the stent and 5 mm proximal and distal margins (in-segment). We defined percentage diameter stenosis as ([reference vessel diameter-minimal luminal diameter]/reference vessel diameter) X 100%; late lumen loss as the difference between minimal lumen diameter after the procedure and minimal lumen diameter at follow-up; and binary restenosis as percentage diameter stenosis of 50% or greater in the target lesion. Independent study monitors (D-Target, Montagny-pres-Yverdon, Switzerland) verified all case reports from data on-site. Data were stored in a database (KIKA Medical, Paris, France), which was maintained by a contract research organisation (Cardialysis, Rotterdam, The Netherlands) in collaboration with an academic clinical trials unit (CTU Bern, Bern University Hospital, Bern, Switzerland). Clinical follow up was done at 1, 6, 9 and 12 months. 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. Angiographies were centrally assessed at one angiographic core laboratory (Cardialysis, Rotterdam, The Netherlands) with assessors unaware of the allocated stent.

Statistical analysis

A stratified analysis of clinical and angiographic outcomes, which was specified after completion of patient recruitment, was performed according to lesion length. Methodology similar to the previously published SIRTAX trial was used.[11] Patients, who underwent stent implantation in lesions with an lesion length ≤20 mm (as measured by quantitative angiography at index procedure), were categorised as having undergone treatment of short lesion. Conversely, patients who underwent stent implantation in lesions with length >20 mm were classified as having had treatment of long lesion. Patients with stent implantations in both short and long lesions were classified as mixed. All randomised patients were included in the analysis of primary and secondary clinical endpoints in the groups that they were originally assigned (intention-to-treat analysis). Analyses of the angiographic substudy were restricted to lesions from patients who attended follow-up angiography. 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. 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

Baseline clinical, angiographic, and procedural data

Of 1,707 patients, 592 patients in the BES group with 832 lesions and 619 patients in the SES group with 876 lesions had only short lesions treated. One hundred and fifty-three patients in the BES group with 166 lesions and 151 patients with 162 lesions in the SES group had long lesions. (Figure 2) 105 patients with 250 lesions in the biolimus group and 69 patients with 164 lesions in the sirolimus group had both short and long lesions.

Baseline clinical and angiographic characteristics are summarised in Table 1. More patients with long lesions tended to present with ST-elevation MI (26-29% vs 12%) in both stent groups. Patients with long lesions treated with BES tended to have less hypertension (67% vs 77% for short lesions, p=0.027). Patients with long lesions treated with either stent had a greater number of current smokers (29%-31% vs 22%-24%; p=0.011). Patients with short lesions tended to have been previously treated with percutaneous revascularisation more often, had more strokes and more multivessel disease.

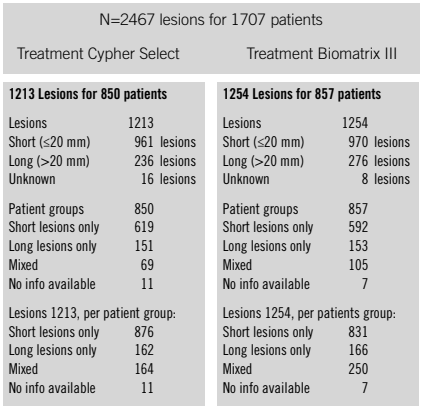


Figure 2. Flow chart.

Mean lesion length for short lesions was 10.5±4.4 mm in the BES group and 10.2±4.4 mm in the SES group. Long lesions measured on average 32.6±14.8 mm in the BES group and 32.2±12.5 mm in the SES group. (Table 1) The distribution for long lesions was skewed to the right with minimum lesion length of 20.03 mm and maximum lesion length of 101.47 mm, 90% of the long lesions were 20-50 mm. Reference vessel diameters did not differ significantly between lesion or stent types. Long lesions tended to have much lower MLD (0.48-0.58 mm vs 1.01-1.05 mm) than short lesions and correspondingly greater percent diameter stenosis (78-82% vs 59-61%; p<0.001). The lower MLD in the long lesion group was significantly correlated with acute myocardial infarction at presentation (data not shown).

Procedural characteristics and results

Procedural results are shown in Table 2. Average numbers of stents per lesion were 1.14-1.15 in the short lesions and 1.99-2.0 in the long lesions. Mean stent diameters per lesion were similar between lesion types and groups. Total stent length per lesion was 20±9 mm in the short lesions and 43±22 mm in the long lesions.

Percent diameter stenosis was 14.1±8.9% and 13.9±7.9% in the short lesions treated with BES and SES, respectively, 17.2±7.4% in the long lesions treated with BES and 17.3±7.8% in the long lesions treated with SES. The differences were not statistically significant. Long lesions had significantly greater absolute gain as the lesions treated had lower initial MLDs (p=0.05). This effect was consistent across stent groups.

Angiographic results

Angiographic follow-up at nine months was obtained in 313 short lesions and 69 long lesions. There was no statistically significant

Table 1. Baseline clinical and angiographic characteristics for short and long lesions.

	Biolimus, short mean (SD)	Sirolimus, short mean (SD)	Biolimus, long mean (SD)	Sirolimus, long mean (SD)	p-value short vs. long	p-value short, Biolimus vs. Sirolimus	p-value long, Biolimus vs. Sirolimus
Patient demographics							
Number of patients	592	619	153	151			
Age>65	305(51)	315(51)	71(46)	72(48)	0.19	0.83	0.82
Male	433(73)	458(74)	122(80)	115(76)	0.12	0.74	0.45
Diabetes	156(26)	140(23)	38(25)	36(24)	0.97	0.13	0.84
Hypertension	454(77)	458(74)	102(67)	108(71)	0.027	0.28	0.36
Hyperlipidaemia	395(67)	427(69)	89(58)	104(69)	0.15	0.4	0.053
Current smoking	131(22)	147(24)	47(31)	44(29)	0.011	0.5	0.76
Previous MI	185(31)	210(34)	47(31)	44(29)	0.37	0.32	0.76
Previous PCI	231(39)	257(41)	49(32)	41(27)	<0.001	0.38	0.35
Previous stroke	26(4.4)	17(2.7)	9(5.9)	10(6.6)	0.034	0.12	0.82
Previous PVD	44(7.4)	49(7.9)	13(8.5)	10(6.6)	0.95	0.75	0.54
Multivessel disease	123(21)	119(19)	9(6)	8(5)	<0.001	0.5	1
Clinical presentation							
Stable angina	200(34)	218(35)	55(36)	45(30)	0.59	0.6	0.25
Acute coronary syndromes	327(55)	332(54)	85(56)	94(62)	0.16	0.58	0.24
Unstable angina	142(24)	151(24)	28(18)	19(13)	0.001	0.87	0.17
STEMI	76(13)	77(12)	40(26)	43(29)	<0.001	0.83	0.65
Non-STEMI	109(18)	104(17)	17(11)	32(21)	0.54	0.46	0.017
Angiographic parameters							
Number of lesions treated	831	876	166	162			
Lesion length	10.5±4.4	10.2±4.4	32.6±14.8*	32.2±12.5*	<0.001	0.41	0.98
Reference vessel diameter	2.62±0.61	2.61±0.57	2.60±0.57	2.64±0.60	0.83	0.75	0.44
Minimal luminal diameter	1.01±0.44	1.05±0.46	0.48±0.51	0.58±0.57	<0.001	0.08	0.25
%diameter stenosis	61±15	59±15	82±19	78±20	<0.001	0.1	0.21

* lesion length distribution was skewed to the right and in both stent groups the minimum lesion length was 20.03 and maximum 101.47 mm with 90% of lesions falling between 20 and 50 mm

Table 2. Procedural outcomes and angiographic follow-up results at nine months for short and long lesions.

	Biolimus, short	Sirolimus, short	Biolimus, long	Sirolimus, long	p-value BES vs. SES in the short lesion groups	p-value BES vs. SES in the long lesion groups
In-stent						
Reference vessel diameter						
Post-procedure	2.78(0.54)	2.76(0.49)	2.74(0.51)	2.73(0.53)	0.46	0.8
*9 month follow-up	2.84(0.50)	2.78(0.53)	2.79(0.47)	2.61(0.49)	0.34	0.18
MLD						
Post-procedure	2.38(0.50)	2.37(0.46)	2.26(0.45)	2.24(0.43)	0.71	0.74
*9 month follow-up	2.33(0.61)	2.18(0.69)	1.89(0.88)	1.86(0.68)	0.07	0.91
Acute gain	1.37(0.51)	1.33(0.48)	1.80(0.64)	1.66(0.64)	0.1	0.03
Late loss	0.11(0.44)	0.18(0.49)	0.32(0.69)	0.24(0.57)	0.37	0.59
%DS						
Post-procedure	14.1(8.9)	13.9(7.9)	17.2(7.4)	17.3(7.8)	0.66	0.88
*9 month follow-up	18.3(15.1)	21.7(18.9)	32.5(28.7)	28.8(21.9)	0.19	0.48
Binary restenosis rate(%)	3.5	8.2	16.7	10.4	0.08	0.12
In-segment						
Reference vessel diameter						
Post-procedure	2.69(0.54)	2.68(0.52)	2.64(0.56)	2.63(0.58)	0.61	0.9
*9 month follow-up	2.79(0.51)	2.70(0.55)	2.73(0.47)	2.56(0.50)	0.17	0.25
MLD						
Post-procedure	2.07(0.52)	2.09(0.50)	2.03(0.49)	1.98(0.48)	0.4	0.38
*9 month follow-up	2.09(0.56)	1.93(0.62)	1.73(0.84)	1.67(0.65)	0.051	0.7
Acute gain	1.05(0.53)	1.04(0.51)	1.56(0.66)	1.40(0.65)	0.73	0.013
Late loss	0.06(0.44)	0.15(0.43)	0.27(0.62)	0.22(0.56)	0.14	0.64
%DS						
Post-procedure	22.9(10.3)	21.9(9.8)	23.1(8.6)	24.8(8.7)	0.019	0.12
*9 month follow-up	25.2(14.1)	28.5(18.1)	36.5(28.4)	35.0(20.4)	0.31	0.57
Binary restenosis rate(%)	4.2	10.6	23.2	13.1	0.036	0.042

* 9 months angiographic follow-up was done in 69 patients with long lesions (30 treated with BES and 39 treated with SES)

difference in late loss, minimal luminal diameter, percent diameter stenosis or binary restenosis in small or large vessels between BES and SES groups, although this could have been due to the relatively low number of lesions, particularly in the long lesion subgroup (Table 2). Late loss increased more with lesion length in the case of BES stents that in the case of SES stents (Figure 4). Corresponding MLDs and percent diameter stenoses were not significantly different (Table 2). Binary in-stent restenosis was present in 3.5% versus 8.2% of short lesions treated with BES and SES respectively, and in 16.7% versus 10.3% of long lesions treated with BES and SES (p=0.12). A similar pattern was observed for in-segment restenosis (23.2% vs 13.1% for long lesions; p=0.042). The proportion of patients and lesions treated with overlapping stents in long lesions did not differ between BES and SES.

Clinical outcomes

Clinical events at one year follow-up, stratified by lesion length, are listed in Table 3 and summarised in Figures 3a and 3b as Kaplan Meier curves. There were no significant differences in the rate of MACE through stent groups or lesion types. The overall rates of MACE were: 8.4% versus 10.2% in the short lesions treated with BES and SES, respectively (p=0.32). In patients with long lesions, MACE rate was 17% vs 14.6% in the BES and SES groups (p=0.62).

TVR rates were 6.9% versus 9.9% in the short lesions in favour of BES (p=0.07), 14.4% versus 7.3% in the long lesions in favour of SES (HR=1.98; p=0.07). TLR rates shown in Kaplan Meier curves demonstrated similar pattern of SES tending to perform better in long lesions. In addition, TLR increased proportionally to the stent length (divided by tertiles). For stent length of less than 12.9 mm, TLR rate was 4.1%, for stent length 12.9-19.5 mm 5.6% and for stent length >19.5 mm, TLR was 7.4% (p=0.0334).

The rates of definite stent thrombosis in the long lesion group were 3.3% in the long lesion group versus 1.3-1.7% in the short lesion group. For the long lesions group total stent thrombosis rates were 0.7% for acute, 3.0% for subacute and 1.3% for late stent thrombosis (at one year). These rates were comparable for short lesions in acute and late stent thrombosis rates. The rate of sub-acute stent thrombosis for short lesions was 0.8% (versus 3.0% for long lesions).

Discussion

We present here a novel stent technology now commercially available in Europe, which combines the biodegradable polymer technology with solely abluminal elution of biolimus. Use of drug eluting stents has improved outcomes in patients with coronary artery disease treated with PCI,[12] including complex lesions.[13,14] However, lesion length has remained a strong predictor of in-stent

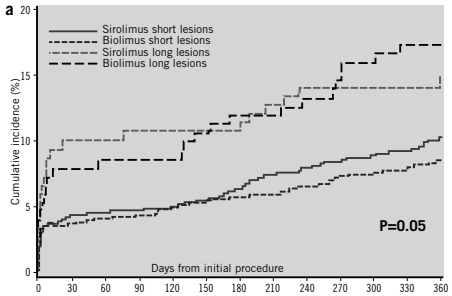
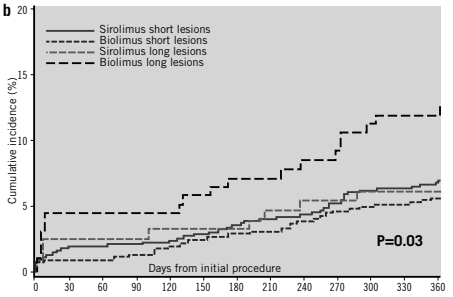


Figure 3a. Kaplan Meier curves for MACE rate at one year follow-up.



3b. Kaplan Meier curves for TLR rates at one year follow-up.

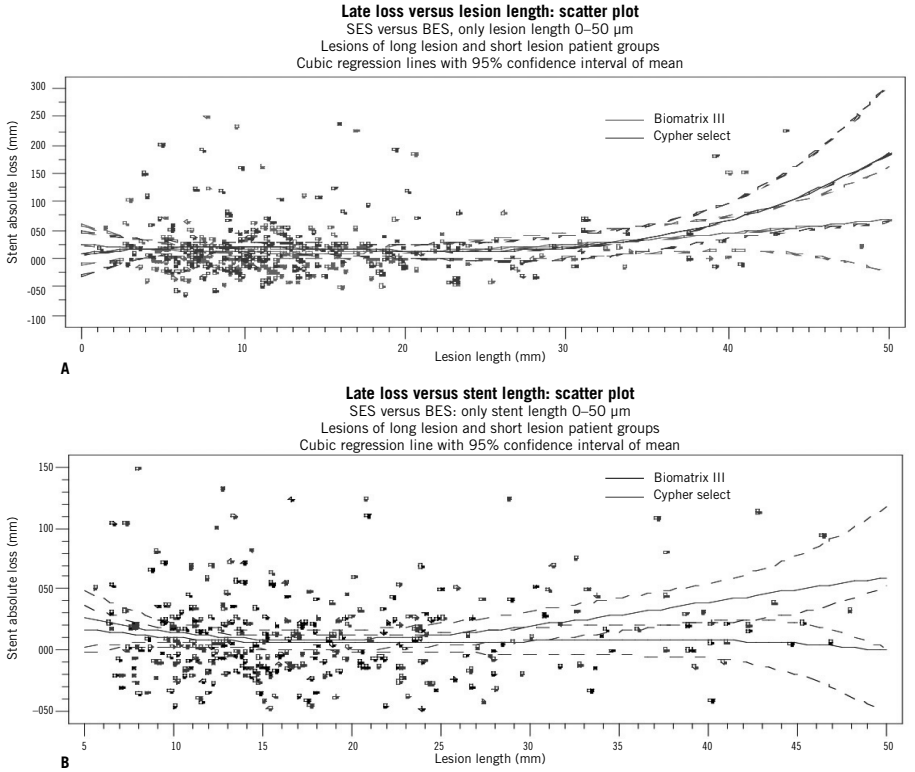


Figure 4. Late loss versus, A) lesion length and B) stent length for BES versus SES.

restenosis.[15,16] Although the pattern of restenosis after drug eluting stents is more focal rather than diffuse, as with bare metal stents, and therefore more easily treated, it still remains increased for long lesions.[5,7] Paclitaxel eluting stents have been shown to be inferior to sirolimus eluting stents with TVR rates of 7.6% versus 3.2% (p=0.03) in recent studies involving long lesions.[5] Our study is the first to compare the performance of a biolimus biodegradable polymer stent (BES) with a sirolimus permanent polymer stent (SES) in long lesions. The population studied was an 'all comers' population within the LEADERS trial, with a considerable number of

Table 3. Clinical outcomes of the short and long lesions stratified with stent type.

	Biolimus, short (n=592)	Sirolimus, short (n=619)	Hazard ratio (95% confidence interval)	p-value	Biolimus, long (n=153)	Sirolimus, long (n=151)	Hazard ratio (95% confidence interval)	p-value
Death	15 (2.5)	12 (1.9)	1.31 (0.62-2.81)	0.48	7 (4.6)	10 (6.6)	0.67 (0.26-1.77)	0.42
Cardiac death	9 (1.5)	9 (1.5)	1.05 (0.42-2.65)	0.91	5 (3.3)	9 (6.0)	0.53 (0.18-1.59)	0.26
MI	26 (4.4)	23 (3.7)	1.19 (0.68-2.08)	0.55	14 (9.2)	10 (6.6)	1.36 (0.60-3.06)	0.46
All TLR	34 (5.7)	44 (7.1)	0.81 (0.52-1.26)	0.35	19 (12.4)	9 (6.0)	2.06 (0.93-4.56)	0.07
TLR percutaneous	32 (5.4)	41 (6.6)	0.82 (0.52-1.30)	0.4	17 (11.1)	9 (6.0)	1.85 (0.82-4.14)	0.14
TLR surgical	6 (1.0)	7 (1.1)	0.9 (0.30-2.67)	0.85	2 (1.3)	0 (0.0)	>100 (0-*)	1
Clinically justified TLR	26 (4.4)	34 (5.5)	0.8 (0.48-1.33)	0.39	16 (10.5)	8 (5.3)	1.94 (0.83-4.52)	0.13
Clinically justified TLR percutaneous	25 (4.2)	32 (5.2)	0.82 (0.49-1.38)	0.46	15 (9.8)	8 (5.3)	1.81 (0.77-4.28)	0.17
Clinically justified TLR surgical	4 (0.7)	4 (0.6)	1.05 (0.26-4.20)	0.95	1 (0.7)	0 (0.0)	>100 (0-*)	1
All TVR	41 (6.9)	61 (9.9)	0.7 (0.47-1.03)	0.07	22 (14.4)	11 (7.3)	1.98 (0.96-4.07)	0.07
TVR percutaneous	37 (6.3)	53 (8.6)	0.73 (0.48-1.11)	0.14	19 (12.4)	11 (7.3)	1.7 (0.81-3.56)	0.16
TVR surgical	8 (1.4)	12 (1.9)	0.7 (0.28-1.70)	0.43	3 (2.0)	0 (0.0)	>100 (0-*)	1
Clinically justified TVR	29 (4.9)	42 (6.8)	0.72 (0.45-1.15)	0.17	18 (11.8)	9 (6.0)	1.95 (0.88-4.34)	0.1
Clinically justified TVR percutaneous	28 (4.7)	39 (6.3)	0.75 (0.46-1.22)	0.25	16 (10.5)	9 (6.0)	1.72 (0.76-3.90)	0.19
Clinically justified TVR surgical	4 (0.7)	6 (1.0)	0.7 (0.20-2.47)	0.58	2 (1.3)	0 (0.0)	>100 (0-*)	1
Stent thrombosis	18 (3.0)	12 (1.9)	1.58 (0.76-3.28)	0.22	7 (4.6)	8 (5.3)	0.84 (0.31-2.33)	0.74
Definite stent thrombosis	10 (1.7)	8 (1.3)	1.31 (0.52-3.32)	0.57	5 (3.3)	5 (3.3)	0.97 (0.28-3.34)	0.96
Possible stent thrombosis	5 (0.8)	5 (0.8)	1.05 (0.31-3.64)	0.93	1 (0.7)	2 (1.3)	0.48 (0.04-5.27)	0.55
Probable stent thrombosis	4 (0.7)	0 (0.0)	>100 (0-*)	0.99	1 (0.7)	2 (1.3)	0.48 (0.04-5.31)	0.55
MACE	50 (8.4)	63 (10.2)	0.83 (0.57-1.20)	0.32	26 (17.0)	22 (14.6)	1.15 (0.65-2.04)	0.62
Target vessel failure	58 (9.8)	75 (12.1)	0.8 (0.57-1.13)	0.21	26 (17.0)	21 (13.9)	1.22 (0.69-2.17)	0.5

Values are n(%), otherwise stated; *Upper limit not defined

high risk lesions, average lesion length in the long lesion group of 32 mm and high proportion of ST elevation myocardial infarctions (28% in the long lesion group). The TVR rate in the long lesions was 14.4% in the BES group and 7.3% in the SES group with a hazard ratio of 1.98 and a trend towards statistical significance. This is compared to 6.9% and 9.9% TVR rates in short lesions, in BES and SES groups respectively. Therefore, SES tended to perform better than BES in long lesions, although the result did not reach statistical significance. Interestingly, in patients with multivessel disease and mixed lesions, the reverse was observed with statistically significant difference in favour of BES (2.9% versus 14.5%, HR=0.18; p<0.001; data not shown). This latter effect did not appear to be explainable by the interaction of stent type with patient diabetic status. In addition, it paralleled the results (presented elsewhere) of stenting by reference vessel diameter, where patients with mixed, small and large diameter reference vessel lesions derived benefit from stenting with BES.

No differences were observed between BES and SES in the rate of MACE, or rate of stent thrombosis in the long lesions although the incidence was rather high in this subgroup.

The angiographic follow-up was limited to one quarter of the patients, and although corresponding differences in late loss and percent diameter stenosis were found between BES and SES stented lesions in the long lesion group, given low patient and lesion numbers the results did not reach statistical significance. Further validation of the results will be needed in larger registries of equally complex patients.

Limitations

This substudy is limited by post hoc nature of the analysis, and limited number of long-lesions with angiographic follow-up. The study may be under-powered to detect differences in the angiographic outcomes. Longer term follow-up will be necessary to fully assess the performance of biolimus stent, especially with respect to stent thrombosis, since polymer fully degrades at six months.

Conclusions

Biolimus and sirolimus eluting stents appear equivalent with respect to MACE rate in long lesions in this "all-comer" patient population, however, biolimus treated long-lesion group appears to have higher TLR rates. There were no statistically significant differences in the late loss, percent diameter stenosis or binary restenosis rates for short of long lesions treated with either stent, although the study may have been underpowered to detect these differences in angiographic outcomes.

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Excerpt from the Reviewers

Since this is a sub-study, the authors should clearly define what presentation of these results add over and above the results of the main analysis. Slicing and dicing the data has led to some particularly small group comparisons, particularly when it comes to the angiographic follow-up data. The study is under-powered, and therefore some of the results could be explained by play of chance.

Chapter 9

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.

Running Title: Outcomes in Bifurcations lesion stenting
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DISCLOSURES

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 conflicts of interest.

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Abstract

Aims: This study investigated the differences in clinical outcomes between patients with bifurcation lesions (BLs) treated with a biolimus eluting stent (BES) with a biodegradable polymer, and a sirolimus eluting stent (SES) with a durable polymer.

Methods & Results: The clinical outcomes were assessed in the 497 patients (BES 258, SES 239) enrolled in the multicenter, randomised LEADERS trial who underwent treatment of ≥1 BL (total=534 BLs). At 12-months follow-up there was no significant difference in the primary end-point 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 BLs the use of BES lead to superior efficacy and comparable safety compared to SES.

Keywords: Biolimus eluting stent, Sirolimus eluting stent, Bifurcation lesions, Biodegradable polymer.

Condensed Abstract

This study reports on the outcomes of 497 patients with bifurcation lesions randomised to treatment with either a biolimus eluting stent with a biodegradable polymer (258 patients) or a sirolimus eluting stent with a durable polymer (239 patients). At 12-months follow-up the primary endpoint, a composite of cardiac death, myocardial infarction, and clinically-indicated target vessel revascularisation, and the rates of stent thrombosis were all comparable between both stents.

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 BLs 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 DESs 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 metabolized 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 9 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 BLs 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 BLs according to the SYNTAX bifurcation score.[12] The angiograms of 497 patients (258 BES, 239 SES) who had a total of 534 BLs (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 guide-wires 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 BLs into 'True' or 'Partial' BLs. Those BLs 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"

BLs, 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" BLs.

Randomization 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 9 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 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, and ≥300 mg of clopidogrel. All patients were discharged on ≥75 mg of acetylsalicylic acid indefinitely, and clopidogrel 75mg 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 9 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 revascularization

(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, 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. Peri-procedural 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 5mm 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 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. 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 BLs 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 BLs 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 BLs to partial BLs; 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 the primary end-point of MACE between BES and SES at 12-months follow-up (BES 12.8% vs. SES 16.3%, p=0.31). The rate of death was equal 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 peri-procedural 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).

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).

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; or the number of stents used.

Discussion

This is the first analysis comparing the management of patients with BLs 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 BLs, is still associated with higher rates of restenosis and ST compared to 'on-label' use.[15, 16] Encouraging evidence from this study suggests newer DESs, 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 DESs in the patients with BLs treated with the same stenting technique. For example Pan *et al* reported a significantly lower rate of TLR with Cypher compared to the TAXUS (Boston Scientific, Natick, 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, 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 peri-procedural MI with BES, which in the vast majority was triggered by the detection of a rise in cardiac enzymes.

Although these peri-procedural 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 peri-procedural 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 peri-procedural 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 peri-procedural 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 3mm BES is 10.8mm compared to 9.5mm 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 embolizing and causing subsequent enzyme release.[21] These observations must be

interpreted with caution not only 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, but also because of the actual lower rates of repeat revascularisation observed with BES in this study.

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 BLs, as these lesions represent an independent risk factor for ST, and have higher rates of ST when compared with non-BLs 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 BLs, the optimal procedural strategy remains to be established. In the current study a single-stent strategy was preferred for BLs, 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 randomized 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 BLs 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 BLs is warranted using dedicated bifurcation software; however the number of patients with BLs 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.

List of Figures and Tables

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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/m^2	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
Multi-vessel 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 infarction, NSTEMI, non-ST elevation MI; PCI, percutaneous coronary intervention, SES, sirolimus eluting stent**s.**

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
Post Procedure			
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
Average stent diameter, mm	2.88±0.33	2.89±0.32	0.89
Average 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

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.

Table 4. 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).

Figure 1. Flowchart indicating the number and type of bifurcation lesions categorized according to make of stent.

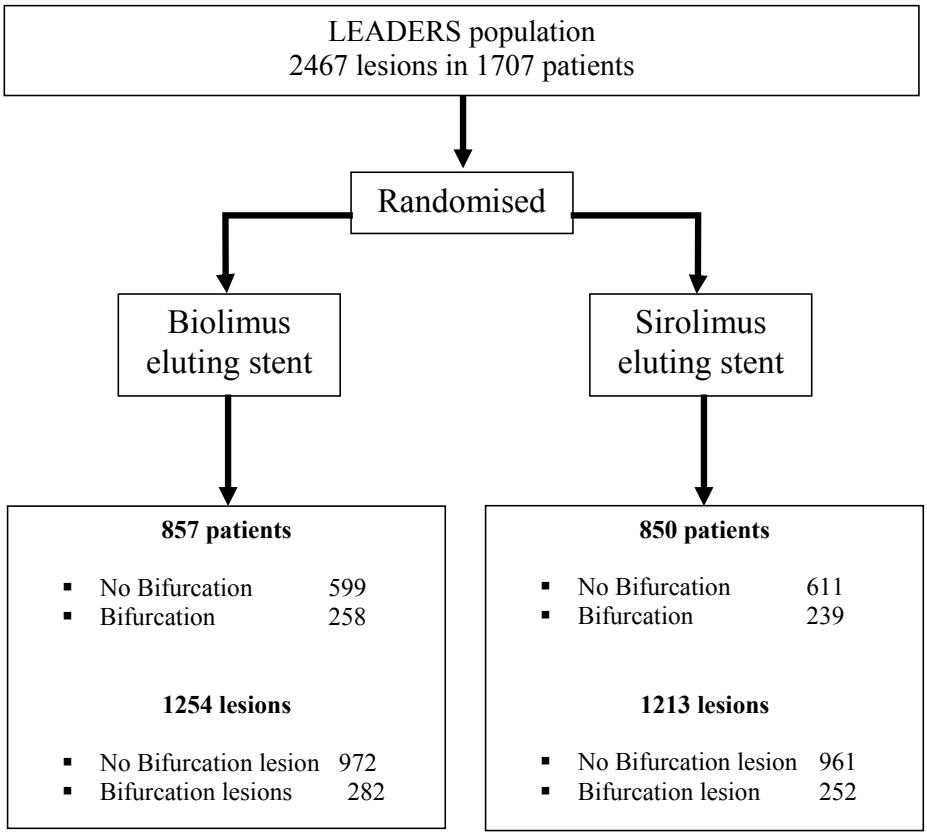
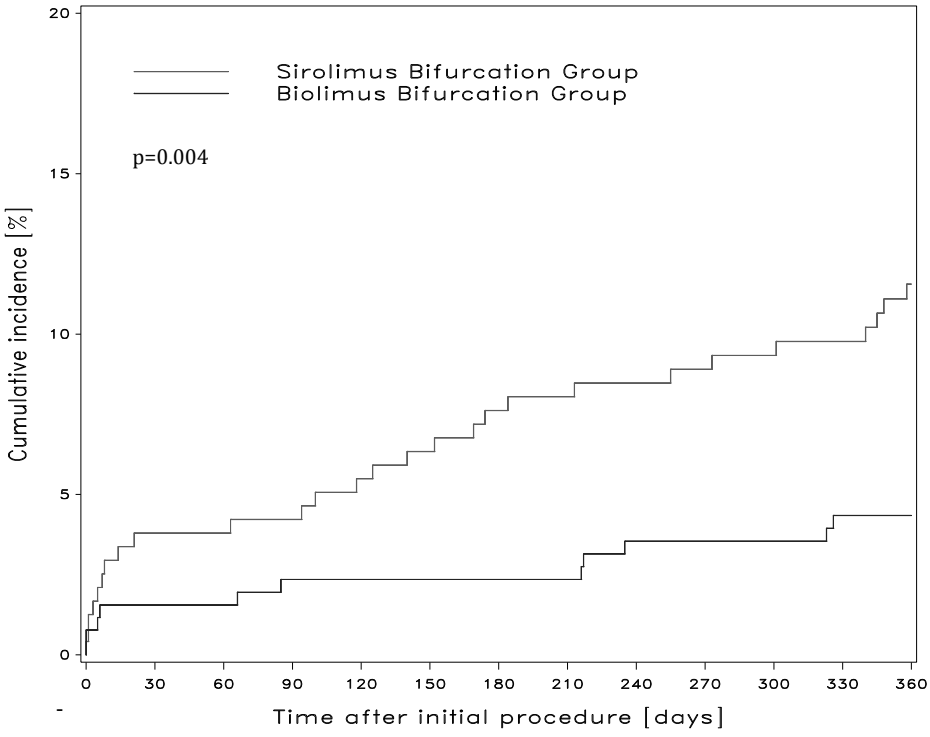
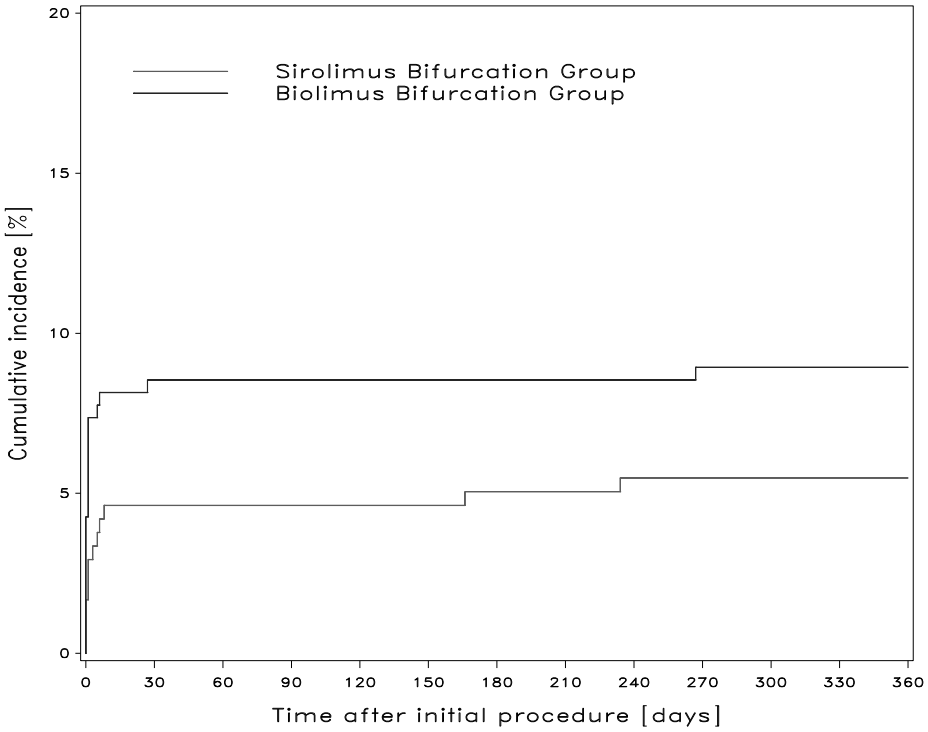


Figure 2: Kaplan Meier survival curves

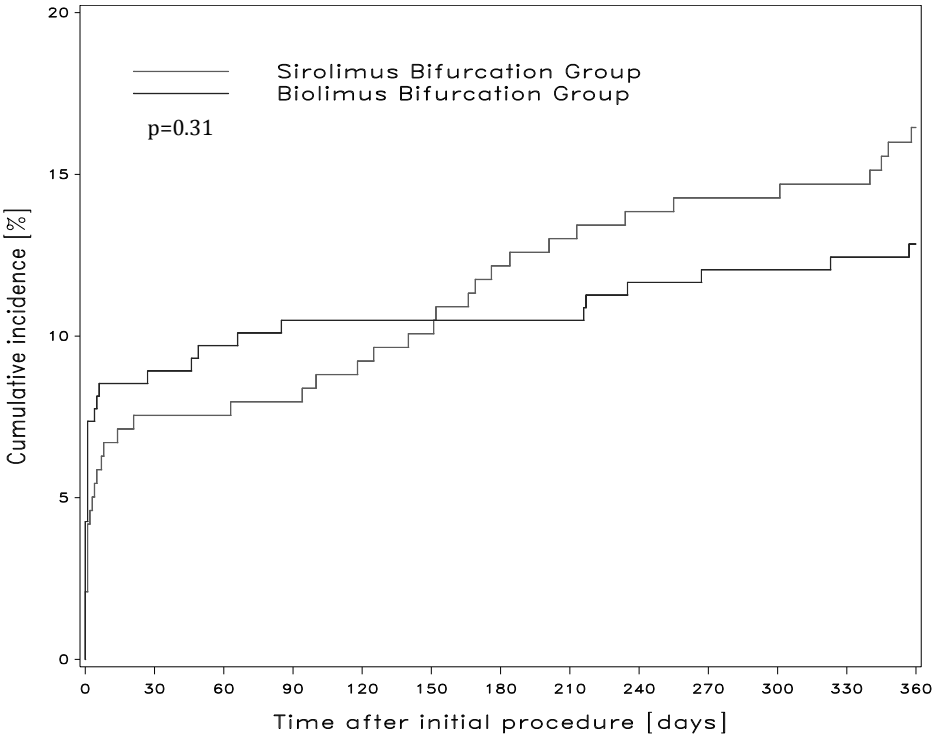
(A) Clinically justified target vessel revascularization



(B) Myocardial infarction



(C) Major adverse cardiovascular events



Chapter 10

Bifurcation Stenting – Have We Made Progress in the Last 10 Years?

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Abstract

Bifurcation stenting is one of the unsolved challenges for interventional cardiologists. Patients with bifurcation lesions tend to have more advanced disease and multiple co-morbidities. Over the last 10 years we have come to understand the importance and made progress in bifurcation imaging for planning the procedure and for assessment of procedural success, from 3D angiography and multislice computed tomography (MSCT) to fractional flow reserve (FFR) and optical coherence tomography (OCT). Recent clinical trials have shown improved results with selective use of a two-stent strategy and drug-eluting stents. Rates of major adverse cardiac events (MACE) and peri-procedural myocardial infarction (MI) for bifurcation lesions still remain high. Many challenges such as side-branch access, wire-trapping, incomplete side-branch coverage and restenosis still remain. No single dedicated bifurcation stent design thus far has been able to solve them all. More long-term, prospective, efficacious studies of these novel stent designs with concomitant imaging are needed for the field to progress.

Keywords

Bifurcation, drug-eluting stent, dedicated bifurcation stents, imaging

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Approach to the Bifurcation Patient

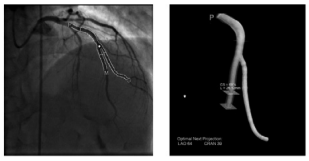
Historically, bifurcation lesions have been associated with lower procedural success and a poorer clinical outcome than non-bifurcation lesions. This may be due to the technical difficulty of the procedure but also due to the complexity of the patients. According to the recently presented LEADERS trial sub-study,[1] patients who have bifurcation disease are significantly more likely to have had a previous myocardial infarction (MI) (37.2 versus 30.4%; p=0.007) and multivessel disease (36.0 versus 17.0%; p<0.001). The latter was reflected in a much higher Syntax score (17 versus 12; p<0.001), indicating that next to the target bifurcation there is, on average, at least one additional lesion. In addition, patients with bifurcation disease tended to have smaller-diameter vessels. The rate of peri-procedural MI in LEADERS was significantly higher in patients with bifurcation disease (6.6 versus 3.6%, p=0.01). Similarly, in the ARTS-II bifurcation sub-study,[2] the bifurcation group had more extensive and complex disease (i.e. diffuse lesions, type C lesions). The procedure itself was also more complex, with a higher number and length of stents implanted and longer procedural time. Thus, the first important step in planning the bifurcation procedure is to carefully evaluate the patient and minimise his or her peri-procedural complication risk. This may include routine use of $2\beta3\alpha$ inhibitors or newer antithrombotic agents on top of the usual dual antiplatelet therapy. In addition, pre-hydration in patients with renal disease and careful assessment of anatomy using state-of-the-art imaging techniques is paramount. Based on this careful assessment of clinical and procedural risk, one may even positively decide to change the revascularisation strategy from percutaneous to surgical.[1]

Imaging Techniques

The treatment of bifurcation lesions requires careful assessment of the bifurcation disease anatomy, including the size of the proximal versus the distal vessel, the extent of the disease in the side branch, the degree of calcification and the side-branch angle. Accurate assessment of these bifurcation features is critical in choosing the strategy and tools that would provide the best side-branch coverage with minimal overlap of struts and good stent apposition, thereby minimising the complication rates. However, angiographic 2D assessment of bifurcations is often incomplete because of vessel overlap, foreshortening and poor reconstruction of angles. 2D-angiography-based Medina classification of bifurcation lesions is the most accepted, and easiest to use, classification system.[3] It divides the bifurcation into main proximal, main distal and side-branch segments and assigns binary (0 and 1) values to describe plaque distribution.

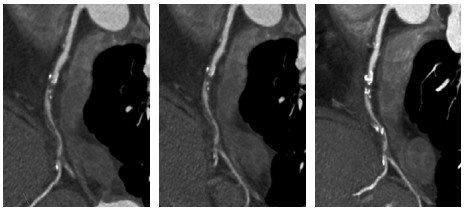
Angiographic assessment of bifurcation lesions was recently summarised by Lansky et al. in 2009.[4] One has to be aware of the inherent inaccuracies in measuring QCA in bifurcation lesions. QCA algorithms have the assumption that the vessel tapers minimally along its course. This assumption is not true for bifurcations where Murray's law must be applied and standard QCA results in the underestimation of the proximal vessel size. Dedicated bifurcation software is now available from Medis and Pie Medical (The Netherlands). The two software programs are described by Lansky et al.[4] and Ramcharitar et al.,[5] respectively. The consensus is that bifurcation lesions should be systematically described according to the Medina classification,[3] at least three projections are required and quantitative analysis

Figure 1A: 2D and 3D Angiography Assessment of Bifurcation Angles



2D-QCA vs. 3D-reconstruction

Figure 1B: Multislice Computed Tomography Assessment of Lesion Complexity and Side-branch Involvement as well as Extent of Calcification



performed in two views with minimal overlap and foreshortening. 2D angulations between the proximal main branch and side branch should be measured. This software has been developed with trial reporting in mind. Single restenosis for the side as well as main branch should be reported and overall restenosis for the entire bifurcation. It is also recommended to perform a more detailed segmental analysis of restenosis, which may give insight into its mechanism.

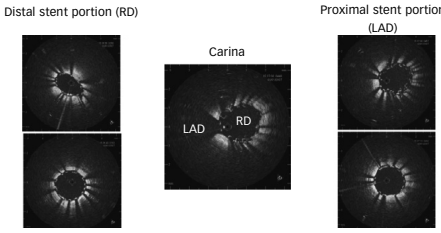
3D Angiography

Given the limitations of 2D angiography, we currently recommend the use of 3D reconstruction of the bifurcation lesions with specialised software such as Paeion Medical (Israel). This system uses two angiographic orthogonal images to reconstruct 3D anatomy and allows the measurement of the bifurcation angle, defined as the angle where the centre lines of the lumen of the main and side-branch cross (see *Figure 1A*). The mean 3D bifurcation angle and the systolic and diastolic angle are then analysed. Careful assessment of angulation not only allows one to choose the proper stenting technique, such as T-stenting for 90º angles and other techniques for lower angulations to avoid side-branch gap, but is also a powerful predictor of clinical outcomes including mortality.[6]

Multislice Computed Tomography

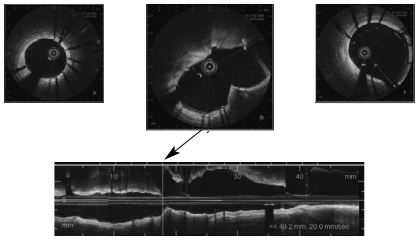
For similar reasons, multislice computed tomography (MSCT) with volume-rendered reconstructions of the coronary tree may facilitate assessment of bifurcations, with respect not only to the angulation but also to the distribution of plaque and calcifications. Knowledge of the plaque distribution and calcifications allows one to better choose the wire, navigate the calcifications and make a decision about the need for pre-dilation, in addition to choosing the best stenting strategy. MSCT 3D reconstruction is less user-dependent than 2D angiography and allows for more accurate angle measurements.[7] As recently shown, steep angles >72º between the left main and circumflex artery are predictive of incomplete apposition and distortion of the side-branch stent with the crush technique, which, in turn, is

Figure 1C: Optical Coherence Tomography Assessment of Carina Coverage After Stenting



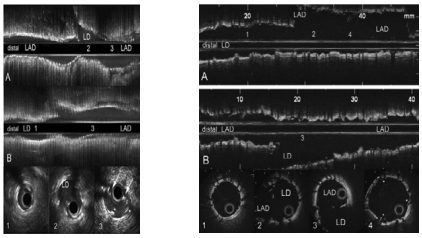
CYPHER stent, optical cohertence tomography (OCT) pullback though RD.

Figure 1D: *In Vivo* Optical Computed Tomography After Bifurcation Stenting with Dedicated Nile Croco



No malapposition is seen.

Figure 1E: Intravascular Ultrasound and Optical Computed Tomography Imaging Post-stenting in a Case of LAD/D1 CTO with Left Main Disease



From the Tryton All Comers Registry in Rotterdam with OCT Substudy.

associated with a higher mortality.[8] Careful review of MSCT data prior to the planned intervention is therefore highly advisable (see *Figure 1B*). In addition, a prior MSCT study may also decrease contrast use during the actual procedure.

Intravascular Ultrasound

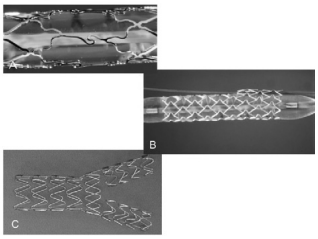
Although intravascular ultrasound (IVUS) is invasive and available intra-operatively, it can offer invaluable insights into the anatomy (size and length) of the bifurcation pre- and post-stenting and guide stent optimisation. Obtaining IVUS data is particularly important, but poor correlation exists between angiography and IVUS measurements of

Table 1: Summary of the Clinical Trials

Study	Number of Patients	Two-stent Strategy	Type of Drug-eluting Stent	Thienopyridine Duration (months)	Number of Centres	Duration of Clinical Follow-up (months)
Pan et al.	91	Any	SES	12	1	11
Colombo et al.	85	Any	SES	3	5	6
NORDIC	413	Any	SES	6–12	28	6
Ferenc et al.	202	T-stenting	SES	6–12	1	12, 24
BBC ONE	500	Crush or culotte	PES	9	20	9
CACTUS	350	Crush	SES	6	12	6, 12
Total	1,641					

Courtesy of Somjot S Brar, MD.

Figure 2: Design of the First Bifurcation Stents



A: Jostent; B: NIR Side Royal; C: BARD.

the mean bifurcation angle.[9] It can be particularly valuable in cases where MSCT is not available or the degree of calcification obscures the ability to assess the lesion severity. With regard to future approaches to bifurcation treatment, pre-procedural imaging may help us to solve two classic bifurcation problems: wire-crossing and/or twisting and re-cross. Importing the imaging data set onto a wire navigation system might facilitate the engagement of even the most difficult side branches. In our current practice, we are actively exploring the use of both MSCT and 3D-angiography with magnet navigation and GPS-systems (RJ van Geuns, personal communication).

Post-stenting Fractional Flow Reserve

The decision to dilate the side branch after stenting of the main branch, and whether a side-branch stent is necessary, often cannot be reliably made based on angiographic appearance. A shift in the carina angle after placement of the stent often creates an illusion of significant 'pinching' of the ostium. Fractional flow reserve (FFR) is a physiological measurement of maximal myocardial flow that can be maintained in the presence of a given stenosis. It is calculated from the ratio of the distal coronary to proximal aortic pressure at maximal hyperaemia. FFR <0.75 denotes significant stenosis. The seminal paper by Koo's group[10] has shown that there was a negative correlation between the per cent diameter of side-branch stenosis and FFR measurement. In addition, fewer than 30% of the lesions with angiographically significant stenosis had flow limitation shown by FFR measurement. FFR has not been evaluated in more complex diffuse side-branch lesions or in cases of elective two-stent strategy.

Post-stenting Optical Coherence Tomography for Optimisation of Results

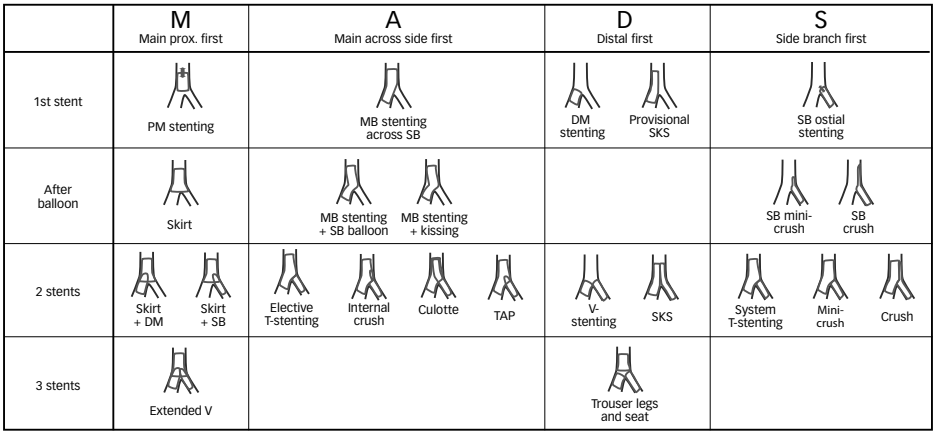
Optical coherence tomography (OCT) is emerging as the preferred technique for post-stent assessment in terms of apposition, strut distortion and protrusion and overlap or presence of gaps (incomplete coverage). At 10–20µ resolution, when performed in both limbs, OCT allows for bifurcation reconstruction at the level of detail similar to that of the 'Ormistogram' model or 'microCT'. Combined assessment of bifurcations with IVUS-VH and OCT can identify plaque composition as well as plaque burden and the presence of a necrotic core with 'thin cap' (fibroatheroma), which is most often present in the proximal bifurcation rim.[11] At follow-up stent-strut coverage and neo-intima thickness can be assessed with great detail. We believe that OCT may be the technology that will give us the best insight into the mechanisms of in-stent restenosis in bifurcation stenting and allow for the evaluation of both two-stent techniques in conventional stenting and dedicated stents. When the full potential of 3D OCT reconstruction is realised, it may be used for high-resolution hydrodynamic modelling of the stented bifurcation. We are currently participating in first-in-man studies and registries of dedicated bifurcation stents, using OCT extensively (see *Figures 1D* and *1E*).

Review of Recent Trials and Evidence

Despite the complexity of bifurcation stenting and the high restenosis rates, particularly in the side branch, several advancements such as the introduction of drug-eluting stents and the more selective use of two-stent strategies – as described in the MADS classification – have reduced major adverse cardiac events. This reduction has been reflected in recent clinical trials.

Over the last few years, Colombo et al.,[12] Pan et al.,[13] Steigen et al.,[14] Ferenc et al.[15] and Tsuchida et al.[2] have shown equivalent major adverse cardiac event (MACE) rates for one- and two-stent strategies, ranging from 3.4 to 19% (see *Table 1*). The meta-analysis of these trials including BBC-One (TCT 2008) has recently been published, and showed that there are no differences in mortality and TLR between one- and two-stent strategies.[16] However, there is a 43% increase in peri-procedural myocardial infarction (MI) rate with two-stent strategy. This early difference (11.2 versus 3.6%) was particularly apparent and drove the overall MACE rate in the BBC-One trial of elective versus provisional T-stenting (15.2 versus 8%, hazard ratio [HR] 2.0; p=0.0009). The Cactus trial[12] showed equivalent outcomes of crush-stenting compared with the provisional approach. One-third of the patients in the one-stent/provisional approach arm have crossed over to the two-stent arm due to residual stenosis in the side branch (72% of cases), poor flow (1.9%) or significant dissection in the side branch (39%). The Nordic 2 trial showed equivalent event rates with culotte versus crush-stenting. In addition, Colombo and his group have demonstrated that over the last several years as the use of kissing-balloon inflation increased, after crush-stenting the rate of restenosis and TLR has decreased by half.[17] The rate of in-stent restenosis in the side branch remains at 13.2% with crush-stenting, even when kissing-balloon inflation is used. Based on these studies,

Figure 3: MADS Classification and How New Dedicated Bifurcation Stents Are Classified



M = main proximal first, i.e. skirt ensuring access to both branches – Axxess Plus (Devax, Irvine, CA, US). A = stents for provisional side-branch stenting facilitate side-branch access after main branch stenting – NILE CROCO (Minvasys, Genevilliers, France). S = stents for side branch first approach – Tryton (Tryton Medical, MA, US).

Table 2: Summary of the Dedicated Bifurcation Stent Studies to Date

MADS Classification	Product	Study Name/Type	Six-month MACE (%)	Angiographic, Restenosis, MB/SB (%)	Number of Patients
M	Axxess	Multicentre registry	7.7	3.6/4.3	302
A	Nile croco	Registry	10.7	N/A	75
A	Frontier	Registry	17.1	9/29	105
S	Tryton	FIM	9.9	4.3/0	30
S	Capella	FIM	12.5	N/A	20
Total					560

M = main proximal branch first; A = main branch (MB) across the side branch (SB); S = SB first; MACE = major adverse cardiac event; FIM = first-in-man.

involving a total of 1,600 patients, the current recommendations for the approach to bifurcation stenting are as follows:

- protect the side branch with a guidewire that facilitates access and marks the ostium;
- perform provisional rather than elective side-branch stenting only, with possible final kissing-inflation; and
- two-stent treatment should be limited to flow-limiting side-branch dissection, side-branch disease extending well beyond the ostium or an unfavourable angle after main-branch stent implantation.

We have recently shown, in the 'all-comers' LEADERS study, that in the major European centres this strategy for true bifurcation treatment is followed in the majority of patients.[1] Two-thirds of the patients have both branches wired and one-third of those are treated with a two-stent approach. In 88% of the lesions treated with a two-stent strategy, kissing-balloon inflation is performed. With these techniques and the use of drug-eluting stents the MACE rate for bifurcation lesions was 16% at 12 months. Even when following these guidelines, bifurcation stenting remains a technical challenge, the major issues being:

- difficulty in maintaining the side-branch access due to jailing of the wire and difficulty in re-crossing through double struts, especially in stent designs that have small cells;[18]
- distortion of the main-branch struts during side-branch dilatation (seen on micro-CT *in vitro* and OCT *in vivo*), which may be one of the reasons for in-stent restenosis and thrombosis; and
- inability to fully cover the side-branch ostium with some angulations (e.g. shallow angles with T-stenting strategy).

Given these challenges, dedicated bifurcation stents that address some of these problems have been developed and, hopefully, will not only facilitate the procedure but also improve the long-term outcomes.

Dedicated Bifurcation Stents – What Progress Have We Made in the Last 10 Years?

Our group was one of the first to report the acute and long-term outcomes of the implantation of dedicated bifurcation stents such as the Jostent, NIR Side Royal and BARD stents.[19,20] Since the cells in the first two stents were larger at the carina, the side branch had incomplete coverage. In particular, the true bifurcation stents were bulky and required a 9Fr guide catheter for delivery. The alignment, especially with the 'trapped-wire' approach stents, was also an issue (see *Figure 2*). The design of the dedicated bifurcation stents has improved and most of them can be delivered via a 7Fr sheath for self-expanding designs and 5 or 6Fr sheath for the balloon-expandable designs. However, none of the current designs has solved all of the challenges.

Table 3: Summary of the Practical Approach to Bifurcation Treatment

Medina Classification (2D angiography-based)	Planning/ Imaging	Wire(s)	Technique/Device	Problems	Solution	Post-procedure Evaluation/Imaging
1.0.0	QCA with optional IVUS and MSCT	1 (for angles >70%, consider 2 wires)	1-stent strategy with provisional side-branch treatment in cases of dissection or slow flow	Plaque shift and angiographic appearance of a 'pinched' ostium	FFR	OCT
X.1.0	QCA and IVUS with optional MSCT	2	1-stent strategy with provisional side-branch treatment as above; possibly side-branch access dedicated bifurcation stent such as Nile croco, Stentys or Frontier (Pathfinder)	Plaque shift and re-crossing through the struts	FFR	OCT
X.X.1	QCA with mandatory IVUS and MSCT	2	2-stent conventional techniques or dedicated bifurcation stents: Tryton or Axxess	Re-crossing through the multiple layers of struts in cases of conventional 2-stent techniques and Tryton	Magnetic navigation and Venture catheter	OCT

FFR = fractional flow rate; IVUS = intravenous ultrasound; MSCT = multislice computed tomography; OCT = optical coherence tomography; QCA = quantitative coronary angiography.

Most of the currently available bifurcation stents are non-drug-eluting except for the Devax stent, which is coated with biolimus and delivered from a biodegradable polymer and the new BiPax (Nile Croco) paclitaxel-eluting stent. The bifurcation stents are meant to facilitate the following:

- main proximal first – Skirt in the MADS classification – ensures access to both branches and obviated the need for any re-crossing with the wires. The best-studied stent in this category is the Axxess Plus (Devax, Irvine, CA);
- side-branch access after main branch-stenting – these stents are designed for provisional side-branch stenting[21] (see *Figure 3*) – one of the examples of main branch across the side branch is the NILE CROCO stent (Minvasys, Genevilliers, France); and
- stents for the side-branch first approach in the MADS classification – severely diseased large side branches may require this approach, which mimics classic culotte-stenting; however, without layers of overlapping struts, an example discussed here is the Tryton stent (Tryton Medical, MA, US).

Table 2 summarises dedicated bifurcation stent studies published to date according to the MADS classification.

Main Proximal Branch First

The best-studied example in this category of dedicated bifurcation stents is Axxess Plus (Devax), with a 302 patient prospective DIVERGE registry published recently in *JACC*.[22] The stent is a 7Fr-compatible, self-expandable, nitinol, single-wire system and elutes biolimus from a biodegradable polymer. It has a modular design, in that it can be tailored based on the bifurcation lesion anatomy, and provides access to both branches but may require three stents in total to complete coverage. DIVERGE enrolled 64% true bifurcation medina (1,1,1) lesions and 64% of the patients had both branches stented. In-segment late loss in the side branch was only 0.17mm at nine-month angiographic follow-up. This translated into a 4.3% target lesion revasularisation (TLR) rate and 7.7% MACE rate at 12 months, which compares favourably to the results of a biolimus stent with a conventional approach to bifurcations in the LEADERS study, where the TLR rate was 11.1% and overall MACE rate was 16%. In addition, the MI rate was 4.3%, which is considerably lower than the 10% MI rate in the recent BBC-One trial.

Main Branch Across

Dedicated stents in this category are designed to provide easier access to the side branch for provisional stenting. All of the stents in this class have only been studied in small first-in-man studies or registries. One of the examples in this category is the Nile Croco stent, which is a 6Fr-compatible, balloon-expandable, cobalt–chromium (73µ strut thickness) stent. It uses a double-balloon, dual rapid-exchange system with two independent catheters that track over two wires. It is designed for 'provisional' side-branch stenting and provides partial side-branch ostium coverage/scaffolding (with a couple of struts). The main balloon has three markers, with the central marker indicating the position of the side-branch ostium. After stent deployment in the main branch, a side-branch balloon is advanced and a simultaneous kissing inflation can be performed. While theoretically this system should obviate the need for re-crossing, the wire twist often observed at the initial attempt of stent delivery necessitates the withdrawal of the wire from the side branch and re-crossing. Although there is no need to re-cross through the struts, this is often done after initial pre-dilation in the presence of potential dissection in the side-branch. The Nile Croco registry of 75 patients by Lefevre et al.[23] demonstrated a MACE rate of 10.7% at six months. This included a 2.7% MI rate and a 6.7% TLR rate. Similarly, the Spanish registry[24] showed excellent procedural success rates and a 12% MACE rate at six months. The NilePax paclitaxel-eluting stent is now available and is undergoing clinical testing in the Bipax study.

The Multi-link Frontier (Abbott Vascular, Santa Clara, C, US) was one of the first stents in this category and was studied in a 105-patient registry.[25] It is a balloon-expandable 316L stainless steel stent pre-mounted on a dedicated delivery system with two balloons (monorail for the main branch and over-the-wire for the side branch) sharing a single inflation port. This stent was 7Fr-compatible and difficult to deliver in calcified vessels. While the procedural success rate was 93%, the MACE rate at six months was 17.1%, with a 44.8% overall restenosis rate (29% for both main branch and side branch). The new-

generation Pathfinder, which incorporates the Xience V platform, is expected to offer better results.

Side Branch First

The best example in this category is the Tryton (Tryton Medical, MA, US), which is a 5 or 6Fr-compatible balloon-expandable cobalt–chromium slotted-tube bare-metal stent. It uses a single balloon and single rapid-exchange system. The stent consists of three zones: distal side branch, transition zone at the carina and main branch zone. The central transition zone has a specific geometry to provide the best scaffolding and is made of three elements, which can be independently deformed. The proximal main branch zone (the so-called collar) has three fronds and a minimal amount of metal, and allows for the delivery of a standard work-horse stent such as the drug-eluting Xience V stent (most often used in our institution). This design minimises the amount of overlapping and protruding struts while still providing adequate coverage and scaffolding. Tryton stent use commits users to the two-stent strategy, similar to culotte.

The first-in-man study of 30 patients with six-month follow-up showed excellent results, with an overall MACE rate of 11.2%. This was composed of an MI rate of 6%, a TLR rate of 7.5% and a stent thrombosis rate of 2.2%.[26] More interestingly, the six-month angiographic follow-up in this study showed an extremely low late loss of 0.17mm in all three bifurcation segments, including the side branch. This is despite the fact that the side-branch portion is covered by a bare-metal stent only. Long-term follow-up in a larger population will be needed to confirm the results. We have been able to successfully use Tryton in very complex cases including left main bifurcations and chronic total occlusions at bifurcation sites with good procedural success and we are performing a careful OCT evaluation of the stent post-procedure in this 'all-comers' population (see *Figure 1E*).

The Side-guard ostium protection device (Capella, MA, US) is a self-expanding trumpet-shaped nitinol device with a low profile that allows for T-stenting and is designed for bifurcation angles between 45 and 135º. The six-month results in the first 20 patients showed a MACE rate of 12.5%.

As illustrated, none of the dedicated bifurcation stents has been studied in large randomised trials with long-term follow-up. The data are limited to small first-in-man and registry studies. While it appears that dedicated drug-eluting bifurcation devices may halve the MACE rate compared with historical controls (MACE of 7.7% in DIVERGE versus 16% in LEADERS), these promising preliminary data must be confirmed.

Summary

Bifurcation stenting is an unsolved challenge for interventional cardiologists. Patients with bifurcation lesions tend to have more advanced disease and multiple co-morbidities. Over the last 10 years we have understood the importance and made progress in bifurcation imaging for planning of procedures and in procedural success (from 3D angiography, IVUS and MSCT to FFR and OCT). Recent clinical trials show an improvement in results with more selective use of a two-stent strategy and drug-eluting stents. Rates of MACE and peri-procedural MI for bifurcation lesions still remain higher than in non-bifurcation lesions and patients. Many challenges, such as side-branch access, wire trapping and incomplete side-branch coverage, still remain and have only partially been addressed by the new dedicated bifurcation stent designs since their development in the 1990s. More long-term prospective studies of these novel stent designs are needed for the field to progress with concomitant imaging. We believe that in addition to randomised trials of the dedicated bifurcation stents, an 'all-comers' registry of these devices, with long-term follow-up, would be invaluable in the assessment of their safety and efficacy compared with conventional approaches. *Table 3* summarises our current practical approach to bifurcation treatment. ■

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Chapter 11

Six month clinical follow-up of the Tryton Side Branch Stent for the treatment of bifurcation lesions - a two centre registry analysis

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ABSTRACT

Background. Treatment of bifurcation lesions with the Tryton Sidebranch stent has been shown to be feasible with an acceptable clinical outcome and low side branch late loss in the first in man trial.

Objective. To report acute procedural and 6 month clinical follow up after the use of the Tryton Sidebranch stent in an 'all comer' registry.

Methods. The first 100 coronary bifurcation lesions assigned for treatment with the Tryton stent were included in a prospective registry. Procedural and angiographic success rates were determined from patient charts and pre and post procedural quantitative coronary angiography. Clinical follow-up was obtained by phone or mail contact.

Results. 96 patients with 100 lesions were included in the study. 72% presented with stable angina, 25% with unstable/NSTEMI and 3% STEMI. The bifurcation was located in the left main in 8%. 2 lesions were chronic total occlusions. 69% were true bifurcation lesions. 1 failure of stent delivery occurred. Acute gain in SB was 0.76±0.64mm and 3 patients had residual stenosis of >30%. Angiographic success rate was 95%; procedural success rate reached 94%. Peri-procedural MI occurred in 2 and there was 1 cardiac death during hospitalisation. At a median 6 months follow-up, TLR rate was 4%, MI 3% and cardiac death 1%. The percentage MACE-free survival at 6 months was 94%. No cases of definite stent thrombosis occurred.

Conclusion. In a real world the use of the Tryton Sidebranch stent is associated with good procedural safety and angiographic success rate and acceptable outcome at 6 months of follow-up.

Keywords: Bifurcation lesions, Percutaneous Coronary Intervention, Procedural success, 6 month MACE

INTRODUCTION

Percutaneous coronary intervention (PCI) for bifurcation lesions is considered high risk with increased procedural adverse events as well as inferior long term outcome when compared to non-bifurcation intervention. [1] Several techniques and strategies have been explored, employing one or two conventional tubular stents but the improvement in outcome remains limited. This is primarily reflected in the increased rates of sidebranch restenosis. [2] Dedicated bifurcation stents, specifically designed to allow minimally traumatic implantation in the main vessel and/or sidebranch while providing adequate scaffolding of the sidebranch ostium may offer an advantage over utilisation of conventional stents. [3]

The Tryton Side-Branch Stent (Tryton Medical, Inc., Newton, MA, USA) is a dedicated bifurcation stent inspired by the 'culotte' stenting technique. [4] This Tryton Side-Branch stenting strategy showed acceptable clinical outcome with no sidebranch restenosis and low side-branch late loss (0.17±0.35mm) at six months in the First-in-Man (FIM) trial that enrolled 30 patients with stable coronary artery disease and de novo bifurcation lesions. Being a FIM, the study had restricted inclusion criteria that does not represent routine clinical practice. [5]

The present registry analysis was conducted to evaluate the procedural success and to assess clinical outcome of bifurcation stenting with the Tryton Side-Branch Stent™ in conjunction with a standard workhorse stent in a 'real world', all comer population.

METHODS

Patient Population

All patients with ischaemia in a myocardial segment supplied by a coronary artery with a bifurcation lesion with disease in both main vessel and sidebranch that were referred for PCI from

December 2006 at two academic tertiary hospitals in the Netherlands (Thoraxcenter, Erasmuc MC, Rotterdam) and Poland (University Hospital of Lord's Transfiguration, Poznan) were eligible. Specifically the bifurcation could be located anywhere in the coronary circulation including grafts. The visually estimated reference diameter of the main vessel could be 2.5-5.0mm and that of the sidebranch in the range 2.0-2.75mm. These dimensions were selected to comply with the available sizes of the Tryton stent. However the decision to treat the bifurcation and employ a Tryton Side Branch Stent remained at the discretion of the treating interventional cardiologist. The first 100 lesions assigned for treatment with the Tryton Sidebranch Stent were included in a collaborative registry between the two institutions.

Study Device and PCI strategy

The Tryton Side-Branch Stent is a slotted tube, balloon expandable cobalt chromium BMS with three zones: a distal sidebranch zone, a central transition zone and a proximal main vessel zone. The distal zone has standard slotted tube workhorse stent design, the central transition zone consists of three panels while the proximal main vessel zone is composed of three fronds that terminate proximally in a circumferential band. The stent is mounted either on a balloon with uniform diameter of 2.5mm (straight type) or on a stepped balloon with a diameter of 3.5mm proximally and 2.5mm distally (tapered type). The stent delivery system has 4 markers to delineate the proximal and distal end of the stent as well as the proximal and distal part of the transition zone. Further details of the stent design as well as the standard technique for implantation have been published [4]. In short, the procedure is typically performed via a 6Fr guiding catheter; after optional wiring of both main vessel and sidebranch for predilation, the Tryton stent is advanced over the wire into the sidebranch, and using the 2 middle markers on the delivery system, the stent is positioned till these markers straddle the carina. Deployment of the stent is followed by retraction of the guidewire from the sidebranch and repositioning it through the fronds of the transition zone into the distal main vessel. A standard stent is then advanced and positioned in

main vessel jailing the stented sidebranch. Once the main vessel stent is deployed recrossing into the sidebranch allows final kissing balloon inflation.

Procedure

Patients were pre-treated with aspirin (75mg) and clopidogrel (300mg or 600mg) unless they were already taking these antiplatelet agents. Intravenous heparin was administered to maintain an activated clotting time of >250 seconds. Glyoprotein IIb/IIIa inhibitor use was left to the treating interventional cardiologist's discretion as was the use of other additional devices such as thrombectomy, excimer laser, rotablator etc. Delivery failures, need for additional overlapping stents to cover the whole lesion, additional ballooning and procedural angiographic and clinical complications were noted. Aspirin was continued indefinitely and clopidogrel was continued for 12 months after the index procedure.

Cardiac enzymes and ECG

Serial cardiac enzymes including creatinine kinase (CK)-MB mass, troponin-T, or troponin-I were measured after the procedure. Pre-procedure biomarkers were assessed in all patients with acute coronary syndrome. These patients were included the biomarker analysis only if preprocedure markers were normal. A 12 lead ECG was obtained before and after procedure as part of routine institutional practices.

Quantitative Coronary Angiography

Angiographic films were analysed with a dedicated bifurcation software (CAAS 5.5, Maastricht, PIE Medical software, The Netherlands). [6] Reference vessel diameter, minimal luminal diameter (MLD) and percentage diameter stenosis were obtained for the proximal main vessel (PMV), distal main vessel (DMV) and sidebranch (SB) in the pre procedural angiographic film. Matched views of

immediate post-procedural films were then selected for determination of the same parameters. Acute gain was determined from the difference between MLD in each of the three segments (PMV, DMV, SB).

Follow-up

Survival data from all patients were obtained from municipal civil registries. A health questionnaire was subsequently sent to all living patients with specific questions on treatment compliance, re-admission and major adverse cardiac events. Patients who did not send the filled questionnaire were contacted by phone to obtain the relevant information. Those who reported events had their medical records, discharge summaries and any repeat angiographic films systematically reviewed. Data was carefully verified and adjudicated by cardiologists according to criteria defined below.

Definitions

Primary device success was defined as successful deployment of the intended stent without system failure or device related complication. Angiographic success was defined as <30% residual stenosis and TIMI 3 flow in both main vessel and sidebranch after the procedure. Procedure success included angiographic success in the absence of in-hospital major adverse cardiac events (MACE). MACE was defined as a composite of cardiac or non-cardiac death, Q–wave or non-Q-wave myocardial infarction (MI) and ischaemia driven target lesion revascularisation (TLR). Non-Q wave MI was defined as clinical signs of myocardial infarction associated with a CK-MB mass or troponin –T/troponin-I increase to ≥3 times the upper limit of normal in the absence of Q waves and not related to an interventional procedure. Q-wave MI occurred when there was chest pain or symptoms consistent with myocardial ischaemia and new pathological Q waves in 2 or more contiguous electrocardiograph leads. TLR was defined as any PCI of the index lesion and including the 5mm persistent segments in either main vessel or sidebranch. Target vessel revascularisation

(TVR) was defined as revascularisation of any part of the index coronary artery. Stent thrombosis was defined according to the Academic Research Consortium (ARC). [7]

Statistical analysis

Continuous data are expressed as mean ± SD or as median (interquartile ranges) whereas dichotomous data are summarized as frequencies. The Kalpan-Meier method was used to study the incidence of events over time relative to the number of patients at risk at each time point. Statistical analysis was performed using SPSS software version 17.0 (SPSS, Chicago, USA)

RESULTS

100 bifurcation lesions in 96 patients were included between December 2006 and March 2010. Baseline characteristics of patients included are shown in table 1. The mean age of patients was 63.9 years and the majority were male (75%). While most patients presented for PCI with stable angina (72%), three patients were treated for an acute myocardial infarction.

Lesion characteristics are described in table 2. Sixty six percent of patients had multivessel disease and 5 patients had two bifurcation lesions that needed revascularisation. Most bifurcations targeted for treatment with the Tryton Sidebranch stent were located in the left anterior descending/diagonal junction (72%). Eight stents were implanted in the left main coronary arteries. Two bifurcations involved the anastomosis of a saphenous venous graft with a native coronary artery; in one on the posterior descending and the other on the left anterior descending artery. A left anterior descending/large septal branch bifurcation was also included. 2 bifurcations were treated after successful crossing of a chronic total occlusion in 2 patients. Sixty nine percent of

lesions were true bifurcation lesions (1,0,1 or 1,1,1 or 0,1,1) with involvement of both the main vessel and the sidebranch.

The mean reference diameters for the proximal main branch (PMB), distal main branch (DMB) and side branch (SB) were 2.91, 2.46 and 2.22mm respectively. The mean percentage diameter stenosis obtained by including all bifurcations, irrespective of the presence of significant disease in the three segments, were 49%, 41% and 40% for PMB, DMB and SB respectively. The mean angle between the PMB and the SB was 152˚ while that between the DMB and the SB was 53˚. These pre-procedural quantitative coronary angiographic measurements are presented in table 3.

Ninety nine of the 100 Tryton Sidebranch stents intended for treatment of 100 bifurcation lesions were successfully implanted resulting in a 99% device success rate. A case example is illustrated in figure 1 with corresponding optical coherence tomography images (Lightlab Imaging, Westford, MA) in figure 2. The tapered balloon delivery system was used in 93% of the procedures. Table 4 lists the various types of stents used as the workhorse principal main vessel stent. Two patients received a bare metal stent. Procedural characteristics are shown in table 5. The mean nominal diameter of the main vessel stent was 3.0±0.5mm with a mean length of 24±6mm. Additional stents overlapping the Tryton stent in the sidebranch were deployed in 16% while in 19% of lesions further overlapping stents were implanted in the main vessel. Predilation was performed in 90% while final 'kissing' ballooning was done in 71%.

Angiographic success was achieved in 95%; 1 failure of Tryton stent delivery with subsequent dissection in a diagonal sidebranch while 4 lesions did not meet the pre-defined angiographic success criterion of 30% residual stenosis. In these 4 lesions 38-47% residual stenosis on QCA was measured, mainly caused by a disproportionate increase in the distal sidebranch vessel diameter by insertion of an additional stent. Periprocedural PCI related MI occurred in the same patient who had unsuccessful delivery of the stent. Another patient who presented with acute myocardial

infarction with cardiogenic shock and who had a bifurcation treated with good angiographic result died within 48 hours of the procedure. Therefore the procedure success was 94%.

The QCA parameters for the whole cohort pre and post procedure are listed in table 3. The mean acute gain in the sidebranch was 0.76±0.64mm. On analysis of a subgroup of bifurcations (n=76) with true sidebranch disease (1,0,1 ; 1,1,1; 0,1,1 and 0,0,1), the mean acute gain was 0.94±0.60mm.

In-Hospital and mid-term clinical outcome

The clinical events are summarized in table 5. In-hospital MACE rate reached 3%. The only case of death was due to cardiac death in the patient treated for STEMI with cardiogenic shock as mentioned above. Post procedural elevations of troponins occurred in 11/33 patients treated for stable angina but two met criteria of a PCI related myocardial infarction. The first occurred secondary to dissection of the diagonal branch in which the Tryton stent could not be delivered. The second occurred secondary to transient slow flow in the distal main branch after placement of the main vessel stent. There were no cases of definite/probable stent thrombosis or target vessel revascularisation.

30 day follow-up was available in all patients. There were no reported events and therefore the MACE is same as the in-hospital outcome.

Patients were followed up for a median of 6 months. All a patients were compliant with their prescribed medications at the time of last contact. 51 patients had at least 6 months follow-up. Up to this time point, one patient suffered a myocardial infarction due to occlusion of a vessel other than that treated in the index procedure 78 days earlier. The same patient had TLR of SB at 155 days. A second patient had a TLR so that the percentage of survival free of MACE at 6 months was 94% as shown in the figure 3. Two other patients with longer than 6 months follow-up had ischaemia-driven target lesion revascularisation (194 and 292 days). Restenosis occurred in the

main vessel in two patients, in the side branch in the other two. No cases of stent thrombosis were reported. Thus cumulative MACE rate over a median follow-up period of 206 days (IQR: 125-386) at follow up reached 8% as shown in table 5.

DISCUSSION

In this registry in an 'all comer' population with implantations including 3 for acute myocardial infarctions, 8 left main lesions and 2 chronic total occlusions has shown that the Tryton side branch stent, used in conjunction with a standard workhorse stent for the treatment of complex bifurcation lesions has resulted in a good procedural success rate (94%) and acceptable 8% MACE rate at 6 months follow-up. More specifically PCI related MI was limited to 2%, the TLR rate at follow up was just 4% and importantly, there were no cases of stent thrombosis.

Bifurcation intervention is historically associated with worse outcome. [1,8] Although stenting has improved the prognosis and DES have further improved it, restenosis and pinching of the sidebranch often triggers the need to intervene on the sidebranch. In a bifurcation registry study by Kaplan et al 80 of 288 (27.8%) bifurcation lesions treated with one stent initially required a second stent due to severe impairment of the SB during the angioplasty procedure. [9] Despite technical improvements in the use of two stent techniques, recent randomised trials failed to show any advantage over use of one stent technique in terms of clinical outcome. More so, the provisional one stent technique is associated with lower procedural cardiac biomarker release, lower contrast dose used and less radiation used. [10-12]

The culotte technique seems to be the safest, most effective, offering the best long term outcome of the two stent techniques.[9,13-15] Table 6 lists the studies that employed the culotte technique in the DES era. A recent randomised study comparing the culotte technique (n=215) and the crush technique (n=209) found significant differences in biomarker release (8.8 % vs. 15.5%) peri-procedurally favouring the culotte technique though the incidence of major adverse cardiac events

including stent thrombosis at 6 months was similar between the two groups. By eliminating the need for crushing the side branch stent, theoretically trauma to the bifurcation vessel walls is reduced as may be the procedural complications. In the same study, at eight months, angiographic follow-up revealed a significantly higher in-stent restenosis in the 'crush' group (10.5% vs. 4.5%). This can be explained by the better scaffolding of the sidebranch ostium. Also recross into the sidebranch is theoretically easier in the culotte group with the guide wire having to cross less layers of struts so that final kissing balloon is more likely to be feasible. This last together with the fewer overlapping layers of metal is thought to reduce the chance of incomplete stent apposition which can then lead to complications such as stent thrombosis and re-stenosis.

In the present all comer study, we have noticed similar rates of procedural success as in the FIM trial reported by our group. [5] The 94% rate in the present study was slightly lower than that reported in a culotte versus T stenting study. [9] One explanation could be the difference in scaffolding and recoil properties between the transition zone part of the Tryton stent and a standard stent utilised in the conventional culotte technique. In fact the 3 patients with residual diameter stenosis (%DS) of >30% after successful Tryton stent implantation, had their MLD located at the sidebranch ostium. The clinical importance of this is however uncertain as there was still a significant acute gain in the side branch and none of these patients had a TLR during follow-up. Moreover as Koo et al demonstrated, QCA is unreliable to assess the functional significance of sidebranch jailing when compared to fractional flow reserve. [16] Of the 4 cases of TLR, 2 occurred in the SB covered by the BMS. While we know that the late lumen loss in side branch at 6 months averaged 0.17mm in the FIM, being even better than that reported for DES (0.34-0.53mm) the TLR rate is less than that reported for two stent techniques. Studies report TLR rates of 24-43% the when two BMS stents are employed and 5.1-28% when two DES are used.[1,9-15,17]

Importantly, we did not observe any stent thrombosis in our cohort at 6 months follow-up which compares well with previous studies that employed the culotte technique. Adriaenssens et al.

reports a 1.5% ST rate at 12 months follow-up in a study with 134 lesions in 132 patients. The high rate of final kissing that aims to ensure adequate strut apposition may be a contributing factor.

Although general evidence supports the use of simple, single stenting with conventional stents, the use of dedicated bifurcation stents especially in cases with significantly narrowed true bifurcations where double stenting is highly likely to be performed is probably justified. More data is therefore needed from the registries and randomised trials of the use of dedicated bifurcation stents in this high risk patient/lesion subset.

Study Limitations

The present study has the intrinsic limitations of a registry. Selection bias could have occurred in treatment of bifurcation lesions with the study stent. No control group was used to compare the use of this dedicated bifurcation stent and stenting strategy with other devices and techniques. The registry was confined to two academic referral centres and the study lesions were limited to 100. Also, the patients enrolled had no angiographic or other invasive imaging follow-up. However the study still very likely represents the utilisation of the Tryton sidebranch stent and its performance in the 'real world' everyday practice.

Conclusions

In a real world, two centre registry, the use of the Tryton Sidebranch stent is associated with good procedural safety and angiographic success rate and acceptable outcome at 6 months of follow-up.

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Table 1

Baseline clinical characteristics

Characteristics	**N=96**
Male	72 (75%)
Age, years (mean±SD)	63.9 ± 8.8
Diabetes mellitus	30 (31%)
Hypertension	58 (60%)
Hypercholesterolaemia	60 (63%)
Family History of coronary artery disease	46 (48%)
Smoker	17 (18%)
Previous myocardial infarction	42 (44%)
Previous PCI	40 (42%)
Previous CABG	8 (8%)
Stable Angina	69 (72%)
Unstable Angina	24 (25%)
ST elevation Myocardial infarction	3 (3%)

Data are presented as numbers (percentages) or mean ± SD unless specified. Percentages have been rounded.

Table 2

Lesion Characteristics

Lesions	N=100
Bifurcation location	
Left Main	8
Left Anterior Descending / Diagonal	72
Left Circumflex / Obtuse Marginal	11
Posterolateral / Posterior Descending	5
Saphenous Vein Graft / Native Vessel	2
Other	2
Medina Classification	
1,0,0	10
1,1,0	11
0,1,0	3
0,0,1	6
1,0,1	13
0,1,1	3
1,1,1	54
ACC classification	
A	0
B1	28
B2	39
C	33
Multivessel disease*	62 (66%)
Chronic total occlusion	2

Data represents actual number which is equivalent to the percentage since the number of lesions is 100 unless specified.

*62 patients out of 96 had disease in a vessel other than the one with the index bifurcation

Table 3

Quantitative angiographic parameters pre and post procedural (n=100)

Parameter	**Pre procedure**	**Post procedure**
Proximal Main Branch		
MLD (mm)	1.49 ± 0.76	3.09 ± 0.48
Reference diameter (mm)	2.91 ± 0.62	3.32 ± 0.56
% Diameter stenosis	49 ± 24	8 ± 8
Acute gain (mm)		1.62 ± 0.74
Distal Main Branch		
MLD (mm)	1.43 ± 0.74	2.54 ± 0.44
Reference diameter (mm)	2.46 ± 0.52	2.77 ± 0.44
% Diameter stenosis	41 ± 29	8 ± 8
Acute gain (mm)		1.12 ± 0.77
Sidebranch		
MLD (mm)	1.30 ± 0.56	2.04 ± 0.36
Reference diameter (mm)	2.22 ± 0.40	2.31 ± 0.35
% Diameter stenosis	40 ± 26	12 ± 11
Acute gain (mm)		0.76 ± 0.64
Bifurcation angles in degrees		
PMB and SB	151.6 ± 1.5	
DMB and SB	52.5 ± 0.5	

Data is expressed in mean ± SD. MLD = minimal luminal diameter; PMB = proximal main branch; DMB = distal main branch; SB = sidebranch

Table 4: Main vessel stents implanted

Stent name	Manufacturer	Drug eluted	Frequency
Xience V	Abbott Vascular, Santa Clara, Calif	Everolimus	47
Xience Prime	Abbott Vascular, Santa Clara, Calif	Everolimus	17
Taxus Liberté	Boston Scientific, Natick, Mass	Paclitaxel	13
ENDEAVOR resolute	Medtronic Vascular, Santa Rosa, Calif	Zotarolimus	7
Cypher Select	Cordis Corp, Warren, NJ	Sirolimus	6
Promus	Boston Scientific, Natick, Mass	Everolimus	3
Biomatrix	Biosensors International, Singapore	Biolimus A9	1
Coroflex Please	B. Braun, Melsungen, Germany	Paclitaxel	1
Luc - Chopin	Balton, Warsaw, Poland	Paclitaxel	1
Skylor	Invatec, Brescia, Italy	None	1
Vision	Abbott Vascular, Santa Clara, Calif	None	1

Table 5. Procedural and Clinical outcome (lesion n=99)

Predilation	
Side Branch	69 (70%)
Main Vessel	83 (84%)
Separate Postdilation	71 (72%)
Final Kissing	70 (71%)
Additional overlapping stent implantation*	
Side Branch	15 (16%)
Main Vessel	19 (20%)
Total stents implanted	275
Stents per bifurcation	2.4 ± 0.7
Stents per patient	2.9 ± 1.3
Multivessel stenting in index procedure	26 (26%)
Acute procedural outcome	N=100
Device success	99
Angiographic success	95
PCI related biomarker elevation	11/33 (33%)
PCI related MI	2
Procedural success	94
In-hospital outcome[¶]	N=96
Cardiac Death	1
Myocardial Infarction	2
CABG	0
Target Lesion Revascularisation	0
Target Vessel Revascularisation	0
Definite/Probable stent thrombosis	0
Cardiac death or MI	2
MACE (cardiac death, MI, CABG or TLR)	2
Median 6 month outcome (cumulative)[¶]	N=96
Cardiac Death	1
Myocardial Infarction	3
CABG	0
Target Lesion Revascularisation	4
Target Vessel Revascularisation	4
Definite/Probable stent thrombosis	0
Cardiac death or MI	3
MACE (cardiac death, MI, CABG or TLR)	8
Device/PCI strategy-related MACE[§]	8

Data are expressed in numbers and percentages. MI= myocardial infarction; CABG= coronary artery bypass grafting; TLR= target lesion revascularisation.*Refers to number of lesions requiring extra stent apart from the Tryton stent and the main vessel stent. [¶] Data expressed in actual numbers which is also equivalent to percentages. [§] Excludes one patient with a MI at follow up in a territory other than that supplied by treated vessel and another who died of cardiogenic shock that commenced prior to index intervention.

	Culotte treated patient	Stent used	Kissing %	Follow-up in months	TLR	Binary Restenosis Rate*	Late loss (mm) MV*	Late Loss (mm) SB	ST	MACE
Hoye et al.	23	SES, PES	74%	8	5%	18.8% 12.5%	0.48±0.56	0.53±0.33	0%	15.4%
Kaplan et al.	45	SES, PES	84.4%	9	8.9%	6.6% 4.4%	0.23±0.52 0.42±0.61	0.28±0.45	2.2%	13.3%
Adriaenssens et al.	134	SES, PES	62%	12	21%	9.1% 16%	0.10(-0.04-0.38) 0.34(-0.03-0.66)	0.30(-0.01-0.72)	1.5%	26%
Erglis et al.	215	SES, PES	92%	6	2.8%	6.6% 4.5%	0.12±0.42 0.19±0.49	0.20±0.48	1.9%	3.7%
Onuma et al.	30	Tryton + SES, PES, EES	100%	6	0%	0%	0.25±0.43 0.00±0.31	0.17±0.35	0%	9.9%

Table 6. Studies with 'Culotte' technique for bifurcation lesions in the drug eluting stent era.

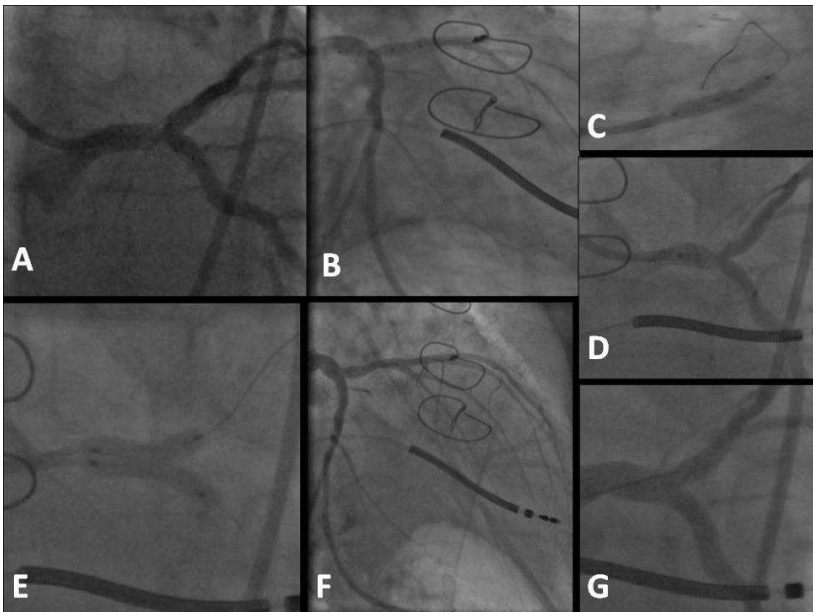
MV= main vessel; SB = side branch; ST = stent thrombosis; MACE = major adverse cardiac events; SES = sirolimus eluting stents; PES = paclitaxel eluting stents; EES = everolimus eluting stents; *first figures indicate value for proximal MV and second figures indicate value for distal MV.

Figure Legends

1. Case example of Tryton Side Branch Stent insertion in the left main (LM) coronary bifurcation. (A) Diagnostic angiogram of a patient with previous left internal mammary graft to the left anterior descending artery, and persistent ischaemia, showing significant disease at the LM bifurcation. (B) Positioning of the Tryton stent in the smaller calibre left anterior descending artery, in this case considered the Side Branch. Note the straddling of the carina with the middle two markers. (C) Deployment of Tryton by inflation of the stepped balloon. Guide wire retraction and redirection into the dominant larger left circumflex artery (main vessel) was followed by deployment of a standard drug eluting stent with proximal part in LM and distal part in left circumflex (D). Wire re-cross into side branch and fenestration with small balloon allowed final kissing balloon inflation (E). Angiographic result at the end of procedure (F,G).

2. Optical coherence tomography performed after treatment of the left main coronary artery bifurcation described in figure 1. Pullback from the left anterior descending artery shows good apposition of the Tryton stent (right upper panel). Pullback from the left circumflex artery also shows good standard stent apposition in left circumflex (right lower panel). Left main coronary imaging shows minimal strut overlap (left upper panel). Imaging at the bifurcation also reveals satisfactory strut apposition (right lower panel).

3. Kaplan Meier curves for cumulative MACE. (A) composite of index bifurcation treatment-related cardiac death, myocardial infarction and target lesion revascularisation. (B) composite endpoint of all cause mortality, cardiac death, any myocardial infarction or target vessel revascularisation.



Case example of Tryton Side Branch Stent insertion in the left main (LM) coronary bifurcation. (A) Diagnostic angiogram of a patient with previous left internal mammary graft to the left anterior descending artery, and persistent ischaemia, showing significant disease at the LM bifurcation. (B) Positioning of the Tryton stent in the smaller calibre left anterior descending artery, in this case considered the Side Branch. Note the straddling of the carina with the middle two markers. (C) Deployment of Tryton by inflation of the stepped balloon. Guide wire retraction and redirection into the dominant larger left circumflex artery (main vessel) was followed by deployment of a standard drug eluting stent with proximal part in
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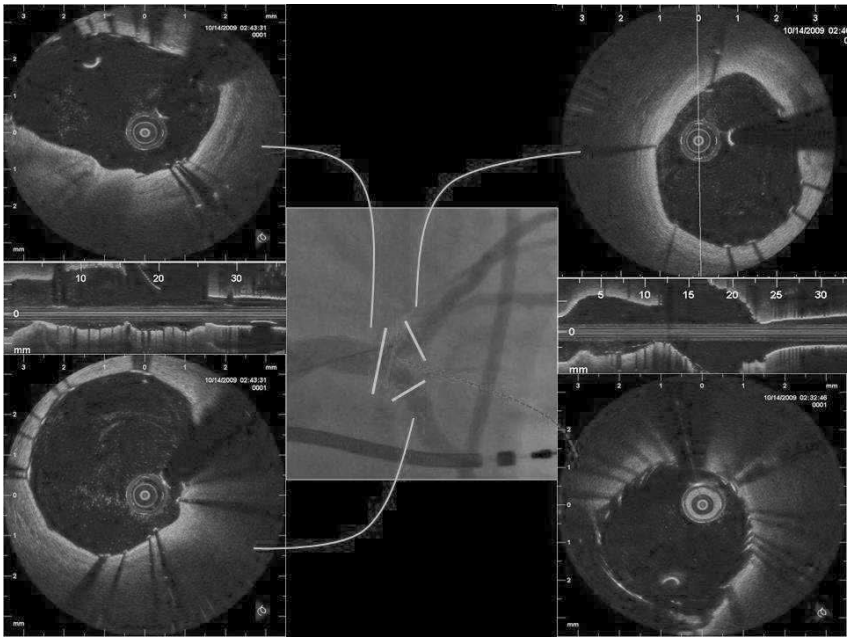
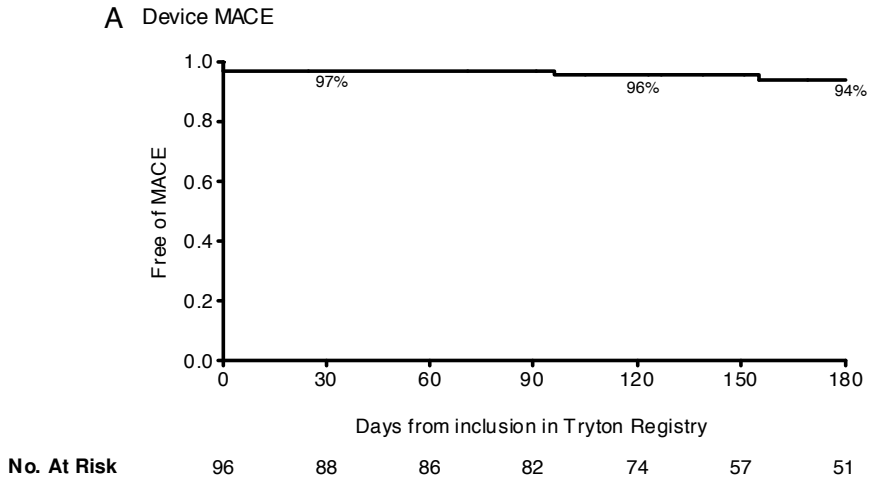
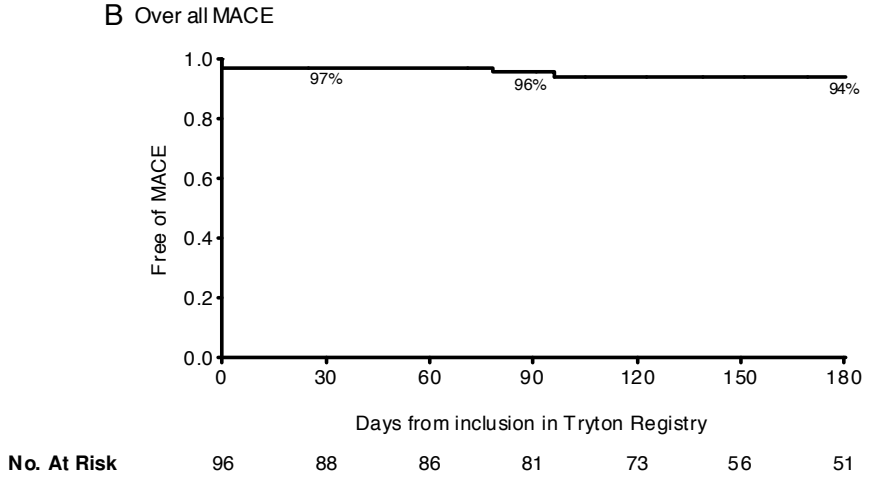
40x30mm (600 x 600 DPI)



Optical coherence tomography performed after treatment of the left main coronary artery bifurcation described in figure 1. Pullback from the left anterior descending artery shows good apposition of the Tryton stent (right upper panel). Pullback from the left circumflex artery also shows good standard stent apposition in left circumflex (right lower panel). Left main coronary imaging shows minimal strut overlap (left upper panel). Imaging at the bifurcation also reveals satisfactory strut apposition (right lower panel).
40x30mm (600 x 600 DPI)

Figure 3


A Device MACE
1.0
0.8
0.6
0.4
0.2
0.0
Free of MACE
97%
96%
94%
0
30
60
90
120
150
180
Days from inclusion in Tryton Registry
No. At Risk
96
88
86
82
74
57
51


B Over all MACE
1.0
0.8
0.6
0.4
0.2
0.0
Free of MACE
97%
96%
94%
0
30
60
90
120
150
180
Days from inclusion in Tryton Registry
No. At Risk
96
88
86
81
73
56
51

Chapter 12

Five year follow-up of coronary revascularization in diabetic patients with multivessel coronary artery disease. Insights from Arterial Revascularization Therapy Study (ARTS)-II and ARTS-I trials.

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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 up to two years revascularization with drug eluting stents has equivalent safety to by-pass surgery up to two-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: In our diabetic population with multivessel disease, the 5-year mortality was comparable between BMS, SES and CABG, while CABG showed superior efficacy in terms

of reducing repeat revascularization compared to BMS and SES. 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)

3, 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 218 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 $\pm$ 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 (listed in table 3). Unadjusted hazard ratios are also reported in table 2. Post hoc Bonferroni correction was performed for ANOVA analysis. All analyses were performed using SPSS.

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 (logrank 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.

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 a 5 years outcome of PCI with the SES in diabetic patients with multivessel disease. At three years follow-up of the ARTS-II trial, patients treated with SES had lower MACCE rates that patients treated with BMS PCI and CABG in ARTS-I, although the differences did not reach statistical significance.(3) In contrast, at 5 years 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 PCI in ARTS-I 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 in ARTS-II. 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:

When compared to the outcome of the diabetic patients with multivessel disease treated with either PCI or CABG, the overall MACCE-free survival rate at 5 years in patients treated with SES is higher than in patients treated with CABG and, while still more favorable than in patients treated with BMS, it appears to approach the rate of events in the BMS treated group. The MACCE rate in diabetic patients treated with SES is predominantly driven by the rate of repeat revascularization. The mortality in the SES treated population is similar to that of CABG patients at 5 years. Myocardial infarction rate was two-fold higher in diabetic patients treated with BMS than in patients treated with either SES or CABG. At five years follow-up CABG appears to have better outcomes than PCI in a diabetic patient population by virtue of reducing repeat revascularization rates making CABG the preferred treatment for this subgroup of patients with multivessel disease.

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Table 1. Baseline clinical and angiographic characteristics

	Diabetic patients				Non-Diabetic patients			
	BMS (N=112)	**SES (N=159)**	**CABG (N=96)**	P-value	**BMS (N=509)**	**SES (N=448)**	**CABG (N=488)**	P-value
Age in years, mean	63	65	63	0.12	60	62	61	0.01
Ejection Fraction, %	61	60	60	0.81	61	60	60	0.66
Male %	73	67	69	0.53	78	80	77	0.56
Diabetes insulin-treated %	21	18	17	0.78				
Hypertension %	64	80	56	**<0.01**	40	63	43	**<0.01**
Hypercholesterolemia %	55	74	49	**<0.01**	59	74	59	**<0.01**
Renal impairment, %*	15	5	15	**<0.01**	13	4	14	**<0.01**
Previous MI %	41	30	49	**<0.01**	41	36	41	**0.02**
Previous PCI %	2	0	2	0.17	1	1	2	0.1
Current Smoking, %	21	12	17	0.15	30	22	28	**0.02**
Unstable Angina %	38	32	33	0.64	38	38	38	1
Stable Angina %	59	54	63	0.35	56	53	57	0.45
Silent Ischaemia %	4	15	4	**<0.01**	7	9	5	**0.04**
2 Vessel Disease, %	65	49	64	**0.01**	69	45	67	**<0.01**
3 Vessel Disease, %	31	50	35	**<0.01**	27	55	29	**<0.01**
Total Number of implanted stent, mean±SD	3.0±1.5	3.6±1.5		**<0.01**	2.7±1.2	3.7±1.5		**<0.01**
Total Stented Length in mm, mean±SD	52.7±25.6	73.9±31.9		**<0.01**	46.4±20.6	72.0±32.1		**<0.01**
Max. Stent Pressure in atm, mean±SD	14.9±2.9	16.2±2.7		**<0.01**	14.6±2.8	16.4±2.9		**<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						
	BMS	**SES**	**CABG**	**HR CABG vs. SES**	**p-value**	**HR BMS vs. SES**	**p-value**	**BMS**	**SES**	**CABG**	**HR CABG vs. SES**	**p-value**	**HR BMS vs. SES**	**p-value**
MACCE	60 (53.6%)	63 (39.6%)	22 (22.9%)	**0.54 (0.34-0.88)**	**0.014**	**1.65 (1.16-2.35)**	**0.006**	187 (38.3%)	102 (22.8%)	103 (20.5%)	0.93 (0.70-1.22)	0.575	**1.94 (1.53-2.47)**	**<0.001**
Death	15 (13.4%)	14 (8.8%)	8 (8.3%)	0.95 (0.40-2.27)	0.911	1.56 (0.76-3.24)	0.229	32 (6.6%)	19 (4.2%)	35 (7.0%)	1.70 (0.97-2.97)	0.063	1.57 (0.89-2.78)	0.118
CVA	7 (6.3%)	9 (5.7%)	6 (6.3%)	1.24 (0.42-3.65)	0.7	1.33 (0.49-3.59)	0.58	16 (3.3%)	13 (2.9%)	14 (2.8%)	0.99 (0.45-2.18)	0.99	1.34 (0.81-2.23)	0.25
MI	12 (10.7%)	7 (4.4%)	5 (5.2%)	1.20 (0.38-3.78)	0.754	**2.65 (1.01-6.51)**	**0.048**	37 (7.6%)	28 (6.3%)	29 (5.8%)	0.96 (0.57-1.61)	0.866	1.25 (0.76-2.04)	0.379
Revasc.	47 (42.0%)	50 (31.4%)	10 (10.4%)	**0.29 (0.15-0.57)**	**<0.001**	**1.58 (1.06-2.35)**	**0.025**	134 (27.5%)	73 (16.3%)	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, MI = myocardial infarction, Revasc. = Revascularization, CABG = coronary artery bypass graft, SES = sirolimus-eluting stent, BMS = bare-metal stent

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)	0.812	1.77 (0.85-3.67)	0.127	1.99 (1.12-3.53)	0.02	1.88 (1.05-3.38)	0.04
CVA	1.24 (0.42-3.65)	0.7	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)	0.763	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% confindence interval in brackets. The cox regression models are constructed to adjust the following variables: age, gender, previous myocardial infarction, history of revascularization, CABG, insuline dependence (only for diabetic patients), current smoking, dyslipidemia and hypertension.
HR = hazard ratio, CVA = cerebrovascular accident, MI = myocardial infarction, Revasc. = Revascularization, MACCE= Major adverse cardiac and cerebrovascular events (a composite of all-cause mortality, myocardial infarction, cardiovascular accident, or revascularization), CABG = coronary artery bypass graft, SES = sirolimus-eluting stent, BMS = bare-metal stent

Figure legend

Figures 1 present cumulative Kaplan-Meier incidence estimates up to 5 years in diabetics and in non-diabetics, i) for MACCE (major adverse cardiac and cerebrovascular events [a composite of all-cause mortality, myocardial infarction, cardiovascular accident, or revascularization]) (A), ii) for all-cause mortality (B), iii) for myocardial infarction (C), iv) cerebrovascular accidents (D), v) for a composite endpoints of death, cerebrovascular accidents, or myocardial infarction (E), and vi) for any revascularization (F).

BMS = Bare-metal stents, SES = Sirolimus-eluting stents, CABG = Coronary artery bypass graft

Figure 1 A. Cumulative incidence of MACCE up to 5 years

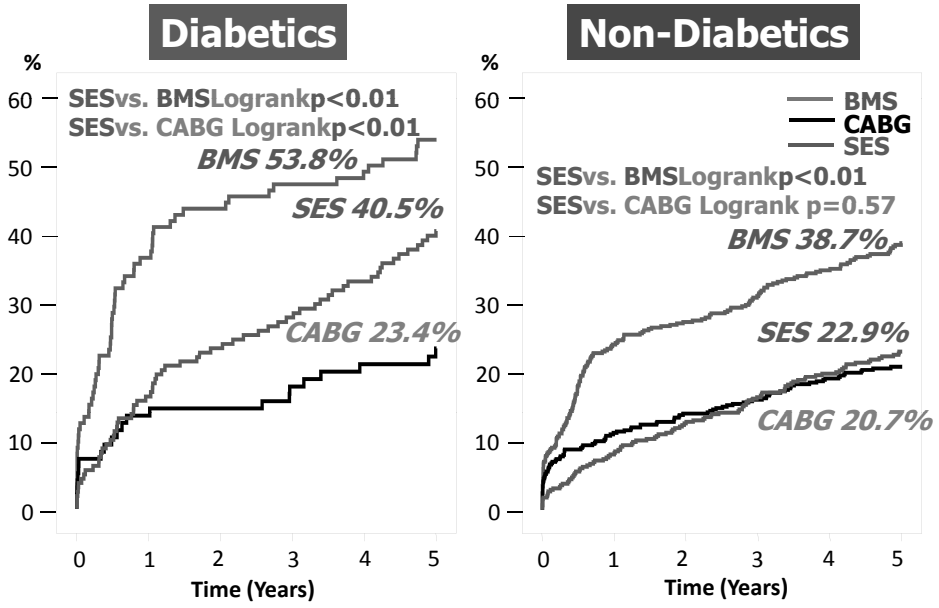


Figure 1 B. Cumulative incidence of all-cause mortality up to 5 years

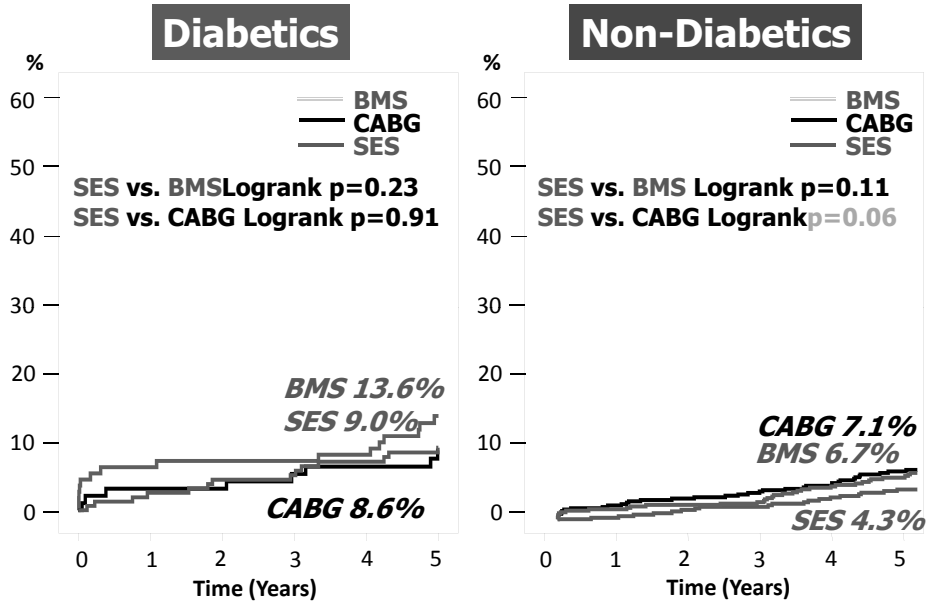


Figure 1 C. Cumulative incidence of Myocardial Infarction up to 5 years

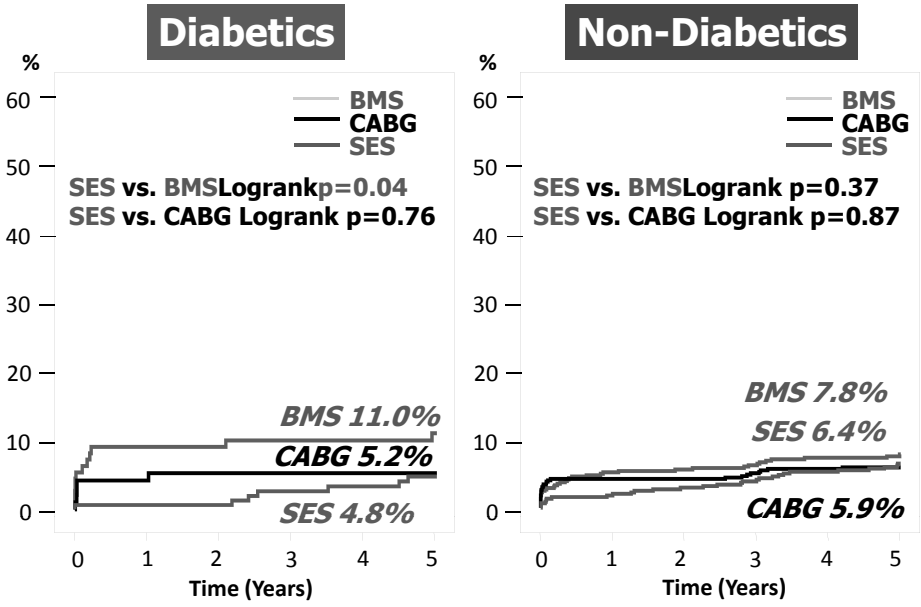


Figure 1 D. Cumulative incidence of CVA up to 5 years

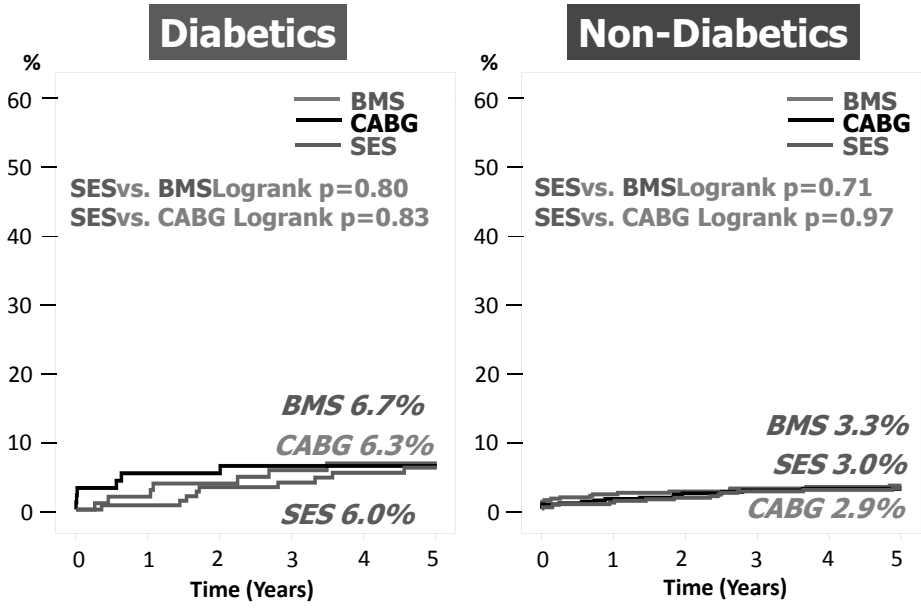


Figure 1 E. Cumulative incidence of Death/CVA/MI up to 5 years

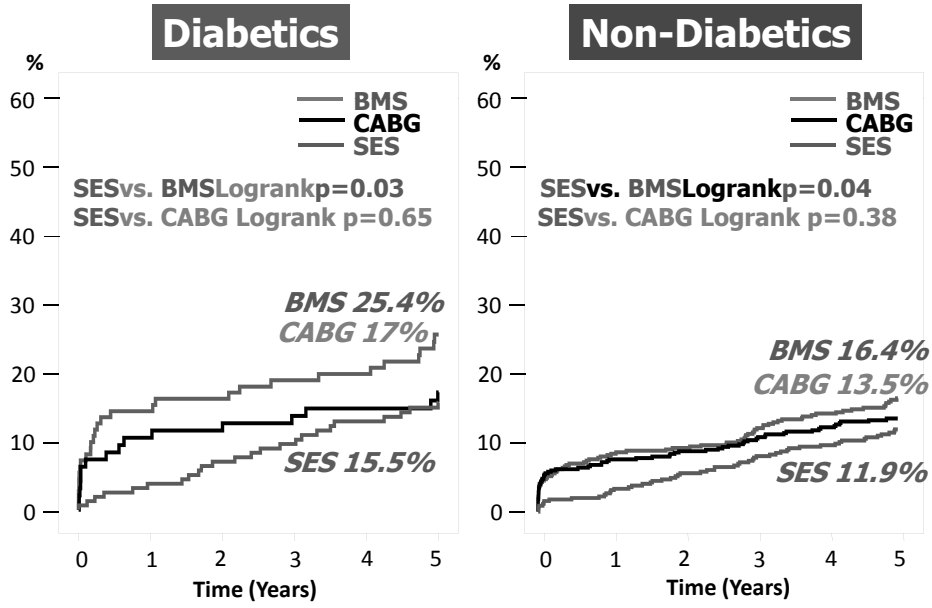
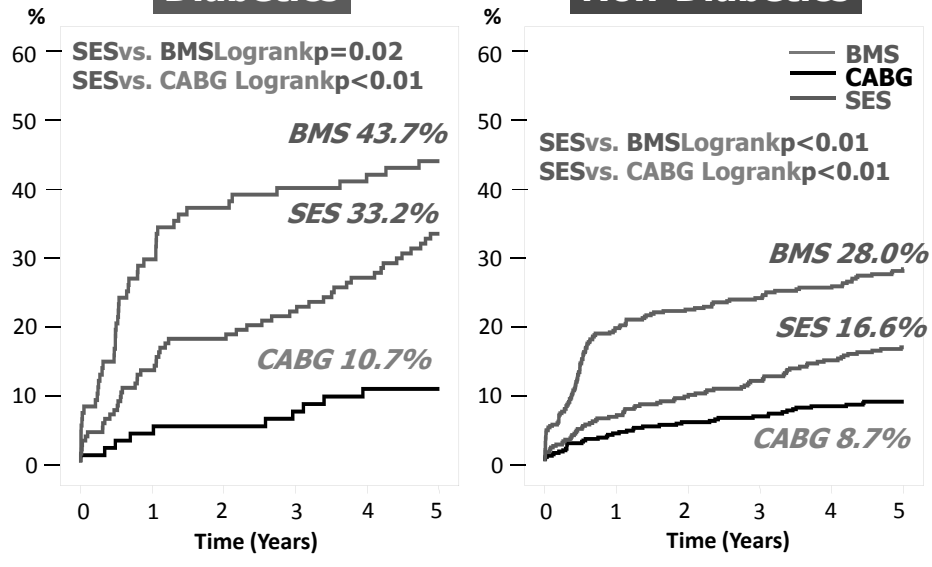


Figure 1 F. Cumulative incidence of Any revascularization up to 5 years



Chapter 13

The three year follow-up of the randomized "all-comers" trial of a biodegradable polymer biolimus eluting stent versus permanent polymer sirolimus eluting stent (LEADERS).

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ABSTRACT:

Objectives: The current study reports clinical outcomes at three year follow-up of the LEADERS clinical trial which was the first all-comers trial comparing a new generation biodegradable polymer biolimus drug eluting stent (BES) with the first generation permanent polymer sirolimus eluting stent (SES).

Methods and results: 1,707 patients were randomized to unrestricted use of BES (n=857) or SES (n=850) in an all-comers population. Three year follow up was available in 95% of the patients, 812 treated with BES and 809 treated with SES. At three years BES remains non-inferior to SES for the primary endpoint of major adverse cardiac events (composite of cardiac death, myocardial infarction (MI), or clinically-indicated target vessel revascularization (CI-TVR) (BES 15.7% versus SES 19%; HR 0.82 CI 0.65-1.03; p=0.09). The MACE Kaplan Meier event curves increasingly diverge with the difference in events increasing from 1.4% to 2.4% and 3.3% at 1, 2 and 3 years, respectively in favor of BES. The rate of cardiac death was non-significantly lower 4.2% versus 5.2% (HR=0.81 CI 0.52-1.26; p=0.34) and the rate of myocardial infarction was equivalent 7.2% versus 7.1% (HR 1.01 CI 0.70-1.44; p=0.97) for BES versus SES, respectively. Thus BES was non-inferior to SES in all the safety end-points. Clinically-indicated TVR occurred in 9.4% of BES treated patients versus 11.1% of SES treated patients (HR 0.84 CI 0.62-1.13; p=0.25). Rates of definite stent thrombosis were 2.2% for BES and 2.9% for SES (HR 0.78 CI 0.43-1.43; p=0.43), with the event rate increase of 0.2% from 1 to 3 years for BES and 0.9% for SES. For patients presenting with ST elevation myocardial infarction.BES was superior to SES in reducing MACE.

Conclusions: The findings of the three year follow-up support the claim that biodegradable polymer biolimus eluting stent has equivalent safety and efficacy to permanent polymer sirolimus eluting stent in an all-comers patient population. Its performance is superior in some subpopulations such as ST elevation MI patients and event rates for BES are overall lower that for SES with a trend toward increasing divergence of outcomes over three years.

INTRODUCTION:

Drug eluting stents (DES) dubbed the third revolution in interventional cardiology (after balloon angioplasty and bare metal stents being first and second) have to a large degree solved the problem of in-stent restenosis.[1] However, the first generation devices such as sirolimus eluting and paclitaxel eluting stents with permanent polymer have relatively high rates of stent thrombosis, including very late stent thrombosis of up to 6% at 5 years in an all-comers unrestricted population (Bern-Rotterdam).[2] The reason for this high event rate is multifactorial but one of the prominent causes may be a hypersensitivity reaction and endothelial dysfunction caused by the permanent polymer from which the drug is eluted in the first generation DES. [3, 4]

For this reason with reduction of stent thrombosis in mind Biomatrix Flex biolimus eluting stent (BES) (Biosensors, Morges, Switzerland) was designed to elute biolimus from a polylactide (PLA) biodegradable polymer applied to the stent's abluminal surface.[5] The polymer is fully metabolized to water and carbon dioxide within six to nine months from implantation leaving only the bare metal stainless steel platform behind. Biolimus is a semi-synthetic highly lipophilic inhibitor of the mammalian target of rapamycin, ten times as potent as sirolimus. BES has been shown to be non-inferior to the sirolimus eluting permanent polymer stent at 9 and 12 months in terms of major adverse cardiac events in the all-comers LEADERS clinical trial.[6] The current study is a report of three year outcomes of the first all-comers trial in an unrestricted population of BES versus SES with focus on special patient populations and very late definite stent thrombosis risk, especially in patients who have interrupted DAPT therapy.

METHODS:

Study population:

LEADERS was a multicenter European non-inferiority trial comparing the safety and efficacy of the BioMatrix™ Flex biolimus eluting stent with a biodegradable polymer (BES) (Biosensors, Morges, Switzerland) to the Cypher® Select™ sirolimus eluting stent with a durable polymer (SES) (Cordis, NJ, USA) in 1,707 'all-comers' patients. Detailed study protocol can be found in the main publication.[6] Briefly, patients included had chronic stable coronary artery disease or acute coronary syndromes including ST elevation myocardial infarction, one of more lesions of >50% and a reference vessel diameter 2.25-3.5 mm. The only exclusion criteria were: known allergy to acetylsalicylic acid, clopidogrel, heparin, stainless steel, sirolimus, biolimus or contrast that cannot be premedicated, planned surgery within 6 months of PCI unless DAPT could be continued through surgery, pregnancy or participation in another trial before reaching its primary endpoint. 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*:**

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. We randomly allocated patients on a1:1 basis to treatment with a BES (Biomatrix Flex, Biosensors Inc., Newport Beach, CA, USA) or a SES (Cypher SELECT, Cordis, Miami Lakes, FL, USA) 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 2.25-3.5 mm and in lengths of 8- 28 mm. SES were available in diameters of 2.25- 3.5 mm and in lengths of 8-33 mm. We performed balloon angioplasty and stent implantation 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 at least 75 mg of acetylsalicylic acid, 300-600 mg loading dose of clopidogrel, and unfractionated heparin at a dose at least 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 intercurrent revascularization procedures requiring stent implantation, treating cardiologists were encouraged to use the study stent. For other details we refer to the primary endpoint publication.[6]

***Study endpoints*:**

Definitions of all endpoints are provided elsewhere.[6] 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 9-months. Secondary endpoints were any target lesion revascularization (TLR) (both clinically and non-clinically indicated), any TVR, cardiac death, death from any cause, myocardial infarction, stent thrombosis (defined according to the Academic Research Council)[7, 8], device success, and lesion success.

***Statistics*:**

The trial was powered for non-inferiority on the primary clinical endpoint. Continuous variables are expressed as mean$\pm$standard deviation and compared with student t-test. Categorical variables are presented as frequency (percentages) and compared using chi-square test. Survival curves were constructed 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 and $p<0.05$ was considered significant.

RESULTS:

***Follow-up rate at three years*:**

Figure 1 flow chart summarizes the follow-up rates at 1, 2 and 3 years. Follow-up was available in 1,621 patients i.e. 95%. In the BES treated group 17 patients were lost to follow-up whereas 20 were lost to follow-up in the SES treated group. 11 patients in each treatment arm withdrew consent.

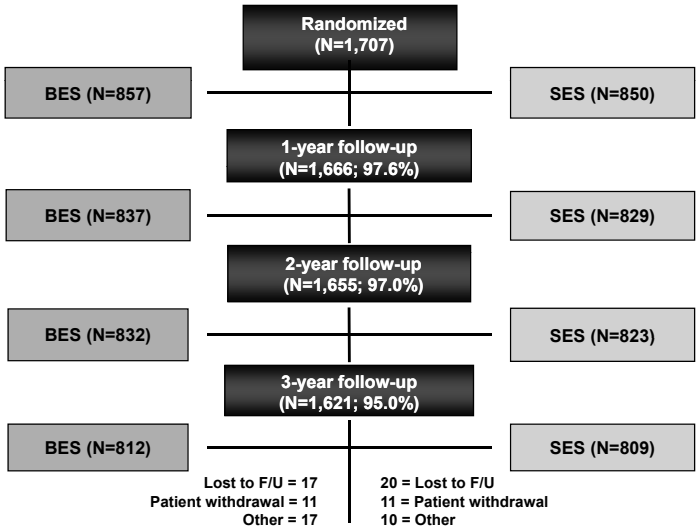


Figure 1. Flow chart showing completeness of follow-up at 1, 2 and 3 years

***Patient demographics and lesion characteristics*:**

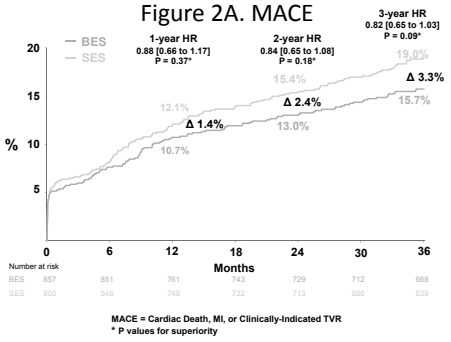
The baseline clinical and angiographic characteristics are summarized in Table 1, respectively. There were no significant differences between the two stent groups.

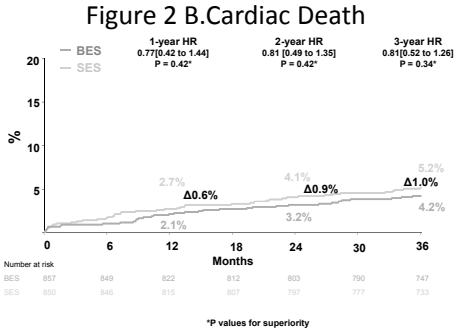
***Clinical outcomes at 36 months (3 years)*:**

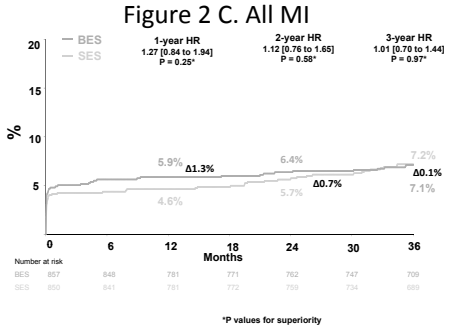
At three years BES remained non-inferior to SES for the primary endpoint of major adverse cardiac events (composite of cardiac death, myocardial infarction (MI), or clinically-indicated target vessel revascularization (TVR)) (BES 15.7% versus SES 19%; HR 0.82 CI 0.65-1.03; p=0.09). The MACE Kaplan Meier event curves tend to increasingly diverge with the difference in events increasing from 1.4% to 2.4% and 3.3% at 1, 2 and 3 years, respectively in favor of BES (Figure 2A). The rate of cardiac death was non-significantly lower 4.2% versus 5.2% (HR=0.81 CI 0.52-1.26; p=0.34; Figure 2B) and the rate of myocardial infarction was equivalent 7.2% versus 7.1% (HR 1.01 CI 0.70-1.44; p=0.97; Figure 2C) for BES versus SES, respectively. Thus BES was non-inferior to SES in all the safety end-points at three years (Figure 3A). Clinically-indicated TVR occurred in 9.4% of BES treated patients versus 11.1% of SES treated patients (HR 0.84 CI 0.62-1.13; p=0.25; Figure 2D). BES was non-inferior to SES in efficacy end-points at three years (Figure 3B).

Table 1: Baseline demographic and angiographic patient data

	BES 857 Patients	SES 850 Patients
Age in years	65 ± 11	65 ± 11
Male gender	75%	75%
Arterial hypertension	74%	73%
Diabetes mellitus	26%	23%
- insulin-dependent	10%	9%
Hypercholesterolemia	65%	68%
Family history	40%	44%
Smoking	24%	25%
Previous MI	32%	33%
Previous PCI	36%	37%
- with drug-eluting	12%	14%
Previous CABG	11%	13%
Chronic stable angina	45%	44%







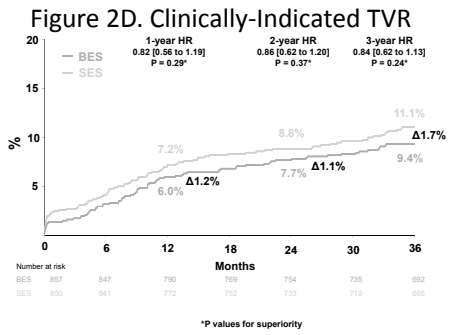
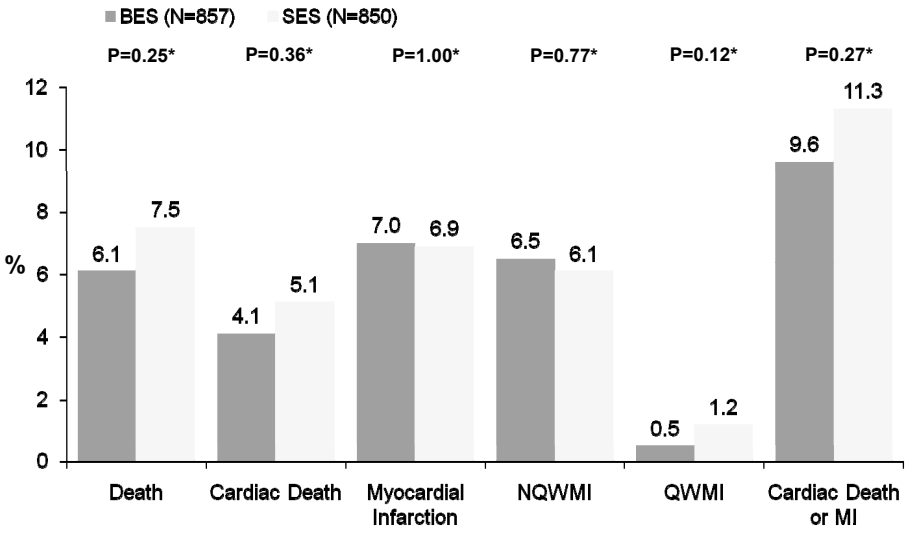
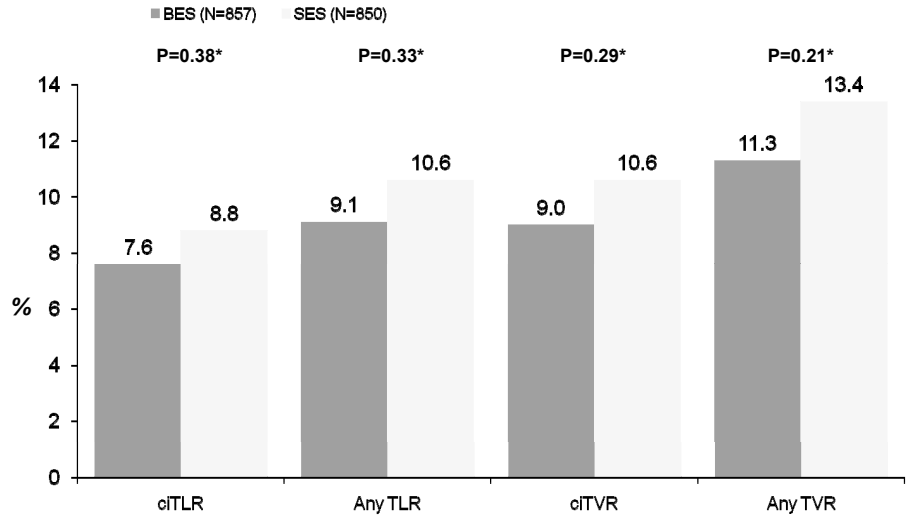


Figure 2A. Kaplan Meier curve for MACE (cardiac death, myocardial infarction and target vessel revascularization) rate at 3 years and Hazard Ratios for superiority: BES (blue) versus SES (yellow). 2B. Kaplan Meier curve for Cardiac Death at 3 years. 2C. Kaplan Meier curve for all myocardial infarctions at 3 years. 2D. Kaplan Meier curve for Target Vessel Revascularization at 3 years.



*P values for superiority (Fisher Exact Test)

Figure 3A. Three year safety endpoints for BES versus SES showing equivalent safety (death, cardiac death, myocardial infarction, non-Q wave myocardial infarction, Q-wave myocardial infarction and combined cardiac death or myocardial infarction.



*P values for superiority (Fisher Exact Test)

Figure 3B. Three year efficacy end-point for BES versus SES showing equivalent efficacy with a trend to lower TVR for BES (clinically indicated TLR, any TLR, clinically indicated TVR and any TVR)

***Subpopulations (pre-specified and post-hoc)*:**

The findings of the primary end-point (MACE) were consistent across the pre-specified analyses for diabetes, acute coronary syndromes, de novo lesions, left anterior descending lesions, off-label use, small vessels and long-lesions except a significant interaction was observed between estimated HR and presence or absence of ST-elevation myocardial infarction at baseline (HR 0.43; CI 0.22-0.83; p=0.01) (Figure 4). In addition, there was a trend to reduction in event rates with the use of BES in patients with multivessel disease (HR 0.65; CI 0.41-1.03; p=0.06). Post-hoc analysis of the highest SYNTAX score tertile patients (defined as SYNTAX score > 16) showed significantly lower cardiac death for patients treated with BES (4.7% versus 10.5%; HR 0.43; CI 0.21-0.89; p=0.02). (Figure 5)

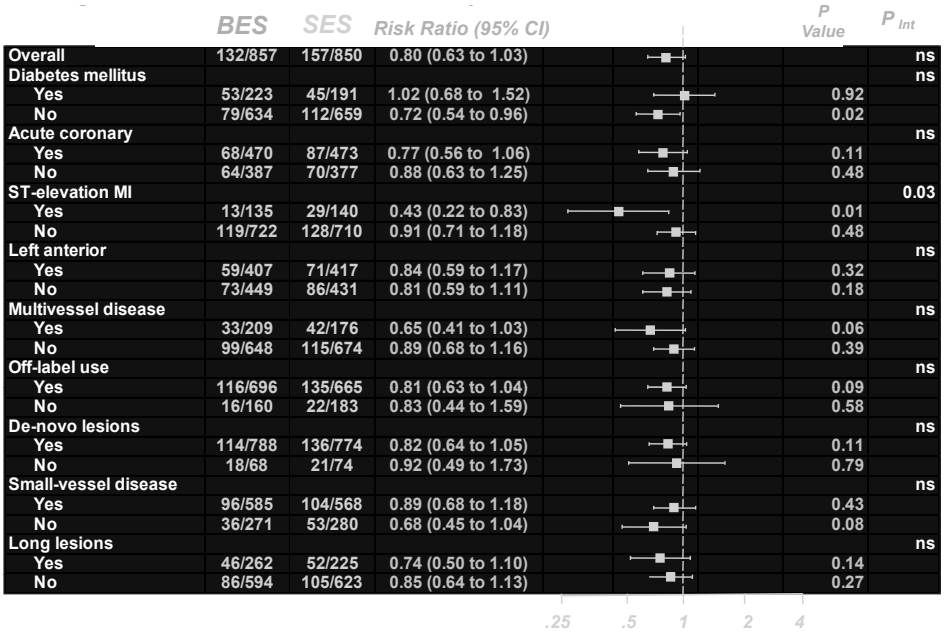


Figure 4. MACE rate for patients treated with BES versus SES stratified by pre-specified subgroups: diabetic patients, acute coronary syndrome at presentation, ST elevation myocardial infarction at presentation, left anterior descending artery disease, multivessel disease, off-label use, de-novo lesions, small vessels and long lesions. BES performs superiorly to DES in patients presenting with ST elevation myocardial infarction.

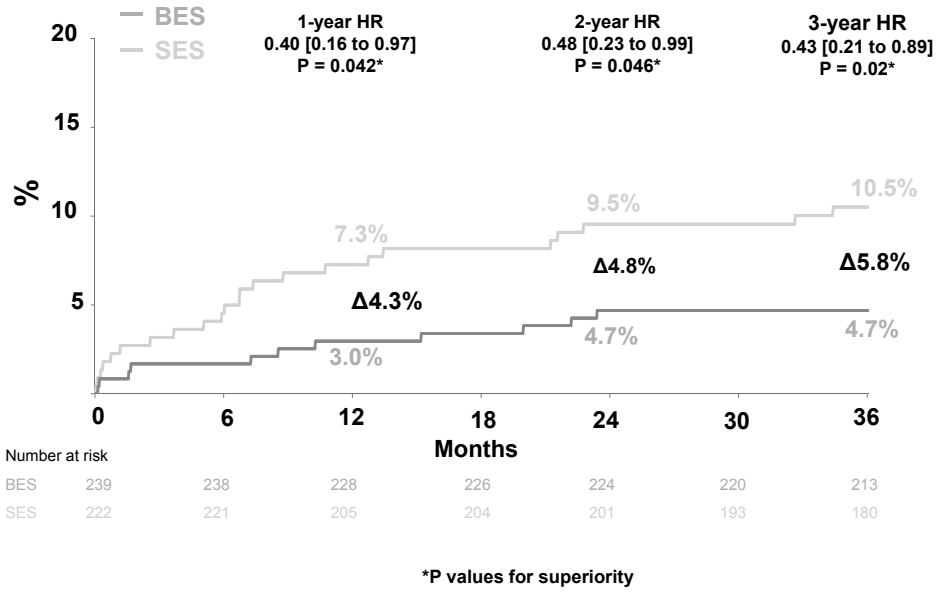


Figure 5. Cardiac death for patients in the highest tertile of the SYNTAX score is lower for patients treated with BES versus SES at three years (HR 0.43; p=0.02).

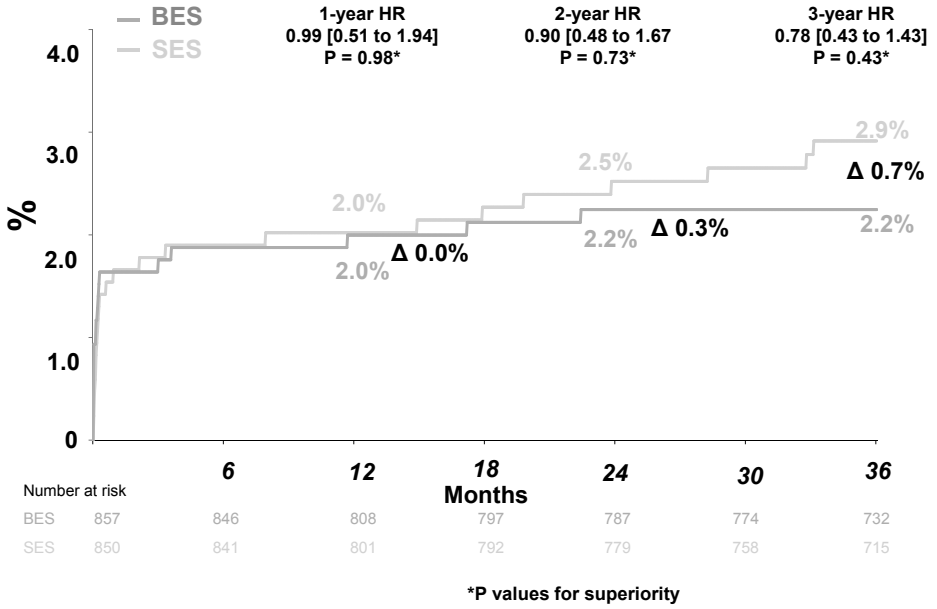


Figure 6. Definite stent thrombosis rate at three years for patients treated with BES versus SES showing greater increases in very late events for SES.

Table 2. Anti-platelet agent utilization at 9, 12, 24 and 36 months for patients treated with BES and SES.

	BES	SES	P value
Aspirin			
- At 9 months	96.6% (n=818)	97.4% (n=798)	**0.39**
- At 12 months	97.0% (n=810)	96.1% (n=801)	**0.34**
- At 24 months	94.9% (n=789)	94.2% (n=778)	**0.58**
- At 36 months	94.3% (n=757)	94.8% (n=746)	**0.73**
Clopidrogel/Thienopyridine			
- At 9 months	95.6% (n=818)	95.2% (n=798)	**0.81**
- At 12 months	68.1% (n=810)	66.5% (n=801)	**0.52**
- At 24 months	23.4% (n=789)	24.3% (n=778)	**0.72**
- At 36 months	19.6% (n=757)	20.4% (n=747)	**0.75**

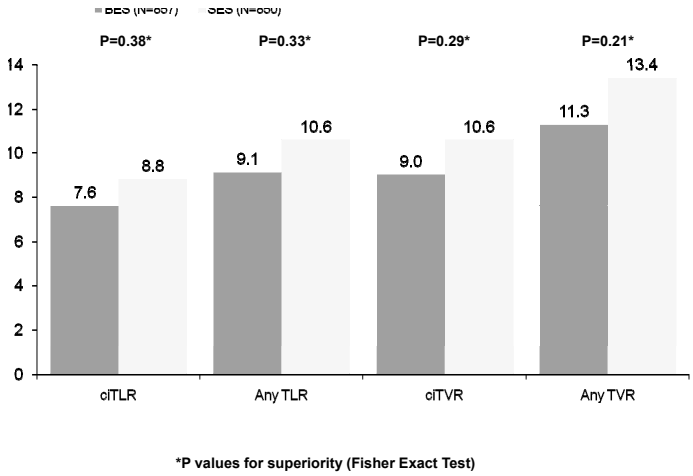


Figure 7. The effect of DAPT discontinuation before 12 months and after 12 months post-procedure on stent thrombosis events in patients treated with BES (no events) versus SES.

***Stent thrombosis and DAPT treatment*:**

Rates of definite stent thrombosis were 2.2% for BES and 2.9% for SES (HR 0.78 CI 0.43-1.43; p=0.43), with the event rate increase of 0.2% from 1 to 3 years for BES and 1.2% for SES (Figure 6). Table 2 summarizes the rates of anti-platelet agent utilization at 9, 12, 24 and 36 months which were non-different in the BES and SES group (aspirin use of 94% and clopidogrel use of 20%). Among patients who discontinued DAPT before 12 months, definite stent thrombosis occurred in 4 patients treated with SES and none treated with BES. Among patients who discontinued clopidogrel after 12 months, definite stent thrombosis occurred in 2 patients treated with SES and none treated with BES. (Figure 7)

DISCUSSION:

This study confirms that biodegradable polymer biolimus eluting stent (BES) is non-inferior to the permanent polymer sirolimus eluting stent (SES) at three year follow-up in the context of an unrestricted use in a randomized "all-comers" trial. The primary clinical end point of MACE (combined cardiac death, myocardial infarction and clinically indicated target vessel revascularization) continues to show lower event rate for patients treated with BES with incremental benefit to the use of BES over SES and trend towards statistical significance. In addition, the subgroup analysis confirms that high risk patients such as patients presenting with acute ST-elevation myocardial infarction have better outcomes with BES treatment. Patients with high SYNTAX score have a lower cardiac death rate when treated with BES when compared to SES.[9]

The major strength of this trial is that it tested the performance of the new generation drug elution stent with biodegradable polymer in a patient population that has close to 80% off-label use and increased risk of adverse events. It reflects the real clinical practice and therefore tests the device in the real-world setting.[10] Thus in both treatment groups the event rates are overall higher than the ones reported from the initial DES trials and some of the more recent randomized trials such as ENDEAVOR IV and SPIRIT III in which simple de novo lesions were treated. [11-14] In addition, while ENDEAVOR and SPIRIT used angiographically-driven outcomes (lesion-based and device-based analysis), LEADERS focused on patient-based clinical outcomes: all cardiac death, all MI and all clinically-driven TVR.

The use of the first generation drug eluting stents has been associated with an increased risk of stent thrombosis, an issue that was of particular importance in off-label indication cases.[15] We show in this study that biodegradable polymer BES has lower stent thrombosis rates than the permanent polymer stent of the first generation. The differences do not reach statistical significance as the trial has not been powered to detect them and registry data with larger patient numbers or longer follow-up will be needed to confirm whether biodegradable polymer DES can reduce stent thrombosis rates. Bern-Rotterdam registry shows that event rates steadily increase for sirolimus eluting stents at 0.6% per year.[2, 16] Similarly in ARTS-II overall stent thrombosis rate reaches 9.4% at 5 years for sirolimus stent treated patients.[17] One can project when the differences in stent thrombosis for BES versus SES may reach statistical significance if average very late definite stent thrombosis rate is 0.1% for BES and 0.6% for SES. OCT analysis at 9 months seems to suggest that biodegradable polymer biolimus eluting stent has better strut coverage than the permanent polymer sirolimus eluting stent.[18] In addition, patients who stopped DAPT do not appear to have any additional events at three years in the BES arm while these events do accrue in the SES arm.

LIMITATIONS

The study was performed in tertiary care center with high volume operators throughout Europe and thus the results might not be generalizable to low volume peripheral centers.

CONCLUSIONS

The findings of the three year follow-up support the claim that biodegradable polymer biolimus eluting stent has equivalent safety and efficacy to permanent polymer sirolimus eluting stent in an all-comers patient population. Its performance is superior in some subpopulations such as ST elevation MI patients and event rates for BES are overall lower that for SES with increasing divergence of Kaplan Meier curves.

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Part III

Chapter 14

Differential protein biomarker expression and their time-course in patients with a spectrum of stable and unstable coronary syndromes in the Integrated Biomarker and Imaging Study-1 (IBIS-1)

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ABSTRACT

Objectives: IBIS-1 was a pilot study undertaken to correlate coronary imaging with circulating biomarker expression in patients with stable angina, unstable angina and acute myocardial infarction. We hypothesized that patients at high risk of future events could be identified in the future by a combination of high risk plaque features by plaque echogenicity and palpography and a set of circulating blood biomarkers.
Results and methods: We assessed the expression of conventional biomarkers and novel marker protein microarray (170 analytes) over 6 months. There were no strong correlations observed between conventional biomarkers and coronary imaging in non-culprit artery. Proteomic microarray was performed in 66 patients. Seventy eight (45%) analytes showed dynamic changes over time. Using hierarchical clustering and principal component analysis two subsets of biomarkers were identified: initial up-regulation and decrease over time (D-dimer, hepatocyte growth factor, CXCL9/MIG, platelet factor 4/CXCL4, CTACK, C-6 Kine, follistatin, and FGF-7) and the opposite increase (PAI-1-anti-apoptotic protein and I-309 — chemokine induced on the human endothelium by Lp(a)).
Conclusions: Proteomic analysis identifies dynamic patterns in circulating biomarkers in a wide range of patients with coronary artery disease. Further large natural history studies are needed to better define multibiomarker sets for identification of patients at risk of future CV events.

1. Introduction

Inflammation is an established component of the pathogenesis of coronary artery disease and some of the biomarkers of systemic inflammation and macrophage activation such as hs-CRP, sCD40L and sICAM or myeloperoxidase expression have been shown to correlate with increased risk of coronary events [1,2]. Given that coronary artery disease often presents for the first time as sudden cardiac death or acute myocardial infarction, it is important to define non-invasive methods of screening for patients at high risk of such events. Lesions that are responsible for causing these events in 60% of cases are not obstructive on invasive angiography [3].

IBIS-1 study was a single center prospective pilot study to assess both invasive and non-invasive methods of identifying coronary lesions with high risk features based on intravascular ultrasound imaging [4], palpography [5], and multislice CT scanning [6] and to correlate this to systemic biomarker expression [7]. We hypothesized that patients at high risk of future events could be identified prospectively by a combination of high risk plaque features by plaque echogenicity and palpography and a set of circulating blood biomarkers.

The results of multimodality coronary imaging in IBIS-1 were previously published. Plasma biomarkers were measured during initial presentation, at three and six months thus providing the opportunity to investigate patterns in various classes of circulating analytes. The results of this pilot study indicate dynamic changes in circulating biomarkers (down regulation and up-regulation) as a result of natural history of coronary heart disease or concomitant therapy. These dynamic changes in the clusters of biomarkers rather than static values in individual analytes may offer prospect of better multibiomarker approach for the identification of patients at risk of cardiovascular events and their response to therapy, along with imaging biomarker. In addition, while imaging of the plaque may reflect local features of high risk plaque, pro-inflammatory and pro-coagulability systemic blood markers may reflect, so-called "blood vulnerability", and it is the combination of these two that creates a "vulnerable patient" at risk of events.

2. Methods

2.1. Study patients

We studied 89 consecutive patients with coronary artery disease and either stable angina or acute coronary syndromes (including 21 non-ST elevation MI and 14 ST elevation

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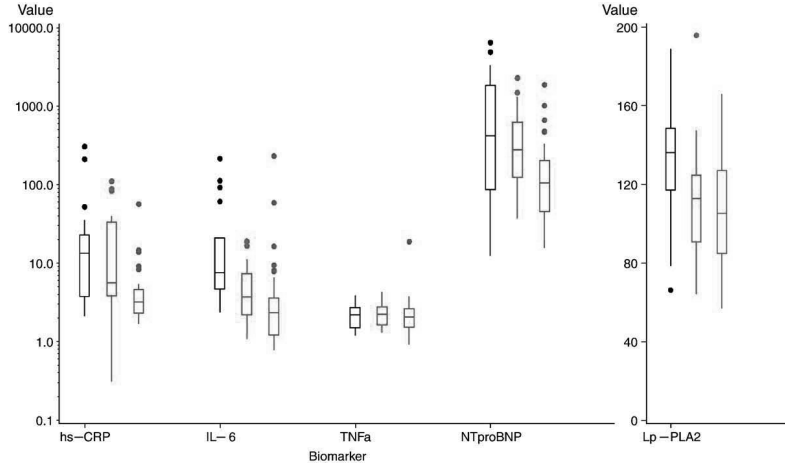


Fig. 1. Change in classical biomarker levels at time of presentation. Data are presented as box-whisker plots, with 25th and 75th percentiles (box) and 10th and 90th percentiles (I). There were significant differences among patient groups with acute myocardial infarction (black), unstable angina (red), and stable angina (green) for systemic values of high sensitivity C-reactive protein (hs-CRP mg/L: $P = 0.0003$), interleukin-6 (IL-6 pg/mL: $P = 0.001$), lipoprotein-associated phospholipase A_2 activity (Lp-PLA_2 nmol/min/mL: $P = 0.035$), and N-terminal pro brain natriuretic peptide (NT-proBNP pg/ml: $P = 0.0012$). Plasma levels of tumor necrosis factor α (TNF-α pg/mL) did not differ significantly among groups. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

MI patients) enrolled in the IBIS-1 study in 2003 at the Thoraxcentrum, Erasmus MC. The study was approved by the Ethics Committee of the Erasmus Medical Center. The basic study design and protocol is described elsewhere [7]. Blood plasma samples were collected from 66 of patients at index cardiac catheterization procedure, 3 and 6 months follow up. Patients enrolled in the study were receiving the standard of care medical treatment that included aspirine (91%), clopidogrel (94%), statins (99% of patients), ACE inhibitors (51%) and beta-blockers (75%), at the discretion of their physician.

2.2. Sample collection

Testing was performed in duplicates. Serum plasma was separated from other blood components and the samples were stored at −70 °C. Biomarker analysis was performed with an MSI amplified microarray to look at 170 analytes and their differential expression between time points.

Classical biomarker quantification was also performed on hs-CRP, IL-6 and lipoprotein-associated phospholipase A_2 and NT-proBNP, TNF-alpha and sCD40L were also assessed by well-established methods. Briefly, blood for biomarker analysis was centrifuged within 30 min and stored at −70 °C. Serum C-reactive protein (Diagnostic Systems Laboratories), plasma interleukin 6 and tumor necrosis factor-α (R&D Systems), were measured in the Human Biomarker Center (GlaxoSmithKline, PA) with the use of protocols provided by the manufacturer. Lipoprotein-associated phospholipase A_2 activity (Lp-PLA_2) assay measures the proportional release of aqueous ^{3}H acetate resulting from the enzymatic cleavage of the ^{3}H acetyl-platelet activating factor 8 substrate (100 ∞ M). N-terminal pro brain natriuretic peptide was measured with the use of a two site electrochemiluminescent assay. The limits of quantification were 0.0048 mg/L for C-reactive protein, 0.057 pg/mL for interleukin-6, 3.92 nmol/min/mL for Lp-PLA_2, 10 pg/ml for N-terminal pro brain natriuretic peptide, and 0.88 pg/mL for tumor necrosis factor-α.

2.3. Protein expression assessment

Microarray was manufactured by Molecular Staging Inc. by printing with a Perkin-Elmer SpotArray Enterprise non-contact arrayer. Antibodies were applied at a concentration of 0.5 mg/ml. Chips were validated using normal human plasma and a mixture of purified recombinant cytokines representing all analytes in the array. Titration curves were generated for every analyte. Rolling circle amplification (RCA) immunoassay was performed according to the standard operating procedures detailed [8].

2.4. Microarray data analysis

Data were logarithm transformed to stabilize variance and improve normality of the data. Only analytes with two-fold higher changes in specific features than in non-specific controls were chosen for further analysis. Ninety four of the 170 analytes were

Table 1
Change in classical biomarker levels over time stratified by angina status. CRP and IL-6 decreased in acute coronary syndrome patients only while LpPLA_2 decreased in all patients over time. There was no significant change in sCD40L levels.

Biomarker (mean change ± STD)	STEMI ($n = 14$)	Unstable angina ($N = 20$)	Stable angina ($N = 31$)	All patients ($N = 65$)
CRP (mg/L)	−7.59 ± 7.73	−19.21 ± 31.22	0.17 ± 7.45	−7.58 ± 20.08
	$P = 0.004$	$P = 0.0038$	$P = 0.91$	$P = 0.0014$
IL-6 (pg/mL)	−9.82 ± 23.04	−2.96 ± 5.39	−3.94 ± 21.27	−4.92 ± 18.26
	$P = 0.0017$	$P = 0.0062$	$P = 0.59$	$P = 0.0001$
LpPLA_2 (nmol/min/mL)	−43.2 ± 26.87	−29.95 ± 30.72	−29.23 ± 27.12	−32.51 ± 28.37
	$P < 0.0001$	$P = 0.0003$	$P < 0.0001$	$P < 0.0001$
NT-proBNP (pg/mL)	−624 ± 1343	−262 ± 384	−47 ± 329	−236 ± 719
	$P = 0.36$	$P = 0.0009$	$P = 0.58$	$P = 0.0022$
TNF-alpha (pg/mL)	1.51 ± 8.29	0.14 ± 1.38	2.06 ± 4.08	1.29 ± 4.85
	$P = 0.64$	$P = 0.65$	$P = 0.0085$	$P = 0.16$
sCD40L (ng/mL)	2.45 ± 2.01	−0.46 ± 3.05	−0.93 ± 3.41	−0.28 ± 3.27
	$P = 0.0124$	$P = 0.78$	$P = 0.62$	$P = 0.75$

Table 2
Correlation between classical biomarkers and imaging parameters. Levels of CRP, IL-6, Lp-PLA_2, proBNP and TNF-alpha are correlated with angiographic percent diameter stenosis (QCA), mean plaque area, vessel area, percent plaque obstruction and hypoechogenicity on IVUS-gray scale as well as strain on palpography. CRP and IL-6 levels are only weakly correlated with plaque hypoechogenicity in the non-culprit vessel.

	Angiography percent stenosis	Ultrasonography mean plaque area (mm2)	Ultrasonography mean vessel area (mm2)	Ultrasonography percent plaque area obstruction	Tissue characterization percent hypoechogenic plaque	Palpography grade 3/4 spots per 10 mm
CRP	−0.16	−0.03	0.12	−0.16	0.32*	0.01
IL−6	0.04	0.08	0.14	−0.02	0.27†	0.13
Lp-PLA_2	−0.01	−0.16	0.08	−0.31*	0.18	0.18
NT-proBNP	0.04	−0.09	0.04	−0.14	0.16	−0.02
TNF-α	−0.05	−0.10	−0.16	0.03	−0.05	−0.03

*$P = 0.005$, †$P = 0.015$.
•The values in the table are the Pearson correlation coefficients.
•CRP: C-reactive protein, IL-6: interleukin 6, Lp-PLA_2; lipoprotein-associated phospholipase A_2, NT-proBNP: N-terminal pro brain natriuretic peptide, and TNF-α: tumor necrosis factor alpha.

chosen for further analysis whose change in expression over time within the patient was larger than the platform imprecision. Paired *t*-test was used to assess for statistically significant changes in analyte levels between baseline index event and three and six months time points, as well as at steady state between 3 and 6 months time points. Repeat mixed model analysis of variance was performed to identify significant changes in expression with time. In addition, a piecewise linear regression was performed to obtain slopes for the change in expression level between time points (baseline to 3 month = slope 1 and 3 months to 6 months = slope 2). Plots with predicted and measured values were compared to verify the correctness of the model.

Hierarchical clustering was performed with analytes demonstrating significant difference in expression observed between patient baseline levels and levels detected after 3 or 6 months. Euclidian distance matrix was calculated between every pair of proteins and patients included in the analysis. Ward linkage was used to form clusters in two dimensions. There were two approximately equal groups of patients: one group with predominantly up-regulation in expression, and the other with predominantly down-regulated expression.

In addition principal component analysis (PCA) was performed to simplify and highlight the differences and similarities between data sets in this complex and multidimensional data set without losing information. Briefly, PCA involves a mathematical procedure that transforms a number of correlated variables into a smaller number of uncorrelated variables called *principal components*. The first principal component accounts for as much of the variability in the data as possible, and each succeeding component accounts for as much of the remaining variability as possible.

2.5. IVUS-based imaging protocol

The reader is referred to the study design manuscript and the main manuscript for details [7,9].

2.6. Other statistical analysis

Finally data obtained on the biomarkers with differential expression between patient groups in time was represented as box plots with whiskers and *t*-tests were performed to obtained *P*-values for the difference in biomarker expression.

3. Results

3.1. Conventional biomarkers

Baseline levels of conventional biomarkers are shown in Fig. 1. There were significant differences among patient groups with acute myocardial infarction, unstable angina, and stable angina for systemic values of high sensitivity C-reactive protein (hs-CRP mg/L: $P = 0.0003$), interleukin-6 (IL-6 pg/mL: $P = 0.001$), lipoprotein-associated phospholipase A_2

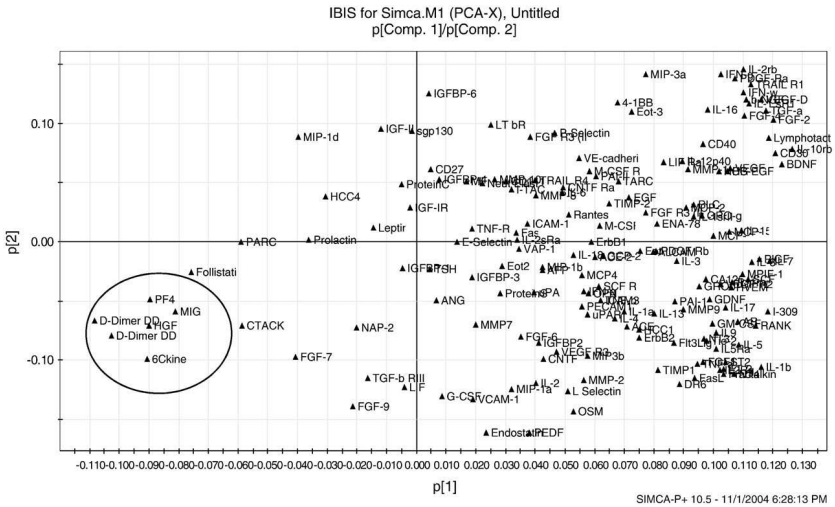
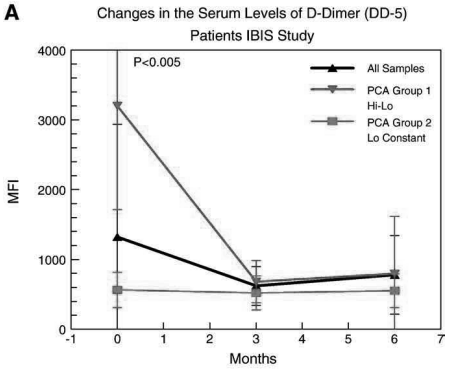
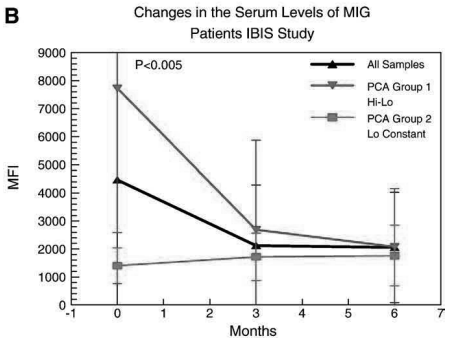


Fig. 2. Hierarchical clustering: lack of correlation between initial angina status and differential biomarker expression.





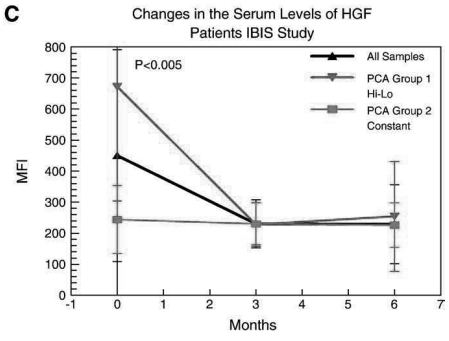
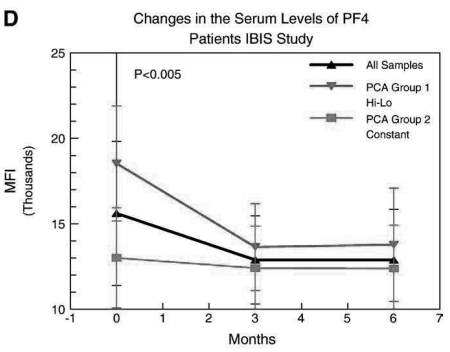
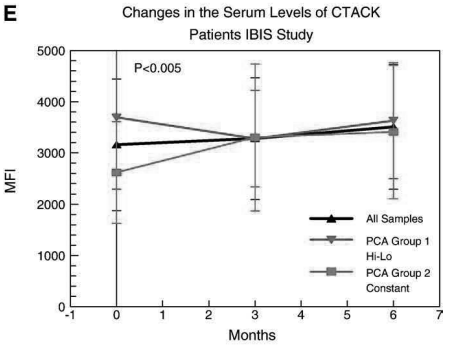


Fig. 3. Principal component analysis — summary.





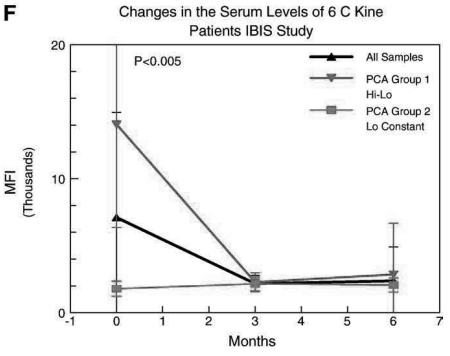


Fig. 3 (*continued*).

activity (Lp-PLA_2 nmol/min/mL: $P = 0.035$), and N-terminal pro brain natriuretic peptide (NT-proBNP pg/ml: $P = 0.0012$). Plasma levels of tumor necrosis factor α (TNF-α pg/mL) did not differ significantly among groups. In addition we investigated changes in classical biomarker levels over time (Table 1). Not surprisingly some inflammatory biomarkers (CRP, IL-6 and Lp-PLA_2) tended to decrease over time mainly in patients with myocardial infarction and unstable angina. There was no difference in TNF-alpha or sCD40L levels. Table 2 shows correlations between these biomarkers and the results of multimodality coronary imaging involving non-culprit artery. Of note, there were no apparent correlations with the measurements of plaque size or lumen narrowing, whereas CRP ($r = 0.31$; $P = 0.005$) and IL-6 ($r = 0.27$; $P = 0.015$) weakly correlated with plaque hypoechogenicity. Lp-PLA2 levels negatively correlated with the percent area obstruction on IVUS

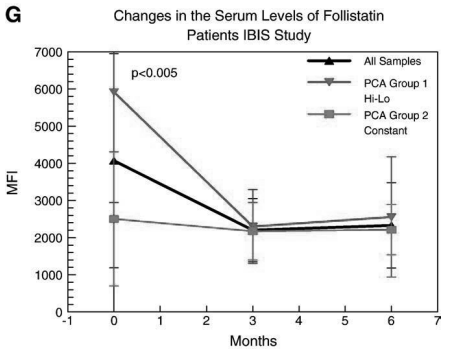


Fig. 3 (*continued*).

and angiography, underlying the fact that non-obstructive lesions are often positively remodeled and contain large lipid cores that are at risk of rupture. More detailed analysis of remodeling index correlation with baseline biomarker levels and change in biomarker levels showed no significant correlations (see Supplemental table).

3.2. Proteomic microarray analysis (novel biomarkers)

Among 170 biomarkers, 78 analytes (46%) showed significant differences in expression between baseline and either 3 or 6 months (paired *t*-test). While the expression of these analytes was different over time in two patient subsets, there was no correlation of expression with anginal status at presentation (stable versus unstable, non-ST elevation MI or ST elevation MI) (Fig. 2).

This complex data set was further compressed using hierarchical clustering and principal component analysis. This yielded two subsets of proteins demonstrating statistically robust differences in abundance between patient groups (Figs. 3 and 4; Table 3). The first subset displayed initial up-regulation of expression and decreased over time in one patient subgroup (D-dimer, hepatocyte growth factor, CXC L9/MIG, platelet factor 4/CXC L4, CTACK, C-6 Kine, follistatin, and FGF-7). The second subset increased over time in the same patient subgroup (PAI-1- anti-apoptotic protein and I-309 — chemokine that is induced

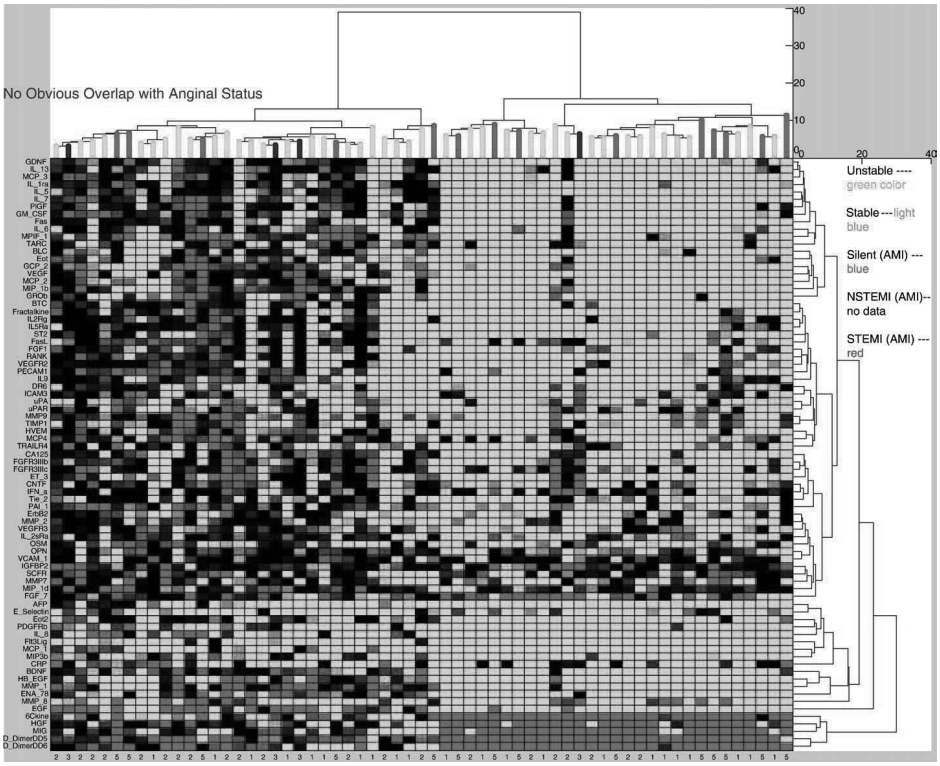


Fig. 4. Plots of novel marker levels with up-regulated expression at baseline and decreasing levels over time identified by principal component analysis.

Table 3
Summary of differential expression patterns in cluster analysis. Pro-inflammatory markers (6C Kine, CTAK, MIG and PF-4), pro-coagulable markers (D-dimer, PF4 and HGF) and marker of shear stress and remodeling (follistatin) all decrease after the index procedure. In contrast anti-apoptotic markers (PAI-10 and I-309) are up-regulated.

Marker class	Direction of change from baseline to 3 and 6 months post-procedure
Pro-inflammatory markers and markers of lymphocyte trafficking	Decreased
6 C Kine	
CTAK	
MIG	
PF-4	
Pro-coagulable markers	Decreased
D-dimer	
PF-4	
HGF	
Shear stress/remodeling marker	Decreased
Follistatin	
Anti-apoptotic markers	Increased
PAI-10	
I-309	

on the human endothelium by Lp(a)). Similarly to the classical biomarkers, multianalyte cluster analysis did not reveal any clustering of analytes that correlated with the baseline angina status (Fig. 4).

4. Discussion

In this pilot exploratory study we examined correlation between classical biomarker expression and the imaging phenotype of the plaque. We tried to identify novel biomarkers that could better define the inflammatory and pro-coagulable ("vulnerable blood") milieu of the high risk patients. Several novel biomarkers were up-regulated differentially in a subset of patients with angina or acute coronary syndromes. D-dimer, HGF, PF-4, chemokines, CCL27 (CTACK), 6-C Kine, MIG and follistatin were all up-regulated at baseline and decreased at 3 and 6 months in a subgroup of patients (group 1). They all appear to denote increased pro-coagulability, endothelial activation or injury or macrophage/monocyte trafficking into the plaque. All these mechanisms are at the root of pathogenesis of vulnerable plaque.

D-dimer has been previously shown to be elevated in patients with unstable angina and acute MI, as a marker of increased pro-coagulability. Although no direct pathogenic role of d-dimer in atherosclerosis progression or plaque instability has been described, fibrin degradation products correlate with platelet activation and other acute phase proteins, as well as plaque burden [10]. Similarly, Platelet factor 4 which belongs to the CXC containing chemokine subfamily, is up-regulated and plays an important role in response to endothelial injury and inflammation, the only confounder being that PF4 release is induced by heparin administration. PF4 can interact with platelet-derived RANTES to up-regulate adhesion molecule expression on the endothelium and thereby is capable of amplifying RANTES-induced monocyte/macrophage trafficking into the plaque and further plaque instability [11]. Platelet-derived RANTES is involved in monocyte trafficking. Similarly HGF is a marker of increased prothrombotic state [12]. However, more importantly, recently together with its c-met receptor it has been implicated in neovessel formation within the plaque or so-called plaque neovascularization [13], which may contribute to plaque instability. On the other hand, HGF can also allow for endothelial progenitor cell and pericyte trafficking to the ischemic myocardium and thus allow for vascular regeneration [14]. CTACK and C-6 Kine are also chemokines that allow for T-cell and macrophage trafficking into the plaque [15]. Lastly, follistatin and activin A are both up-regulated in unstable coronary syndromes [16] and increased follistatin expression has been recently found in the aortic wall endothelium exposed to turbulent flow together with bone morphogenic protein-4 [17]. This later association may possibly provide a link between high stress/stain areas of the coronary arteries and the proclivity of plaques in those areas to rupture.

Two additional markers that became up-regulated at 3 months PAI-10 and I-309 are anti-apoptotic protein and a chemokine involved in Lp(a) induced endothelial activation and macrophage trafficking [18] but also to increase matrix metalloproteinase 2 production [19]. It is possible that this increase may be induced by medications such as statins, which are known to increase Lp(a) expression and its related proteins [20].

Although these novel biomarkers correlated poorly with the initial angina status of the patient, this can be easily explained by heterogeneity of the patient population enrolled and small sample size. The correlation with imaging plaque characteristics of vulnerable plaque was also only weak. The technology used for plaque imaging, however, was mostly limited to gray scale IVUS, which has poor ability to discriminate fibrous from fatty/necrotic core plaque based on echogenicity alone. In addition, only one out of the three coronary arteries was sampled, which may have caused us to miss some high risk plaques in other vessels. Plasma biomarker levels reflect an overall diffuse nature of coronary and other vascular disease, as well as overall inflammatory and metabolic state of an individual patient. This global biomarker milieu might not necessarily correlate with activity at one local site of vascular injury.

While this study was exploratory in nature, it lays a foundation for further large scale natural history studies of vulnerable patients, which are underway in our and many other institutions. We hope that with larger patient populations such as in AtheroRemo and Biomarcs studies we will be able to further characterize the molecular/proteomic footprint of high risk patients and correlate these finding with state of the art imaging technologies, such as IVUS-virtual histology, near-infrared spectroscopy, optical coherence tomography and Raman spectroscopy. These novel technologies may allow us to more accurately investigate the interplay between vulnerable/high risk plaque and vulnerable blood.

Acknowledgement

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [21].

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijcard.2009.11.003.

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Chapter 15

Longitudinal distribution of the necrotic rich plaques in non-culprit vessels of patients presenting with acute coronary syndromes. Substudy of the PROSPECT trial.

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ABSTRACT:

Background and objectives: In several landmark angiographic studies it has been demonstrated that 60-70% of myocardial infarctions occur at the site of non-obstructive lesions and that they tend to occur preferentially in the proximal one third of each of the coronary vessels. In prior small IVUS studies, the distance from the vessel ostium has been an independent predictor of the necrotic core rich plaque. In this sub-study of the PROSPECT trial we attempted to validate whether there is a plaque burden and necrotic core content gradient along the vessel from proximal to distal in the three coronary vessels.

Methods and results: Of the 697 patients with acute coronary syndrome who underwent successful PCI for the index lesion, 673 underwent IVUS greyscale examination of the proximal 6-8 cm of the coronary vessels. Virtual histology recordings were available for analysis in 623 patients. The percent plaque volume although greater in the proximal 60 mm of the vessel than the very distal portion was not different in the first and mid 30 mm of the vessel (50% vs 50% vs 47.8%; p=0.0033). The numbers of plaque ruptures decreased from proximal to distal but the difference did not reach statistically significant level (7% vs 5.8% vs 3.8%; p=0.2379). Total necrotic core volume was also the highest in the proximal 30 mm of the vessel (19.7 mm^3 vs 14.4 mm^3 vs 9.3 mm^3; p<0.001), however, the percentage necrotic core volume was no different from proximal to distal vessel (21.5% vs 21.5% vs 22%; p=0.4093). The distance from the ostium was not a statistically significant predictor of the presence of TCFA or necrotic core rich lesions.

Conclusions: We have found that the distance from the ostium is not a significant predictor of the necrotic core content or presence of TCFAs. It appears that the clustering of plaque ruptures in the proximal vessel segments observed in the epidemiological studies cannot be simply mechanistically linked to percent necrotic core or presence of the IVUS-VH derived TCFA. There is likely a more complex interplay between this vessel wall substrate and other local and hemodynamic factors that leads to plaque rupture and consequent acute vessel occlusion and myocardial infarction.

INTRODUCTION:

The majority of acute coronary syndromes are caused by coronary plaque rupture at the site of thin cap fibroatheroma with subsequent local thrombosis.[1, 2] In several landmark angiographic studies it has been demonstrated that 60-70% of myocardial infarctions occur at the site of non-obstructive lesions [3-5] and furthermore that they tend to occur preferentially in the proximal one third of each of the coronary vessels [6]. It has been previously demonstrated in a pilot single center study of 51 patients that the percentage of necrotic core content was increased in the first 10 mm of the vessel relative to the distal segment (first 10 mm segment versus third and fourth 10 mm segment)[7]. In addition, the distance from the ostium appeared to be an independent predictor of relative necrotic core content, together with parameters such as age, unstable angina, lack of statin use and diabetes mellitus. This could potentially suggest a mechanism for the above mentioned proclivity of myocardial infarctions to occur at the proximal portion of the coronary artery and thus imply that one should direct therapies to stabilize "vulnerable" high risk plaques at the proximal portion of the coronary tree.

PROSPECT trial was the first natural history multicenter trial to examine plaque distribution and plaque composition in non-culprit vessels with intravascular ultrasound (IVUS) and virtual histology (VH) in patients presenting with acute coronary syndromes, and to relate the features of the coronary disease to major adverse cardiac events at three years (Stone G. et al, 2010 NEJM). In this sub-study of the PROSPECT trial (623 patients in whom VH analysis was available) we attempted to validate whether there is a plaque burden and necrotic core content gradient along the vessel from proximal to distal in the three coronary vessels.

METHODS:

Patient population:

The enrollment criteria and the methodology of the PROSPECT study have been previously described in detail elsewhere (Stone G et al., 2010). In brief, of the 697 patients with acute coronary syndrome who underwent successful PCI for the index lesion, 673 underwent IVUS grayscale examination of the proximal 6-8 cm of the coronary vessels. Virtual histology recordings were available for analysis in 623 patients.

Imaging acquisition and analysis:

Imaging with grayscale IVUS was performed using a phased-array, 20 MHz, 3.2 Fr catheter (Eagle Eye, Volcano Corporation, Rancho Cordova, CA). During a motorized catheter pullback at 0.5 mm/s, grayscale IVUS was recorded and raw frequency data were captured gated to the R-wave (In-Vision Gold, Volcano). In contrast to conventional grayscale IVUS, radiofrequency IVUS uses spectral analysis in addition to the amplitude analysis. This radiofrequency spectral

analysis has been correlated to histological samples and validated for its high specificity and sensitivity to define tissue subtypes (calcified, fibrotic, fibrofatty and necrotic core).[8]

Angiographic qualitative and quantitative measures (QCA) of the entire length of the coronary tree were made as previously described[9, 10], including each major epicardial coronary artery and every sidebranch ≥1.5 mm in diameter, using a proprietary methodology modified from standard Medis CMS software (Version 7.0, Lieden, the Netherlands). This 3-vessel angiographic analysis served as a roadmap to identify each lesion based on longitudinal axis location (mm). For each 1.5mm of vessel, the interpolated reference and the minimal lumen diameter (MLD) were recorded and used to derive the percent diameter stenosis [(1-MLD/ reference) x100]. Angiographic lesion, coronary segment and vessel level parameters were also assessed.

All IVUS images were analyzed at independent core laboratories. Off-line grayscale and radiofrequency-IVUS analysis were performed using (1) QCU-CMS (Medis) for contouring; (2) pcVH 2.1 software (Volcano) for contouring and data output; and (3) proprietary qVH software (Cardiovascular Research Foundation) for segmental qualitative assessment and quantitative data output. External elastic membrane (EEM) and lumen borders were contoured for all recorded frames (each ~0.5mm in length). Quantitative IVUS measurements included EEM cross-sectional area (CSA), lumen CSA, plaque and media (P&M; EEM minus lumen) CSA, plaque burden (P&M divided by EEM CSA), and minimal lumen area (MLA). Radiofrequency-IVUS plaque components were color-coded as dense calcium (white), necrotic core (red), fibrofatty (light green), and fibrotic tissue (dark green), and reported as CSA and percentages of total plaque area.[8] Volumetric data was calculated using Simpson's rule. A lesion was defined as a segment with ≥3 consecutive frames with ≥40% plaque burden, and classified as (1) thin-cap fibroatheroma (TCFA); (2) thick cap fibroatheroma; (3) pathological intimal thickening; (4) fibrotic plaque; and (5) fibrocalcific plaque.[11] (Garcia-Garcia HM et al., 2009; Supplemental Figure 1) Each grayscale and radiofrequency-IVUS frame was co-registered to the angiographic roadmap using fiduciary branch points to align the imaging modality outputs. Corresponding IVUS lesions were thereby assigned angiographic landmarks and measures.

The vessels examined were divided into30 mm segments from the ostium to the distal vessel for the purpose of establishing the longitudinal differences in the plaque burden and necrotic core content.

Statistical analysis:

Categorical variables are presented using frequencies and percentages, continuous variables with mean and standard deviations or median and quartiles as indicated. Comparisons between vessel segments proximal to distal with respect to variables such as plaque burden and necrotic core content and percentage were performed using a linear mixed model with a compound symmetry correlation structure and the intercept as only random effect. The values for the IVUS and IVUS-VH variables were compared between segments using chi-square test for trend for categorical data and Jonckheere-Terpstra test for continuous data. In order to

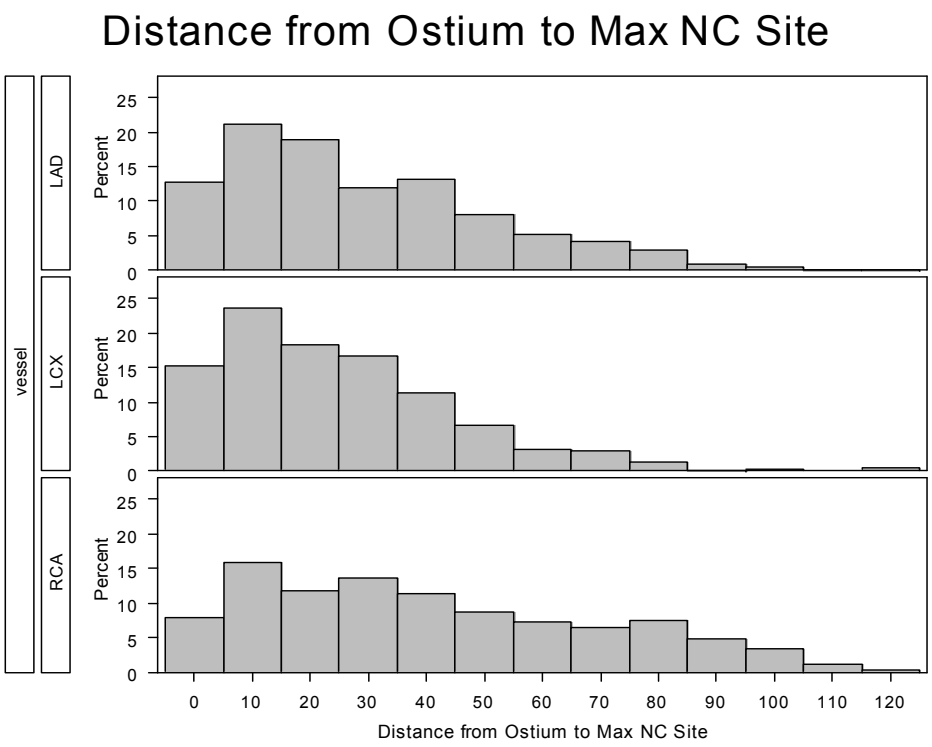

Figure 1. Distribution of necrotic core rich lesions from proximal to distal in the LAD, RCX and RCA in 10 mm segments.

establish determinants of necrotic core content and evaluate the distance from the ostium as an independent predictor of relative necrotic core content, a univariate and multivariate linear mixed models were applied. The following patient level variables were used in the analysis: age, gender, diabetes, smoking, insulin dependent diabetes, history of angina, body mass index, congestive heart failure, hypertension, hypercholesterolemia, prior myocardial infarction, HDL, chronic kidney disease, number of culprit vessels, history of cardiac interventions and aspirin use in the last 7 days. For lesion level data, a model with generalized estimating equations (GEE) approach was used to compensate for any potential cluster effect of multiple lesions in the same patient. All statistical analyses were performed using SAS version 9.1.3, Cary, NC.

RESULTS:

Baseline characteristics of the 697 patients enrolled in the study have been reported elsewhere (Supplemental Table 1; Stone G. et al., 2010). Briefly, Median age of the patients was 58.1 years, 24% were women and 17.2% had diabetes.

Table 1. Grayscale IVUS plaque longitudinal distribution from the ostium in all three coronary vessels excluding left main.

	Ostium to Max NC <30mm	Ostium to Max NC 30-60mm	Ostium to Max NC ≥60mm	Combined	P-Value[1] All Groups
Lesion Length & Volumetric Data					
Lesion Length (mm)					
median [IQR]	20.61 (12.34, 32.44)	17.13 (10.07, 32.98)	15.98 (7.05, 28.60)	18.95 (10.47, 31.75)	0.0122
Total EEM Volume (mm^3)					
median [IQR]	347.54 (191.93, 545.43)	260.38 (123.99, 558.20)	197.23 (78.58, 408.51)	302.27 (146.57, 528.64)	<.0001
Total Lumen Volume (mm^3)					
median [IQR]	176.04 (97.53, 262.30)	130.80 (59.05, 268.98)	105.96 (43.05, 214.11)	152.25 (75.43, 258.52)	<.0001
Total Plaque & Media Volume (mm^3)					
median [IQR]	170.93 (93.47, 294.29)	130.44 (60.48, 281.68)	97.54 (37.29, 201.06)	145.66 (70.69, 272.90)	<.0001
% Plaque Volume (%)					
median [IQR]	49.88 (45.48, 54.31)	49.78 (45.12, 53.02)	47.80 (42.37, 51.07)	49.44 (44.99, 53.48)	0.0033
Average EEM CSA (mm^3/mm)					
median [IQR]	16.97 (14.00, 20.24)	15.25 (11.27, 18.66)	13.52 (10.09, 17.71)	15.91 (12.39, 19.39)	<.0001
Average Lumen CSA (mm^3/mm)					
median [IQR]	8.37 (6.73, 10.39)	7.50 (5.60, 9.72)	6.87 (5.18, 9.19)	7.81 (6.15, 9.96)	<.0001
Average Plaque + Media CSA (mm^3/mm)					
median [IQR]	8.44 (6.81, 10.41)	7.24 (5.55, 9.53)	6.38 (4.55, 8.50)	7.73 (5.96, 9.80)	<.0001
Morphology Data					
Plaque Rupture	7.0% (22/314)	5.8% (11/191)	3.8% (4/104)	6.1% (37/609)	0.2379
Remodeling Index					
median [IQR]	0.88 (0.77, 0.98)	0.93 (0.84, 0.98)	0.95 (0.87, 1.01)	0.90 (0.81, 0.99)	<.0001

1 P-Value calculated using chi-square test for trend for categorical data and Jonckheere-Terpstra test for continuous data

Plaque burden and necrotic core content of lesions in the proximal 30 mm of the vessels versus 30-60 mm segment versus >60 mm distance from the ostium (Table 1 and 2):

TCFA lesions in the proximal 30 mm of the vessels were longer (20.6 mm vs 17.1 mm vs 16 mm; p=0.0122) and had greater plaque volume (171 mm^3 vs 130 mm^3 vs 98 mm^3; p<0.001). The percent plaque volume although also greater in the proximal 60 mm of the vessel than

Table 2: IVUS-VH longitudinal TCFA distribution from the ostium in all three coronary vessels (excluding left main).

	Ostium to Max NC <30mm	Ostium to Max NC 30-60mm	Ostium to Max NC ≥60mm	Combined	P-Value[1] All Groups
Lesion Phenotype					
TCFA	100.0% (314/314)	100.0% (191/191)	100.0% (104/104)	100.0% (609/609)	N/A
Volumetric Data					
Total Necrotic Core Volume (mm^3)					
median [IQR]	19.70 (9.46, 34.28)	14.42 (5.69, 30.50)	9.29 (3.41, 20.53)	16.05 (6.56, 31.54)	<.0001
Total Dense Calcium Volume (mm^3)					
median [IQR]	7.15 (3.04, 15.08)	4.97 (1.94, 12.70)	3.21 (1.52, 7.50)	5.80 (2.23, 12.70)	<.0001
Total Fibrous Tissue Volume (mm^3)					
median [IQR]	55.27 (27.95, 92.69)	34.66 (14.66, 93.85)	24.94 (8.70, 65.78)	43.79 (19.05, 87.14)	<.0001
Total Fibrofatty Volume (mm^3)					
median [IQR]	11.20 (5.09, 22.61)	5.71 (2.09, 19.53)	4.51 (1.12, 16.44)	8.87 (2.76, 20.49)	<.0001
Total Media Volume (mm^3)					
median [IQR]	73.60 (40.75, 114.21)	59.64 (30.65, 114.17)	49.24 (22.49, 91.22)	65.16 (34.15, 109.93)	0.0004
Average Necrotic Core CSA (mm^3/mm)					
median [IQR]	0.96 (0.67, 1.35)	0.79 (0.49, 1.20)	0.64 (0.37, 0.86)	0.85 (0.53, 1.25)	<.0001
Average Dense Calcium CSA (mm^3/mm)					
median [IQR]	0.33 (0.21, 0.56)	0.31 (0.16, 0.48)	0.23 (0.14, 0.36)	0.31 (0.17, 0.52)	<.0001
Average Fibrous Tissue CSA (mm^3/mm)					
median [IQR]	2.67 (1.86, 3.65)	2.17 (1.33, 3.40)	1.71 (0.96, 2.65)	2.40 (1.51, 3.46)	<.0001
Average Fibrofatty CSA (mm^3/mm)					
median [IQR]	0.57 (0.33, 0.98)	0.39 (0.16, 0.82)	0.29 (0.13, 0.69)	0.49 (0.21, 0.86)	<.0001
Average Media CSA (mm^3/mm)					
median [IQR]	3.62 (3.19, 3.97)	3.45 (2.98, 3.81)	3.21 (2.79, 3.67)	3.50 (3.05, 3.88)	<.0001
% Necrotic Core Volume					

Table 2: Continued

	Ostium to Max NC <30mm	Ostium to Max NC 30-60mm	Ostium to Max NC ≥60mm	Combined	P-Value[1] All Groups
median [IQR]	21.48 (16.02, 26.76)	21.50 (15.86, 28.36)	21.97 (16.17, 27.17)	21.67 (15.91, 27.17)	0.4093
% Dense Calcium Volume					
median [IQR]	7.77 (4.70, 12.51)	7.88 (5.01, 13.13)	7.49 (4.99, 12.65)	7.77 (4.94, 12.81)	0.7036
% Fibrous Tissue Volume					
median [IQR]	56.91 (51.10, 61.67)	57.60 (51.88, 62.58)	58.63 (51.47, 62.63)	57.43 (51.24, 62.12)	0.1587
% Fibrofatty Volume					
median [IQR]	12.09 (8.33, 17.69)	10.65 (6.41, 15.84)	10.04 (6.74, 15.27)	11.33 (7.25, 16.61)	0.0012

1 P-Value calculated using chi-square test for trend for categorical data and Jonckheere-Terpstra test for continuous data

the very distal portion was not different in the first and mid 30 mm of the vessel (50% vs 50% vs 47.8%; p=0.0033). The numbers of plaque ruptures decreased from proximal to distal but the difference did not reach statistically significant level (7% vs 5.8% vs 3.8%; p=0.2379). Total necrotic core volume was also the highest in the proximal 30 mm of the vessel (19.7 mm^3 vs 14.4 mm^3 vs 9.3 mm^3; p<0.001), however similar difference in volumes of dense calcium, fibrous tissue and fibrofatty volume were observed and the percentage necrotic core volume was no different from proximal to distal vessel (21.5% vs 21.5% vs 22%; p=0.4093).

Tables 3 summarizes the plaque burden and necrotic core content differences along the proximal, mid and distal segments of LAD, Circumflex (RCX) and RCA respectively. Notably, the number of plaque ruptures in the proximal LAD 5.1% is statistically significantly different than in the mid and distal LAD (1.8% and 0%; p=0.0018; data not shown). The pattern of plaque volume and necrotic core content distribution is similar to that shown in the pooled analysis of all vessels. The percent necrotic core was 13.5% vs 13.8% vs 13.8% (p=0.1158). The percentage of lesions classified as thin cap fibroatheromas (high risk lesions) did not differ between the proximal and distal LAD (24.4% vs 22.2% vs 24.2%; p=0.7167). Thin cap fibroatheromas were in fact more frequent in the mid and distal rather than in the proximal circumflex vessel (18.2% vs 28% vs 30.4%; p=0.0022) and percent necrotic core volume was higher in the most distal segment (10.4% vs 12.9% vs 13.5%; p=0.0002). In the right coronary artery there was no difference from proximal to distal in the number of plaque ruptures (5.2% vs 5.7% vs 3.4%; p=0.3316), there was no statistically significant difference in the proportion of thin cap fibroatheromas from proximal to distal and percentage of the necrotic core was highest in the distal segment (9.8% vs 9.1% vs 11.1%; p=0.0357). **Figure 1** illustrates the distribution of the necrotic core rich lesions along the three main coronary arteries every 10 mm. While the necrotic core lesions are almost equally distributed in the proximal, mid and distal 30 mm of the vessel, there is clearly lower number of necrotic core lesions in the most distal vessel (>90 mm distance from the

Table 3. Distribution of IVUS-VH plaques in the three coronary vessels

	Ostium to Max NC <30mm	Ostium to Max NC 30-60mm	Ostium to Max NC ≥60mm	Combined	P-Value[1] All Groups
LAD					
TCFA	24.4% (138/566)	22.2% (61/275)	24.2% (24/99)	23.7% (223/940)	0.7167
ThCFA	49.5% (280/566)	39.6% (109/275)	29.3% (29/99)	44.5% (418/940)	<.0001
PIT	22.4% (127/566)	32.7% (90/275)	40.4% (40/99)	27.3% (257/940)	<.0001
Fibrotic	2.3% (13/566)	3.6% (10/275)	5.1% (5/99)	3.0% (28/940)	0.0947
Fibrocalcific	1.4% (8/566)	1.8% (5/275)	1.0% (1/99)	1.5% (14/940)	0.9859
Any FA (TCFA or ThCFA)	73.9% (418/566)	61.8% (170/275)	53.5% (53/99)	68.2% (641/940)	<.0001
LCX					
TCFA	18.2% (87/477)	28.0% (56/200)	30.4% (14/46)	21.7% (157/723)	0.0022
ThCFA	36.3% (173/477)	27.5% (55/200)	21.7% (10/46)	32.9% (238/723)	0.0059
PIT	41.7% (199/477)	41.0% (82/200)	47.8% (22/46)	41.9% (303/723)	0.6523
Fibrotic	2.5% (12/477)	3.5% (7/200)	0.0% (0/46)	2.6% (19/723)	0.7963
Fibrocalcific	1.3% (6/477)	0.0% (0/200)	0.0% (0/46)	0.8% (6/723)	0.1015
Any FA (TCFA or ThCFA)	54.5% (260/477)	55.5% (111/200)	52.2% (24/46)	54.6% (395/723)	0.9480
RCA					
TCFA	21.2% (89/420)	24.8% (74/298)	25.0% (66/264)	23.3% (229/982)	0.2179
ThCFA	36.0% (151/420)	32.2% (96/298)	35.2% (93/264)	34.6% (340/982)	0.7441
PIT	39.5% (166/420)	39.3% (117/298)	36.4% (96/264)	38.6% (379/982)	0.4334
Fibrotic	2.1% (9/420)	2.3% (7/298)	2.7% (7/264)	2.3% (23/982)	0.6702
Fibrocalcific	1.2% (5/420)	1.3% (4/298)	0.8% (2/264)	1.1% (11/982)	0.6430
Any FA (TCFA or ThCFA)	57.1% (240/420)	57.0% (170/298)	60.2% (159/264)	57.9% (569/982)	0.4587

ostium) with skewing of the distribution to the right. The skewing is most prominent in the LAD followed by RCX and least prominent in the RCA. **Figure 2** shows similar distribution for thin cap fibroatheroma lesions (TCFAs).

Comparison between thin cap fibroatheromas (TCFA) and other tissue types (non-TCFA) (Table 4):

TCFA lesions were longer than non-TCFA lesions (18.7 mm vs 9.9 mm; p<0.0001), had larger plaque volume (144 vs 70 mm^3; p<0.0001) and slightly higher percentage plaque volume (49% vs 47%; p<0.0001). Plaque ruptures were present in 6.2% of TCFAs vs 2.9% of non-TCFAs

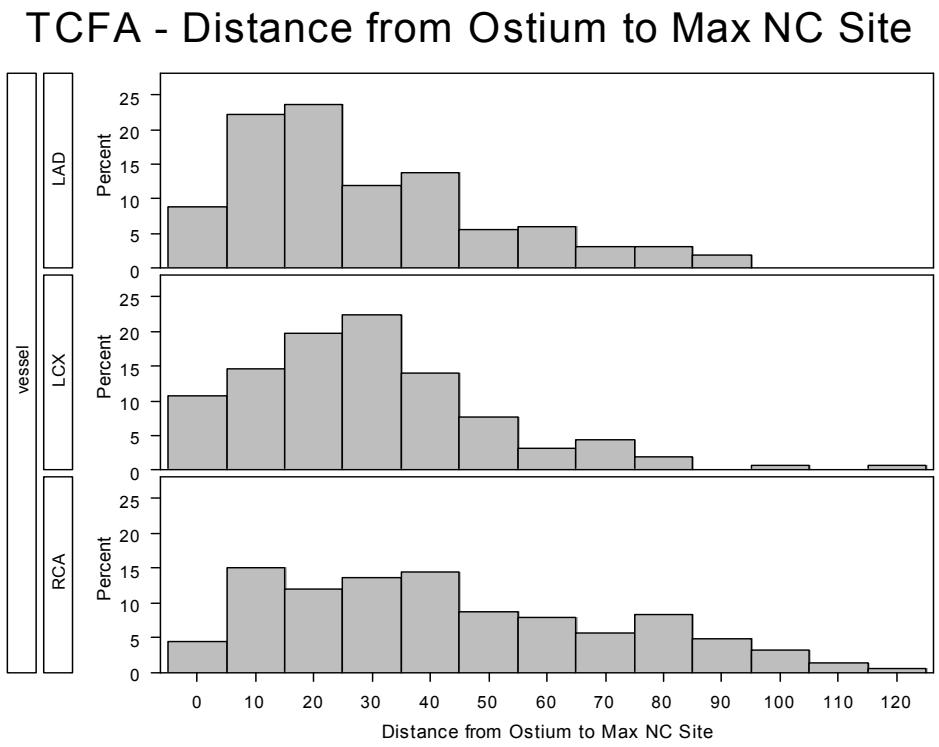

Figure 2. Distribution of thin cap fibroatheroma lesions from proximal to distal in the LAD, RCX and RCA in 10 mm segments.

(p<0.0001). Median distance from the ostium to a maximal necrotic core lesion was 28.8 mm for a TCFA lesion and 24 mm for non-TCFA lesion (p=0.0002). Median volume of necrotic core in the TCFA lesion was 15.9 mm^3 versus 3 mm^3 in a non-TCFA (p<0.0001). Median percent necrotic core volume was 21.8 percent for TCFA versus 9.2 percent for non-TCFA (p<0.0001).

Multivariate logistic model:

In order to determine whether the distance from the ostium was an independent predictor of necrotic core rich plaque a multivariate logistic regression was performed. Of all the clinical characteristics used as co-variates the following were used in the final model: history of cardiac interventions, lesion length measured by IVUS, percent plaque volume, remodeling index, age, history of angina, use of aspirin in the last 7 days and hypercholesterolemia. There was no multicollinearity in the model and the model was adjusted for clustering. The distance from the ostium was not a statistically significant predictor of the presence of TCFA or necrotic core rich lesions (**Table 5 and 6**).

Table 4. Comparison of the TCFA and non-TCFA lesions with respect to their IVUS grayscale and VH characteristics and distance from the vessel ostium.

	TCFA	Non TCFA	Combined	P-value
Geometrical Data				
Lesion Length (mm)				
median [IQR]	18.73 [10.07,31.32]	9.85 [5.15,18.31]	11.52 [5.73, 21.64]	<0.0001
Total EEM Volume (mm^3)				
median [IQR]	301.13 [145.88,525.98]	147.92 [74.15,291.28]	171.72 [82.41, 352.05]	<0.0001
Total Lumen Volume (mm^3)				
median [IQR]	151.60 [74.21,255.43]	77.23 [39.24,148.85]	88.45 [43.62, 176.04]	<0.0001
Total Plaque & Media Volume (mm^3)				
median [IQR]	143.81 [69.69,271.82]	70.23 [33.92,142.57]	82.09 [37.78, 172.06]	<0.0001
% Plaque Volume (%)				
median [IQR]	49.3 [44.9,53.5]	47.2 [43.7,51.2]	47.6 [43.9, 51.7]	<0.0001
Average EEM CSA (mm^3/mm)				
median [IQR]	16.06 [12.52,19.80]	15.50 [11.81,19.98]	15.63 [11.97, 19.94]	0.08
Average Lumen CSA (mm^3/mm)				
median [IQR]	7.94 [6.22,10.21]	7.90 [6.04,10.40]	7.90 [6.07, 10.34]	0.97
Average Plaque + Media CSA (mm^3/mm)				
median [IQR]	7.89 [6.02,9.85]	7.32 [5.55,9.63]	7.46 [5.60, 9.68]	0.002
Compositional data				
Total Necrotic Core Volume (mm3)				
median [IQR]	15.91 [6.53,31.66]	3.02 [1.04,8.18]	4.39 [1.43, 12.62]	<0.0001
Total Dense Calcium Volume (mm3)				
median [IQR]	5.76 [2.18,12.89]	1.15 [0.32,3.81]	1.77 [0.45, 5.75]	<0.0001
Total Fibrous Tissue Volume (mm3)				
median [IQR]	42.17 [18.89,87.14]	21.39 [9.33,49.28]	25.32 [10.35, 56.38]	<0.0001
Total Fibrofatty Volume (mm3)				
median [IQR]	8.85 [2.67,19.88]	7.83 [2.93,18.26]	8.04 [2.89, 18.94]	0.72
Total Media Volume (mm3)				
median [IQR]	64.29 [33.48,108.91]	33.02 [17.16,62.89]	38.60 [19.09, 75.19]	<0.0001
Average Necrotic Core CSA (mm3/mm)				
median [IQR]	0.87 [0.54,1.28]	0.31 [0.16,0.57]	0.40 [0.20, 0.76]	<0.0001
Average Dense Calcium CSA (mm3/mm)				
median [IQR]	0.31 [0.17,0.53]	0.12 [0.05,0.29]	0.16 [0.06, 0.36]	<0.0001

Table 4: Continued

	TCFA	Non TCFA	Combined	P-value
Average Fibrous Tissue CSA (mm3/mm)				
median [IQR]	2.42 [1.54,3.52]	2.28 [1.47,3.45]	2.33 [1.47, 3.45]	0.34
Average Fibrofatty CSA (mm3/mm)				
median [IQR]	0.49 [0.21,0.88]	0.83 [0.42,1.47]	0.74 [0.36, 1.34]	<0.0001
Average Media CSA (mm3/mm)				
median [IQR]	3.53 [3.07,3.91]	3.49 [2.99,3.93]	3.50 [3.02, 3.92]	0.45
% Necrotic Core Volume				
median [IQR]	21.8 [15.9,27.2]	9.2 [4.9,14.7]	11.5 [5.9, 18.3]	<0.0001
% Dense Calcium Volume				
median [IQR]	7.8 [4.9,12.9]	3.4 [1.4,7.4]	4.4 [1.8, 8.8]	<0.0001
% Fibrous Tissue Volume				
median [IQR]	57.2 [51.2,62.1]	61.4 [54.9,66.9]	60.2 [54.0, 65.8]	<0.0001
% Fibrofatty Volume				
median [IQR]	11.3 [7.2,16.6]	21.8 [14.8,30.7]	18.9 [12.2, 27.9]	<0.0001
IVUS Distances				
Distance from Ostium to MLA				
median [IQR]	32.16 [16.41,50.68]	26.06 [9.71,47.25]	27.40 [11.15, 47.83]	<0.0001
Distance from Ostium to Distal Edge				
median [IQR]	40.95 [23.73,59.72]	32.15 [14.66,53.41]	34.71 [16.53, 55.22]	<0.0001
Distance from Ostium to Proximal Edge				
median [IQR]	16.45 [2.38,38.27]	15.92 [2.30,38.02]	16.02 [2.33, 38.10]	0.80
Distance from Ostium to Max NC				
median [IQR]	28.78 [13.32,46.73]	23.95 [9.25,45.09]	24.97 [10.18, 45.63]	0.0002

DISCUSSION

The main finding of this substudy of the PROSPECT trial aimed at examining the longitudinal distribution of necrotic core rich high risk plaque and IVUS-VH derived thin cap fibroatheromas (TCFAs) are the following: 1. The distance from the vessel ostium is not a significant predictor overall of TCFA or necrotic core rich plaque location., 2. Plaque ruptures appear to be more frequent in the proximal 30 mm of the LAD but not in the LCX or the RCA., 3. Plaque ruptures are in fact more frequent in the mid and distal vessel for the RCX and distal segment in the RCA., 4. Percent necrotic core volume is non-different in the first, second and third 30 mm segment of the vessel.

While histopathologic data from the post-mortem specimens[12] and epidemiological data from the acute myocardial infarction patients[3, 5] gathered over the decades appeared

Table 5. Multivariate GEE model. The distance from the ostium is not a significant independent predictor of TCFA distribution.

# Subjects	Multivariate Predictors*	Coefficient	Standard Error	p value	Odds Ratio [95% C.I.]
2550	Distance from Ostium to Max NC (10mm increase)	0.0288	0.0182	0.1126	1.03 [0.99, 1.07]
	History of cardiac intervention prior to the current ACS	-0.5990	0.2578	0.0202	0.55 [0.33, 0.91]
	IVUS lesion length (1mm increase)	0.0370	0.0038	<0.0001	1.04 [1.03, 1.05]
	% Plaque Volume (10 mm3 unit increase)	0.1797	0.1026	0.0800	1.20 [0.98, 1.46]
	Remodeling index (1 unit increase)	-0.6383	0.3603	0.0765	0.53 [0.26, 1.07]
	Age (10 year increase)	-0.1911	0.0648	0.0032	0.83 [0.73, 0.94]
	History of Angina	-0.4246	0.1763	0.0160	0.65 [0.46, 0.92]
	Use of aspirin in the last 7 days	0.1751	0.1508	0.2456	1.19 [0.89, 1.60]
	Hypercholesterolemia Requiring Medication	0.1515	0.1453	0.2973	1.16 [0.88, 1.55]

Table 6. Multivariate GEE model. The distance from the ostium is not a significant independent predictor of necrotic rich lesion distribution.

# Subjects	Multivariate Predictors*	Coefficient	Standard Error	p value
2094	Intercept	16.5342	1.9940	<0.0001
	Distance from Ostium to max NC	0.0061	0.0062	0.3262
	History of cardiac intervention prior to the current ACS	0.9028	1.0637	0.3960
	Gender: Male	-1.3185	0.6936	0.0573
	History of angina	-1.3689	0.6585	0.0376
	Use of aspirin in the last 7 days	0.6063	0.6459	0.3479
	Hypercholesterolemia requring medication	0.8516	0.6115	0.1638
	Tobacco use within last month	-0.8712	0.5702	0.1266
	% Plaque Volume	0.0539	0.0319	0.0910
	MLA	-0.5217	0.0741	<0.0001
	Remodeling index	-2.2607	0.8556	0.0082

to suggest that the proximal one third of each major coronary vessel tends to be the site of plaque ruptures[6], up until recently the characteristics of these plaque rupture-prone lesions could not be examined in vivo due to lack of appropriate intravascular imaging tools. With the availability of IVUS and Virtual histology we have gained the ability to examine vessel walls and the plaque characteristics including its necrotic core content [8], (Garcia-Garcia HM et al; 2009). Small single center pilot studies appeared to suggest that using this new methodology we could indeed see that necrotic core rich lesions and IVUS-VH derived TCFAs tended to be

more proximally distributed and the distance from the ostium was a predictor of higher lipid content.[7] This finding opened an attractive option of targeting therapy to the proximal one third of the major coronary vessels to prevent progression of atherosclerosis or even restore the normal architecture of the vessel by scaffolding the rupture-prone plaque ([13]; Serruys et al., personal communication; Wykrzykowska et al., TCT 2009).

In this large multicenter natural history study of patients with acute coronary syndromes we failed to replicate the preliminary findings of the single center trial with respect to clustering of the necrotic rich core lesions in the proximal one third of the vessel. One of the obvious differences between the methodologies used in the Valgimigli study[7] is that it imaged a small number of patients and focused on the most proximal 40 m of the vessel, breaking it up into 10 mm segments to examine the gradient of necrotic core distribution. Only one vessel was imaged. With such small number of highly selected patients there may have been a chance effect occurring in the multivariate model which established the distance from the ostium as a significant predictor of necrotic core rich plaque content. It is also possible that in our study, patients who had plaque ruptures in the proximal vessel were treated as an index lesion and that segment was subsequently excluded from analysis biasing the results. In addition while the necrotic core content of the plaque may be similar in all three 30 mm segments of the vessels, we have noted that in the LAD plaque ruptures were more frequently observed in the proximal 30 mm segment. This may have to do with local conditions such as low shear stress which is known to up-regulate pro-inflammatory markers on the endothelium[14] and presence of bifurcations. The latter factor may explain potentially why plaque ruptures would be more frequent in the distal RCA bed as the major bifurcation in that vessel into RPL and RDP is indeed located in its distal portion. In the LAD, on the other hand bifurcation with diagonal vessels occurs more proximally. We have recently demonstrated in fact that proximal rim of the bifurcations tends to be rich in necrotic core plaque.[15] In addition, in the pilot study recently performed in our institution which randomized patients with IVUS-VD derived TCFAs to medical therapy versus scaffolding with a nitinol vShield device, the TCFAs were located in an equal distribution in the proximal or mid vessels. (Wykrzykowska et al., *submitted*).

Lastly, while the absolute plaque burden and necrotic core volume do decrease gradually from proximal to distal vessel (Figure 1), the percentage plaque burden and percentage necrotic core remain the same. This may relate to the conservation of mass and flow at the bifurcations previously shown by Murray, Hess and Kassab.[16, 17] Just as the branching of the coronary arteries and the relationship of parent and daughter vessels on quantitative angiography is based on the principle of minimizing the cost function and according to Murray's law the cube of the radius of a parent vessel equals the sum of the cubes of the radii of the daughter vessels, similar phenomenon may apply to the plaque burden and necrotic core volume. When the pullback is done in the segment 6 of the LAD before the bifurcation with the D1 (first 30 mm) and subsequently into segment 7 after the branch point (second 30 mm), plaque burden and necrotic core volume

decrease as the proportion of the volume is distributed into the daughter diagonal vessel and more distal LAD vessel. The percentages of plaque and necrotic core, however, stay the same.

LIMITATIONS

Although this was a large multicenter study which performed three-vessel intravascular IVUS and IVUS-VH examination there are several limitations that may have affected the results reported here: 1. The IVUS and IVUS-VH examination was performed after successful PCI treatment of the culprit lesion which was then excluded from examination. Thus the primary necrotic core rich plaque was treated and only secondary more quiescent TCFAs/necrotic core rich lesions were included in the study., and 2. In most patients 6-8 cm of the proximal vessels were examined and the most distal segment of the coronary tree was often excluded from analysis due to small diameter and risk of dissection with IVUS catheter.

CONCLUSION

In summary, we have found that the distance from the ostium is not a significant predictor of the necrotic core content or presence of TCFAs. It appears that the clustering of plaque ruptures in the proximal vessel segments observed in the epidemiological studies cannot be simply mechanistically linked to percent necrotic core or presence of the IVUS-VH derived TCFA. There is likely a more complex interplay between this vessel wall substrate and other local and hemodynamic factors that leads to plaque rupture and consequent acute vessel occlusion and myocardial infarction.

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Table 1S. Baseline characteristics

Age (years, median [IQR])	58.1 [50.5, 66.6]
Sex (female)	167/697 (24.0%)
Diabetes mellitus	119/694 (17.2%)
- Insulin requiring	21/694 (3.0%)
Metabolic syndrome	327/673 (48.6%)
Current cigarette use	328/687 (47.7%)
Hypertension	320/691 (46.3%)
Hyperlipidemia	279/632 (44.1%)
Prior myocardial infarction	73/693 (10.5%)
Family history of coronary artery disease	276/616 (44.8%)
Framingham risk score	7.0 [5.0, 9.0]
Prior percutaneous coronary intervention	77/696 (11.1%)
Clinical presentation	
- ST-segment elevation myocardial infarction	211/697 (30.3%)
- Non ST-segment elevation myocardial infarction	457/697 (65.6%)
- Unstable angina with ECG changes	29/697 (4.2%)
Body mass index (kg/m^2, median [IQR])	27.9 [25.1, 31.2]
Total cholesterol (mg/dl, median [IQR])	170.0 [149.0, 198.0]
LDL cholesterol (mg/dl, median [IQR])	93.6 [62.6, 121.4]
HDL cholesterol (mg/dl, median [IQR])	38.6 [33.0, 45.0]
Triglycerides (mg/dl, median [IQR])	124.0 [88.6, 177.1]
Hemoglobin A1C (median [IQR])	5.8 [5.3, 6.2]
Estimated creatinine clearance (ml/min, median [IQR])	97.8 [76.4, 123.6]
High sensitivity C-reactive protein (mg/dl, median [IQR])	7.2 [2.5, 18.9]
Number of diseased epicardial coronary arteries (core laboratory)*	
- One	149/697 (21.4%)
- Two	283/697 (40.6%)
- Three	265/697 (38.0%)
One vessel PCI performed	507/697 (72.7%)
Two vessel PCI performed	190/697 (27.3%)

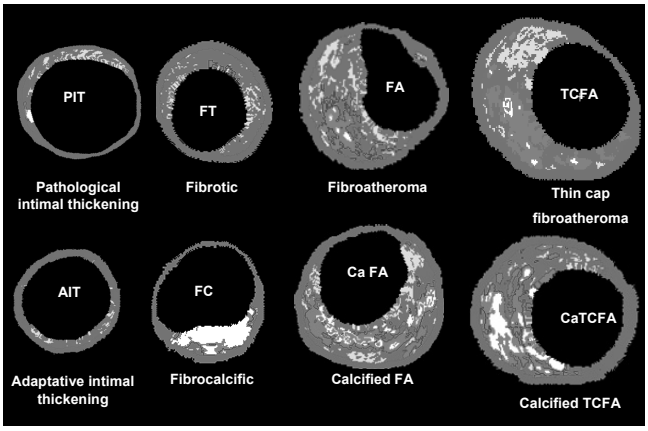

Figure 1S. Classification of plaque types based on IVUS-VH derived composition (Garcia-Garcia, HM et al., 2009)

Chapter 16

Effect of clopidogrel discontinuation at 1 year after drug eluting stent placement on soluble CD40L, P-selectin and C-reactive protein levels: DECADES (Discontinuation Effect of Clopidogrel After Drug Eluting Stent): a multicenter, open-label study

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Abstract Antiplatelet therapy with clopidogrel has been shown to reduce major adverse cardiac events in acute coronary syndromes and after percutaneous interventions. This effect is not only due to its anti-platelet effect but also possibly due to an anti-inflammatory effect. The effect of clopidogrel cessation after one year of therapy on markers of inflammation has been investigated in diabetics and showed an increase in platelet aggregation as well as hsCRP and surface P-selectin levels. This was an exploratory multicenter prospective open-label single arm study of 98 non-diabetic patients who had received one or more drug eluting stents and were coming to the end of their 12 months course of clopidogrel therapy. The effect of clopidogrel cessation on expression of biomarkers: sCD40L, soluble P-selectin and hsCRP was measured right before clopidogrel cessation (day 0), and subsequently at 1, 2, 3 and 4 weeks after drug withdrawal. A median increase in sCD40L expression from 224 to 324.5 pg/ml was observed between baseline and 4 weeks after clopidogrel cessation, which corresponded to a 39% mean percent change based on an ANCOVA model ($P < 0.001$). Over the 4 weeks observation period the change in sCD40L expression correlated weakly with soluble P-selectin levels (at 4 weeks Spearman's correlation coefficient = 0.32; $P = 0.0024$). Increase in P-selectin expression from baseline was statistically significant at week 1 and 2. Conversely, hsCRP level decreased by 21% at 1 week ($P = 0.008$) and was still reduced by 18% by 4 weeks ($P = 0.062$). The change in sCD40L expression appeared to vary with the type of drug eluting stent. Patients treated with drug eluting stents at 1 year after implantation display significant increase in sCD40L and decrease in hsCRP after clopidogrel cessation. Further studies should elucidate if this increase in sCD40L levels reflects solely the removal of the inhibitory effects of clopidogrel on platelet activity or rather an increase in pro-inflammatory state. The latter hypothesis may be less likely given decrease in hsCRP levels. Randomized studies are urgently needed to establish potential link of clopidogrel discontinuation and vascular outcomes.

Keywords Clopidogrel cessation · Platelet inhibition ·

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Introduction

Addition of clopidogrel to aspirin results in reduction in platelet reactivity [1]. This effect is particularly important in patients that have been treated with percutaneous coronary angioplasty and stenting [2]. Those who are non-responders to clopidogrel may be at higher risk of adverse events. Similarly, patients who interrupt their clopidogrel therapy may be at risk of major adverse cardiovascular event, among them stent thrombosis. Late stent thrombosis has been shown to occur after drug eluting stent implantation at a rate of 0.6% per year for up to 4 years [3]. While the pathogenesis of stent thrombosis is likely multifactorial, from stent malapposition (initial and acquired), geographic miss [4], through polymer-induced inflammation and incomplete tissue coverage [5], it has also been suggested that discontinuation of dual anti-platelet therapy plays a role in a large proportion of cases [6, 7]. Increased pro-coagulability after withdrawal of platelet inhibition is likely a major factor, as incomplete platelet inhibition has emerged as a significant risk factor for major adverse cardiac events [8–11]. What has also emerged as a possible mechanism is a potential increase in inflammation after clopidogrel cessation. The role of clopidogrel, as well as GP IIb/IIIa inhibitors, in modulating inflammation has been documented in multiple studies in the context of acute coronary syndrome and percutaneous coronary intervention [12–17]. The effect of clopidogrel cessation on inflammatory marker expression has not been investigated to date, other than in a small cohort of 54 diabetic patients [8]. In this study, platelet aggregation as well as hsCRP levels and surface platelet P-selectin levels increased significantly at 4 weeks after cessation of clopidogrel. It is not known whether cessation of treatment in non-diabetic patients also leads to pro-inflammatory marker upregulation and, if so, whether this could cause an increase in late stent thrombosis in a proportion of patients. In this exploratory study, we set out to describe the changes in the levels inflammatory markers sCD40L, P-selectin and hsCRP within 4 weeks of clopidogrel withdrawal in a 100 non-diabetic patients treated with stable doses of aspirin and statin.

Methods

Study design

The Discontinuation Effect of Clopidogrel After Drug Eluting Stent (DECADES) trial was an exploratory, multicenter, open-label, single-arm study to determine the effects of withdrawing clopidogrel therapy 12 months after implantation of DES on markers of inflammation and platelet activation in a non-diabetic population. The trial took place between 31 October 2007 and 30 June 2008 and was conducted at 6 sites in 4 European countries. The trial was approved by the institutional review board/independent ethics committee at every study centre. Written informed consent for trial participation was obtained from each patient. The trial was conducted in line with the guidelines of the current amendment to the Declaration of Helsinki, in accordance with the International Conference on Harmonization of Good Clinical Practice and applicable regulatory requirements.

Study population

Patients older than 18, who had received ≥ 1 DES of any type, were receiving statin and low-dose aspirin therapy, and were coming to the end of 12 months of therapy with clopidogrel 75 mg/day, were eligible to participate in the trial. Current medication doses (including aspirin and statins) must have been stable for 3 months. Patients were excluded from the study if they had a clinical history of diabetes mellitus, had uncontrolled hypertension (systolic blood pressure $>$ 180 mmHg or diastolic BP $>$ 100 mmHg), were intolerant of (or had contraindications to) aspirin or statins. The following patients were also excluded: those who had used within the previous 3 months or were currently using oral anticoagulants, dipyridamole or oral glucocorticoids; or were taking another investigational study medication or had taken an investigational study medication within the previous 30 days of the enrolment visit. Use of antiplatelet agents, other than stable doses of low-dose aspirin, was prohibited during the study.

Study protocol

After obtaining written informed consent, eligible patients were enrolled in the study. At this time, therapy with clopidogrel 75 mg/day was stopped, and stable dosages of statins and low-dose aspirin continued. The aim of the study was to evaluate the discontinuation effect of clopidogrel on biomarkers by taking blood samples prior to or on the day of

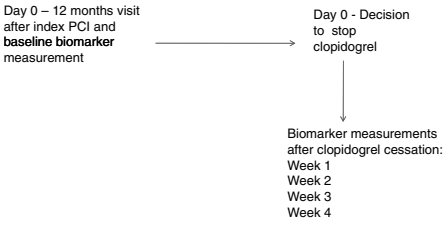


Fig. 1 Study flow chart

discontinuation of clopidogrel (baseline), and then at follow-up visits at the end of weeks 1, 2, 3 and 4 (Fig. 1).

Safety was evaluated during the entire study period by reporting any adverse events and serious adverse events. At each follow-up visit patients were asked if they had experienced any symptoms since clopidogrel withdrawal.

Biomarker assessments

Blood samples were obtained by direct venipuncture by an experienced phlebotomist. The primary endpoint was the mean change from baseline to week 4 in levels of sCD40L. Secondary endpoints included changes from baseline in plasma soluble P-selectin and hsCRP levels. All blood samples were frozen and sent for analysis to a central laboratory (Quintiles Limited, Livingston, UK). sCD40L, soluble P-selectin and hsCRP levels were analysed.

Inflammation markers

The blood samples collected for immunoassays were centrifuged at 1400 *g* for 10 min. Measurements of hsCRP, CD40L and P-selectin were performed in duplicate by enzyme-linked immunosorbent assay using commercially available kits from R&D Systems (Minneapolis, MN) for sCD40L and P-selectin and DPC Immulite for hsCRP (Block Scientific, Holbrok, NJ).

Statistical methods

This was an exploratory study and therefore data on the effect of withdrawing clopidogrel on sCD40L were not available for this study population. The sample size was not based on power considerations. Analyses were performed in the clopidogrel cessation population. All patients signed informed consent. The primary and secondary endpoint variables were evaluated using an ANCOVA model with baseline as covariate and investigative site as the main effect. As all three biomarkers showed a log-normal distribution at week 4, all ANCOVA analyses were performed on log-transformed values (using the natural logarithm transformation). The least-square mean was computed using a weighting scheme based on the actual sample sizes at each site. Data in the pre-specified analysis are presented as mean change from baseline, with 95% confidence intervals (CI). For all changes from baseline analyses, only subjects with at least a baseline and one post-clopidogrel withdrawal measurement were included. No imputation technique was used to attempt to account for missing data. Demographic and baseline characteristics, as well as safety data, were summarized using descriptive statistics, medians and interquartile ranges. Analyses were performed using the SAS 8.2 statistical package.

As post-hoc analysis, correlation between P-selectin levels and sCD40L was performed. In addition, the effect of the type of DES on the change from baseline in levels of sCD40L was assessed using an ANCOVA model with baseline as covariate and type of DES as the main effect.

Results

Study population

A total of 103 patients were enrolled in the study and 98 patients completed the protocol. Two patients failed to have baseline biomarker measurements. Two patients withdrew their consent and one patient no longer met the criteria for enrolment after baseline evaluation. Baseline characteristics are summarized in Table 1A. They were predominantly male with high proportion of patients having risk factors of hypertension, hypercholesterolemia and a prior history of myocardial infarction (63%) and none of the patients were diabetic by trial design. Mean total duration of clopidogrel use was 386 $\pm$ 62 days. All patients were also on stable aspirin and statin regimens (Table 1B). The type of stent implanted in the last procedure is listed in Table 2.

Adverse clinical events

There were no deaths, myocardial infarctions or stent thrombosis in this patient cohort after clopidogrel cessation. Two patients represented with symptoms, one with non-cardiac chest pain and another with angina symptoms, which did not require catheterization.

Biomarker assessments

Changes in inflammatory markers such as sCD40L, soluble P-selectin and hsCRP over 4 weeks after withdrawal of clopidogrel are shown in Table 3 (medians and interquartile ranges) and as mean percentage changes from baseline levels obtained at 12 months after clopidogrel administration. CD40L levels increased from a median of 224 to 324.5 pg/ml by week four after clopidogrel cessation (Table 3A).

P-selectin levels, on the other hand, appeared to increase slightly two weeks after clopidogrel cessation (from 44 to 50 ng/ml; $P < 0.001$) and then decreased to the baseline levels (45 ng/ml; $P = 0.488$) after 4 weeks (Table 3B). Changes in soluble P-selectin levels correlated only weakly with changes in sCD40L levels (correlation coefficient reached 0.32 at 4 weeks with $P = 0.024$; Fig. 2).

hsCRP levels decreased by 21% at 1 week ($P = 0.008$) and was still reduced by 18% by 4 weeks ($P = 0.062$) (Table 3C).

Table 1 (A) Demographic baseline patient characteristics; (B) length of clopidogrel, aspirin and statin treatment

Variable	Total ($N = 98$)
(A) Baseline characteristics	
Age (years)	
Mean	63.3
SD	8.5
Median (min, max)	63 (44, 81)
Gender, *N* (%)	
Male/female	78/20 (79.6/20.4)
Race, *N* (%)	
Caucasian	93 (94.9)
Asian oriental	5 (5.1)
Risk factors/comorbidities, *N* (%)	
History of hypertension	53 (54.1)
Hypercholesterolemia	80 (81.6)
Congestive heart failure	2 (2.0)
Prior myocardial infarction	62 (63.3)
Atrial fibrillation	3 (3.1)
Stroke	4 (4.1)
Transient ischemic attack	5 (5.1)
Peripheral arterial disease	8 (8.2)
CABG	6 (6.1)
Peripheral angioplasty or bypass surgery	1 (1.0)
Current smoker	16 (16.3)
Extent of exposure to clopidogrel and ASA and statins	Total ($N = 98$) Mean; SD
(B) Time elapsed from initial clopidogrel administration	
Clopidogrel use prior to withdrawal	
Duration (days)	385.8; 62.4
Last dose (mg/day)	75.0; 0.0
ASA use prior to clopidogrel withdrawal	
Duration (days)	763.5; 1041
Last dose (mg/day)	101.2; 27.2
Statin use prior to clopidogrel withdrawal	
Duration (days)	887.3; 1394
Last dose (mg/day)	43.1; 20.5

Table 2 Type of stent implanted at index procedure

Type of DES	Total ($N = 98$)
Implanted in most recent year, *N* (%)	
Paclitaxel eluting stent	45 (45.9)
Sirolimus eluting stent	33 (33.7)
Zotarolimus eluting stent	18 (18.4)
Everolimus eluting stent	2 (2.0)
Other type of stent	6 (6.1)
No stent implanted in most recent year	4 (4.1)
Type of stent implanted missing	2 (2.0)

sCD40L and stent type

Increase in CD40L varied with drug eluting stent used. Patients who were treated with zotarolimus stents appeared to have the greatest upregulation of sCD40L after clopidogrel discontinuation compared to the patients treated with paclitaxel, sirolimus eluting stents or bare metal stents (Fig. 3). The degree of sCD40L upregulation was dependent on baseline levels. There was no difference in total stent length between stent types implanted to confound the results.

Discussion

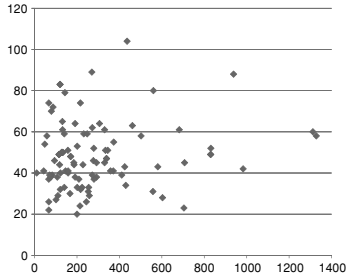
To our knowledge this is the first study to evaluate the effect of clopidogrel cessation at 1 year after initial stenting with drug eluting stents on inflammatory markers and markers of platelet activation in non-diabetic patients. This study was exploratory in nature, but nevertheless demonstrated a significant increase in CD40L expression after clopidogrel cessation indicative of possible enhanced platelet activation. Although not statistically significant at 4 weeks, P-selectin level increase seemed to parallel the CD40L changes, at least for the first 2 weeks, and correlated only weakly. P-selectin levels returned to baseline by 4 weeks suggesting that the stimulus causing this transient increase has disappeared. P-selectin is expressed upon platelet activation and binds the P-selectin glycoprotein ligand-1 on leukocytes [18]. P-selectin expression ultimately results in tissue factor expression by the monocytes and other inflammatory cytokines [12, 19]. More general marker of inflammation hsCRP decreased by 21% at 1 week. This opposite effect suggests that the increase in sCD40L levels reflects solely the removal of the inhibitory effects of clopidogrel on platelet activity rather than an increase in pro-inflammatory state. The interpretation of this result is greatly limited by lack of measure of platelet inhibition or overall thrombogenicity assay (such as thromboelastography) [20–22].

While considerable data are now available on inflammatory markers and their modification with anti-platelet therapy in the context of acute coronary syndromes and percutaneous intervention [23, 24] it is not clear what impact cessation of an anti-platelet agent in a stable patient 1 year post-procedure has on inflammation and procoagulability. Even more difficult to interpret are confounding effects of drug eluting stent type. There may be a significant interaction between endothelial dysfunction due to local inflammation from the drug eluting stent polymer and platelet activation. Based on the animal data from Nakazawa et al. [25], the zotarolimus stent should have the greatest late loss and restenosis rate but also the best

Table 3 Change in the levels of (A) sCD40L, (B) P-selectin and (C) hsCRP over 4 weeks presented as medians and interquartile ranges as well as mean percentage change

	Baseline	Week 1	Week 2	Week 3	Week 4
(A) sCD40L levels over 4 weeks after clopidogrel cessation					
CD40L					
Median	224	298	285.5	292	324.5
Max	1450	2483	2559	2871	2474
Min	10	36	23	42	18
Q3	364.5	478	569.5	509	541
Q1	129.5	161	160.75	155	199.5
Upper limit of normal	0 pg/ml				
Lower limit of normal	5000 pg/nl				
Average	310.2	434.9	469.1	412.9	446.1
Std	282.3	453.8	483.7	431.3	409.5
Mean percent change from baseline + SE		35% + 10%	39% + 11%	33% + 10%	39% + 11%
		$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$
(B) P-selectin levels over 4 weeks after clopidogrel cessation					
P-selectin					
Median	44	49	50	45.5	45
Max	104	114	138	147	150
Min	20	22	9	17	23
Q3	58	60.25	60.25	59	55.25
Q1	37	40	39	35	35
Upper limit of normal	51 ng/ml				
Lower limit of normal	113 ng/ml				
Mean	47.2	51.3	51.7	49.2	48.1
Std	16.2	17.2	18.7	20.1	20.3
Mean percent change from baseline + SE		9% + 2%	11% + 2%	4% + 3%	2% + 3%
		$P < 0.001$	$P < 0.001$	$P = 0.173$	$P = 0.488$
(C) Levels of CRP over 4 weeks after clopidogrel cessation					
hsCRP (mg/L)					
Median	1.59	1.25	1.1	1.11	1.22
Min	0.1	0.1	0.2	0.2	0.1
Max	57.9	27.7	15.6	62.9	19.5
Q3	3.70	2.61	3.46	3.29	2.83
Q1	0.74	0.72	0.66	0.62	0.61
Average	3.92	2.39	2.33	2.87	2.76
Std	7.73	3.60	2.63	6.70	3.96
Lower limit of normal	0 mg/L				
Upper limit of normal	11 mg/L				
Mean percent change from baseline + SE		−21% + 7%	−23% + 7%	−19.% + 8%	−18% + 8%
		$P = 0.008$	$P = 0.004$	$P = 0.038$	$P = 0.062$

endothelialization and the least local inflammation compared to sirolimus and paclitaxel stents. These results in animal models were ascribed to better biocompatibility of phosphotylcholine polymer used in zotarolimus-eluting stents than polyethelyne co-vinyl acetate and poly-n-butyl methacrylate (sirolimus eluting stents) and polystyrene-b-isobutyle-b-styrene (paclitaxel eluting stents). The latter two polymers have been shown to cause inflammation, local upregulation of tissue factor and macrophage activation [26]. We observed, however, the greatest sCD40L upregulation after clopidogrel discontinuation in patients treated with zotarolimus-eluting stents compared to sirolimus and paclitaxel drug eluting stents. This observation needs to be explored further in future studies and may



Spearman correlations between sCD40 Ligand and P-selectin

Visit	Baseline	Week 1	Week 2	Week 3	Week 4
Correlation	0.1034	0.2525	0.2323	0.2233	0.3183
(P-value) (1)	(0.3189)	(0.0152)	(0.0267)	(0.0334)	(0.0024)
Number of observation (N) (2)	95	92	91	91	89

Fig. 2 Correlation between sCD40L and P-selectin levels

reflect a complex interaction between systemic pro-inflammatory state, platelet activation and local peri-stent polymer-induced inflammation.

Our results in this cohort of patients with stable coronary disease are in agreement with Azar et al. [27], who found only a modest decrease in sCD40L after starting clopidogrel in stable patients (17% decrease after 8 weeks of therapy). It appears, however, that even at 12 months post-stenting clopidogrel still has an effect on inflammatory biomarkers and these effects are detectable in patients treated with stable doses of aspirin and statins. The poor correlation between sCD40L and P-selectin while somewhat perplexing, seem to echo the findings from the ELAPSE study on proinflammatory marker levels at 12 months after commencement of therapy [9]. Similarly, no correlation between more systemic hsCRP and more-platelet/atherosclerosis specific sCD40L/P-selectin was found in that study.

Lastly, a source of variability and the lack of strong correlations between different markers in our data set could be due to different doses of statins and potencies used in the study. Although a given patient had to be on a stable statin dose as the inclusion criteria, using variable doses with different down-modulation of the pro-inflammatory state (as reflected by hsCRP) could have made the patients on lower statin doses more likely to upregulate inflammatory markers after clopidogrel withdrawal. Ideally, when a larger study is performed all patients should be on a single statin such as rosuvastatin with LDL and hsCRP suppression goals optimized [28].

Limitations

Our study was limited by lack of biomarker level measurements before starting clopidogrel treatment as well as lack of concomitant data on platelet inhibition levels. The sample size was small and the study was exploratory in nature, and therefore not powered to detect clinical outcomes.

Conclusions

Patients treated with drug eluting stents at 1 year after implantation display significant increase in sCD40L and decrease in hsCRP after clopidogrel cessation. Further

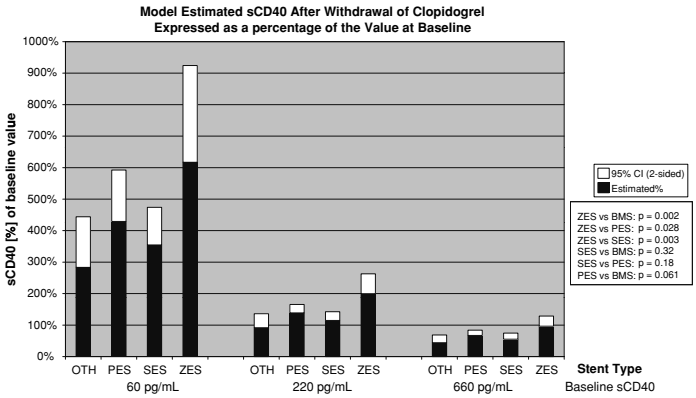


Fig. 3 Change in sCD40L at 4 weeks after clopidogrel cessation in patients treated with different types of drug eluting stents. *PES* paclitaxel drug eluting stent; *SES* sirolimus eluting stent; *ZES* zotarolimus eluting stent; *OTH* other; *BMS* bare metal stent

studies should elucidate if this increase in sCD40L levels reflects solely the removal of the inhibitory effects of clopidogrel on platelet activity or rather an increase in pro-inflammatory state. The latter hypothesis may be less likely given decrease in hsCRP levels. Zotarolimus stent implantation appears to be associated with the highest sCD40L upregulation after stopping clopidogrel but the clinical significance of this observation is uncertain.

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Chapter 17

EU grant Proposal full title: **Late stent thrombosis prevention using novel stent technologies assessed by combining frequency domain optical coherence tomography (OFDI) imaging with investigation of platelet biology.**

Proposal acronym: **LAST PROPHET**

LAte Stent Thrombosis prediction and PRevention based on frequency domain OPtical coHErence Tomography.

Coordinator: Prof. Dr. P.W.J.C. Serruys, EMC, The Netherlands

Synopsis:

Prevalence of late stent thrombosis has increased as the use of drug eluting stents spread to larger patient population with more complex coronary artery disease. Despite improvements in stent design and anti-platelet regimen patients with complex disease have a 9.4% incidence of definite and probable stent thrombosis at 5 years with 45% mortality. Acute coronary syndrome is one of the major risk factors for stent thrombosis.

The aim of the project will be:

1. To **integrate** basic, translational science and clinical trial results in order to gain insights into mechanisms of late stent thrombosis
2. To **solve** within 5 years important issues related to late stent thrombosis and develop a systematic approach aimed at prediction and prevention of late stent thrombosis strategies.
3. To **deliver** to the EU commission a detailed strategy to eliminate late stent thrombosis

This research project will be carried out by 12 Partners collaborating intensively in 11 work packages

Permanent endovascular metallic stent prosthesis and coronary vessel caging, as well as lack of stent strut coverage, strut malapposition and intraluminal defects have been proposed as possible imaging correlates of stent thrombosis risk.

LAST PROPHET aims to use novel molecular (metabolomic, proteomic, genomic) and imaging (Optical Frequency Domain Imaging) strategies to characterize the patients at risk for late stent thrombosis and stent platforms that minimize this risk.

The main driving hypothesis of the project is that:

1. biocompatible durable polymer;
2. biodegradable polymer and ;
3. polymer free platforms will reduce the risk of late stent thrombosis due to decreased inflammation; and that the
4. fully biodegradable stent platform will provide the ultimate solution to the late stent thrombosis problem. The latter technology uses a polylactic acid polymer (with fully biological catabolic products). In addition it elutes the drug everolimus drug which promotes autophagy of macrophages and thereby further reduces inflammation.

The LAST PROPHET project will enroll 400 patients with acute coronary syndromes randomized to 4 different stent platforms. All patients will be treated with aspirin and ticagrelor (novel P2Y12 inhibitor) and the lesion will be examined with IVUS VH for the presence of necrotic core.

Optical Frequency Domain Imaging (OFDI) will be performed after stent placement for optimization of result. Patients will be investigated after discontinuation of their ticagrelor at 1 year with OFDI for Neointimal Healing Index, endothelium-dependent vasomotion and shear stress measurement. These parameters will allow to differentiate which of the stent technologies allows for the best restoration of normal endothelial function and structure, thereby reducing the risk of late stent thrombosis.

Patients will undergo characterization of their pro-thrombotic phenotype and genotype. Patients will be clinically followed for 3 years for MACE and stent thrombosis events.

Pre-clinical studies in LAST PROPHET will correlate the imaging (OFDI) findings with its Neointimal

Healing Index to the histological and pathological findings.
This interdisciplinary medium scale project, based on translational approaches will demonstrate that the transient bioabsorbable scaffold could effectively replace the permanent metallic prosthesis in the treatment of atherosclerotic coronary stenosis while restoring normal vascular structure and function, thereby preventing the phenomenon of late stent thrombosis.
(Full proposal is available electronically on demand)

Part IV

Chapter 18

First case of stenting of a vulnerable plaque in the SECRITT I trial—the dawn of a new era?

Steve Ramcharitar, Nieves Gonzalo, Robert Jan van Geuns, Hector M. Garcia-Garcia, Joanna J. Wykrzykowska, Jurgen M. R. Ligthart, Evelyn Regar and Patrick W. Serruys

First case of stenting of a vulnerable plaque in the SECRITT I trial—the dawn of a new era?

Steve Ramcharitar, Nieves Gonzalo, Robert Jan van Geuns, Hector M. Garcia-Garcia, Joanna J. Wykrzykowska, Jurgen M. R. Ligthart, Evelyn Regar and Patrick W. Serruys

Background. A 63-year-old man presented with class II anginal symptoms.

Investigations. Cardiac catheterization, intravascular ultrasound (IVUS) virtual histology, optical coherence tomography and off-line palpography.

Diagnosis. The patient was diagnosed as having a culprit lesion in the left circumflex artery and a vulnerable plaque in the left anterior descending artery.

Management. The culprit lesion was treated with two overlapping drug-eluting stents. The vulnerable plaque was then treated with a self-expanding stent tailored to shield vulnerable plaques (vProtect® Luminal Shield). After dilatation of the stent with a low-pressure balloon, IVUS and optical coherence tomography showed excellent apposition of the stent to the vessel wall, with no signs of tissue prolapse or edge dissections. At the 6-month follow-up appointment, the stent showed complete tissue coverage without signs of in-stent restenosis.

Conclusions. Six months of follow-up has demonstrated that a patient with an IVUS-derived, thin capped fibroatheroma was successfully treated with a stent tailored to shield vulnerable plaques.

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The case

A 63-year-old man complained of chest pains during exercise. He was a retired public servant who exercised regularly in the gym. Risk factors for coronary artery disease included being an ex-smoker (he stopped smoking 18 months before his presentation but had smoked for 30 years previously), diabetes (oral hypoglycemics), hypertension, hypercholesterolemia and a strong family history of ischemic heart disease. On admission the patient had a pulse rate of 70 bpm and a blood pressure of 140/70 mmHg. Electrocardiography showed sinus rhythm (75 bpm) with good R wave progression and no apparent signs of cardiac ischemia. Transthoracic echocardiography demonstrated good left ventricular function with no significant valvular abnormalities. A significant lesion in the left circumflex coronary artery together with a non-flow-limiting lesion in the left anterior descending artery was noted on coronary angiography performed at the referring hospital. The right coronary artery was dominant and nondiseased.

The patient gave written informed consent to be enrolled in a prospective, randomized study investigating the proactive shielding of an intravascular ultrasound (IVUS)-derived, thin-capped fibroatheroma (IDTCFA).[1] The SECRITT I (Santorini Criteria[2] for Investigating and Treating Thin Capped Fibroatheroma) trial (Figure 1) required treatment of the culprit lesions with a drug-eluting stent, followed by treatment of the IDTCFA with a self-expanding stent tailored to treat vulnerable plaques—the vProtect® Luminal Shield (Prescient Medical, Inc., Doylestown, PA).[3]

The culprit lesion in the left circumflex coronary artery was crossed with a magnetically enabled Titan™ 3 mm wire (Stereotaxis, St Louis, MO) and stented with overlapping Xience V® stents, 2.5 × 12.0 mm and 2.5 × 28.0 mm (Abbott Vascular, Santa Clara, CA).

Quantitative coronary angiography of the lesion in the left anterior descending artery revealed a minimal luminal diameter of 1.76 mm, a proximal reference diameter of 2.94 mm, 40% diameter stenosis, and a lesion length of 11 mm (Figure 2a). Brightwire™ II Pressure Guide Wire (Volcano, Rancho Cordova, CA) demonstrated a fractional flow reserve of 0.84 with infused adenosine. IVUS virtual histology (IVUS-VH) performed using a 20 MHz Eagle Eye® catheter (Volcano, Rancho Cordova, CA) revealed a plaque with calcified IDTCFA morphology (Figure 3a, parts 1 and 2). The plaque had a minimal luminal area of 4.2 mm^2 and a plaque burden of 71%. The tissue composition of the plaque was 23% necrotic core (15.9 mm^3), 22% calcified tissue (14.9 mm^3), 8% fibrofatty tissue (5.8 mm^3) and 47% fibrotic tissue (31.9 mm^3). More than 10% of the confluent necrotic core was in direct contact with the vessel

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Competing interests
The authors declared they have no competing interests.

lumen on three consecutive frames. Use of optical coherence tomography (OCT; ImageWire™, LightLab Imaging Inc., Westford, MA) confirmed the presence of a thin fibrous cap (60 μm) encasing the necrotic core (Figure 3a, part 3).[4] A palpogram acquired simultaneously during an IVUS pullback (0.5 mm per second) with the Eagle Eye® catheter recorded a maximum Rotterdam classification (ROC) score of II (Figure 4a).[5]

The IDTCFA was treated with a 4.0 × 15 mm vProtect® Luminal Shield stent. Withdrawal of the distal outer sheath that houses the vProtect® Luminal Shield within the retractable delivery system deployed the self-expanding Nitinol stent. After low-pressure (6 atm) balloon dilatation (Voyager™ 4.0 × 12 mm, Abbott Vascular, Santa Clara CA) of the stent, quantitative coronary angiography showed a minimal luminal diameter of 3.05 mm and 0% diameter stenosis (Figure 2b). Post-stent IVUS-VH analysis (Figure 3b, parts 1 and 2) showed complete lesion coverage with good stent expansion and apposition. OCT (Figure 3b, part 3) revealed the stent struts fully apposed and superficially embedded in the underlying fibrous cap without evidence of fracture of the cap, prolapse of atherosed material between the vProtect® Luminal Shield scaffolding struts or edge dissections. The maximum ROC score after stent implantation was II (Figure 4b).

The patient was observed overnight and discharged home following a normal cardiac biochemical profile (creatine kinase = 125 ng/ml, creatine kinase–MB isoenzyme = 0.5 ng/ml and troponins <0.05 ng/ml). Medications on discharge were metformin 1 g twice daily, and aspirin 75 mg, atorvastatin 40 mg and felodipine 5 mg, once daily. The patient was also told to continue with clopidogrel 75 mg daily for 6 months.

At the 6-month follow-up, angiography showed no signs of stent restenosis (Figure 2c). On IVUS-VH the stent struts were well apposed and had an appearance similar to dense calcium (Figure 3c, parts 1 and 2). OCT examination showed complete tissue coverage of the stent, and there was no demonstrable increase in strain pattern on palpography (Figure 3c, part 3 and Figure 4).

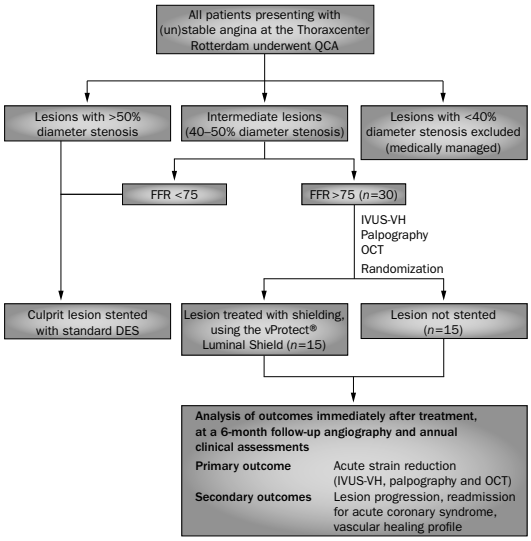

Figure 1 | Trial profile of the SECRITT I (Santorini Criteria for Investigating and Treating Thin Capped Fibroatheroma) trial. Abbreviations: DES, drug-eluting stent; FFR, fractional flow reserve; IVUS-VH, intravascular ultrasound virtual histology; OCT, optical coherence tomography; QCA, quantitative coronary angiography.

Discussion of diagnosis

Sudden cardiac death and acute coronary syndromes caused by acute thrombotic occlusion of the coronary lumen are common initial manifestations of coronary atherosclerosis.[6] Pathological examinations have demonstrated that intraluminal thrombi usually arise from plaque rupture, and thin-capped fibroatheroma (TCFA) has been identified as the plaque type most prone to rupture.[7] Such lesions are characterized by a large necrotic core (tissue with lipid-rich necrotic areas containing remnants of foam cells, lymphocytes, cholesterol clefts and microcalcification) covered by a thin fibrous cap (usually less than 65 μm thick) with outward remodeling, paucity of smooth muscle cells and intense macrophage infiltration.[8] Several biological factors (for example, focal inflammation and intraplaque hemorrhage) and mechanical factors might contribute to the weakening and final rupture of the fibrous cap that exposes the underlying thrombogenic material to the blood stream.[9]

The majority of TCFAs occur in the proximal portion of the three major epicardial coronary arteries, and more than 80% have luminal narrowing of less than 75% of the cross-sectional area (that is, less than 50% diameter stenosis).[10,11] Indeed, postmortem findings have suggested that most myocardial infarctions result from non-flow-limiting lesions rather than a critical blockage.[12] Similarly, coronary angiography in the months preceding an acute infarction often show that the culprit lesion had less than 50% diameter stenosis;[13] only approximately 15% of culprit lesions arise from lesions that had greater than 60% stenoses.[14] These findings tell us that even though coronary flow is not obstructed (because of outward [positive] remodeling), a critical plaque volume exists for determination of lesion vulnerability. The data suggest that the long-term prognosis of a patient might depend on far more detailed plaque assessment than angiography, and on adequate treatment of plaques at risk of rupture. The rationale for IVUS-VH analysis in plaque characterization has been supported by autopsy findings, particularly for TCFA identification.[15] Studies from our

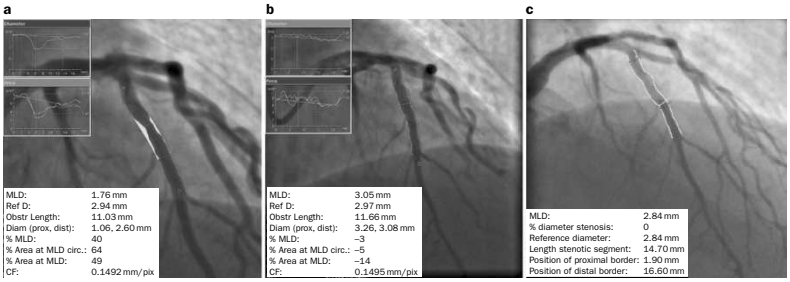

Figure 2 | Quantitative coronary angiography analysis of the intravascular-ultrasound-derived, thin-capped fibroatheroma. Analysis was performed **a** | before stenting **b** | immediately after treatment with the vProtect® Luminal Shield and **c** | at the 6-month follow-up appointment. Abbreviations: CF, calibration factor; MLD, minimal luminal diameter.

institution on IVUS-VH assessment of three vessels,[11,16] as well as the PROSPECT trial,[17] suggest that the frequency of IDTCFA correlates with postmortem pathological specimens from patients who had a myocardial infarction and IVUS-documented plaque ruptures (mean 2.08 per patient; range 0–6).

Identification of a ruptured plaque within the culprit lesion was first reported in 2002 in 24 patients referred for percutaneous coronary intervention after first acute coronary syndrome with troponin I elevation.[10] Interestingly, plaque rupture in the culprit lesion was found in only nine patients (37%). In 19 patients (79%), at least 1 plaque rupture was found somewhere other than the culprit lesion, such as in a different artery (in 70%) and in two other arteries (in 12.5% of the patients). Increasing evidence supports the notion that patients referred for coronary percutaneous interventions can often have non-flow-limiting plaques with high-risk morphology remotely located from the culprit lesion that cause the presenting symptoms. The identification and treatment of these prone-to-rupture or 'vulnerable' plaques could potentially prevent the occurrence of future coronary events. The limited number of TCFAs in each patient suggests that the pathology could be treated by focal approach. However, no large, published studies linking the presence of TCFA—detected *in vivo* by invasive techniques—to their imminent rupture and their associated clinical events exist to date.

Treatment and management

Currently, there are two strategies for managing patients after the identification of a TCFA. The conservative approach is based on the premise that as long as the positive and negative predictive value of these imaging techniques (OCT,[18] IVUS-VH[19]) in predicting the eminence of a clinical event has not been established, no local treatment is warranted. In the more liberal approach, a limited number of focal pathologies are randomly allocated to treatment or no treatment to allow the clinical and physiologic effect of TCFA shielding to be determined.

SECRITT I is a randomized, controlled pilot study ($n = 30$) conceived to evaluate the safety and feasibility of stenting a vulnerable plaque with a dedicated stent (the vProtect® Luminal Shield) compared with a medically treated, non-stented (control) group (Figure 1). In the study, intermediate lesions (quantitative coronary angiography 40–50%) remote from the culprit lesion are evaluated by fractional flow reserve measurements. Lesions with fractional flow reserve greater than 0.75 are then analyzed by IVUS-VH to identify IDTCFA before randomization to therapy. Lesions with a fractional flow reserve less than 0.75 are managed as the culprit lesions. Palpographic assessment, of the change in strain pattern of the IDTCFA, and OCT are used together in the evaluation of cap thickness and the effect of vProtect® Luminal Shield implantation on the morphology of the fibrous cap. These imaging modalities are normally not sufficiently accurate to detect TCFA when used alone, but are thought to offer an increased precision when used in combination. Change in strain pattern was used as a primary outcome in the SECRITT I trial because in the ABSORB trial palpography in 12 patients demonstrated that the mean number of frames with ROC III–IV per centimeter decreased from 1.22 ± 1.91 before stenting to 0.12 ± 0.31 after the procedure ($P = 0.0781$).[20] Similarly, the mean cumulative strain values (that is, all frames with ROC I–IV scores) changed from $0.50 \pm 0.27\%$ to $0.20 \pm 0.10\%$ ($P = 0.0034$).[20] Investigators involved in the ABSORB trial hypothesized that reductions in high strain values immediately after stenting might be because of a decrease in deformability of the stented vessel wall.[20]

The vProtect® Luminal Shield is uniquely designed so that it has mechanical properties that include self-expandable scaffoldings and an austenitic finish, and is precision engineered for stabilizing nonobstructive and relatively soft lesions. Standard workhorse drug-eluting stents are not ideally suited in this setting as the required high deployment pressure can critically deform the cap and result in rupture.[21] Animal studies, involving rabbit

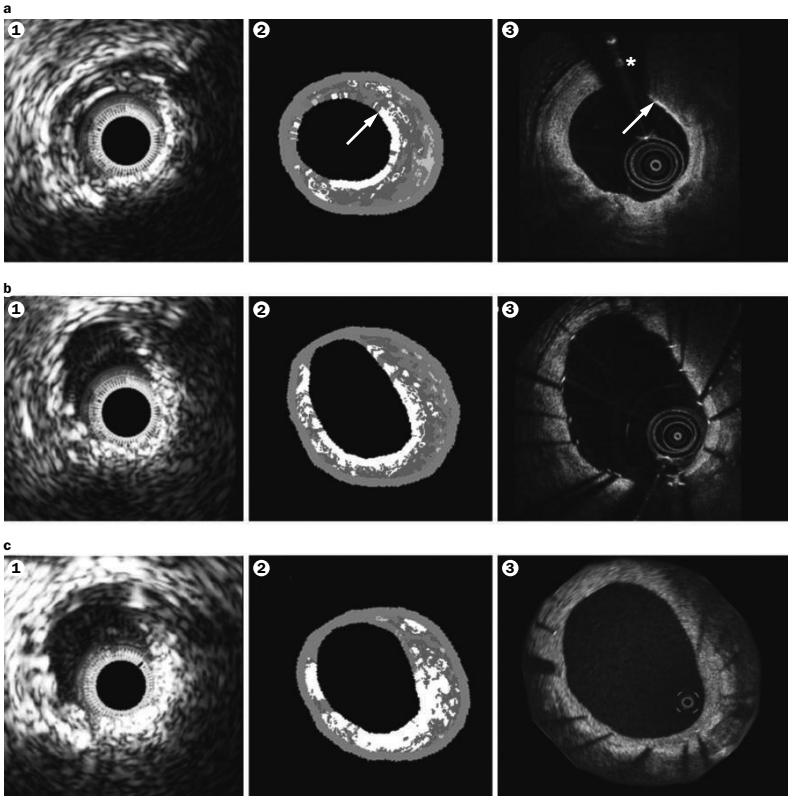

Figure 3 | Morphology of the patient's plaque with IVUS-derived, thin-capped fibroatheroma. Matched grayscale IVUS (1), IVUS-VH (2) and OCT (3) images of the IVUS-derived, thin-capped fibroatheroma **a** | before stenting with the vProtect® Luminal Shield, **b** | immediately after treatment with the vProtect® Luminal Shield and **c** | at the 6-month follow-up appointment. The arrow in panel a part 2 indicates the necrotic core in contact with the lumen. The arrow in panel a part 3 indicates the thin fibrous cap, and the asterisk indicates a guidewire artifact. In the IVUS-VH images (parts 2): red, necrotic core; dark green, fibrotic tissue; light green, fibrofatty tissue; and white, dense calcium. Abbreviations: IVUS, intravascular ultrasound; IVUS-VH, intravascular ultrasound virtual histology; OCT, optical coherence tomography.

iliac artery injury models, demonstrated that the vProtect® Luminal Shield can promote vascular healing to achieve complete endothelialization of the stented vessel segment in 7 days.[3]

Although atherosclerosis is a systemic disease, and aggressive management of cardiac risk factors is warranted,[22,23] many patients are on appropriate medical therapy, including statins and antihypertensives, when they present with an acute coronary syndrome. Mechanical modification of the plaque might be considered crude, but stent technology has radically changed over the years. New generation stents, such as the vProtect® Luminal Shield, push the frontier of stenting technology in a different direction and allow us to address the issue of the vulnerable plaque. However, as with conventional stenting approaches, procedural related acute complications, such as restenosis and thrombotic events, might occur. No long-term data on the vProtect® Luminal Shield exist to date, so the follow-up of this and other patients in the SECRITT I study will ultimately determine the success of mechanical shielding of a vulnerable plaque.

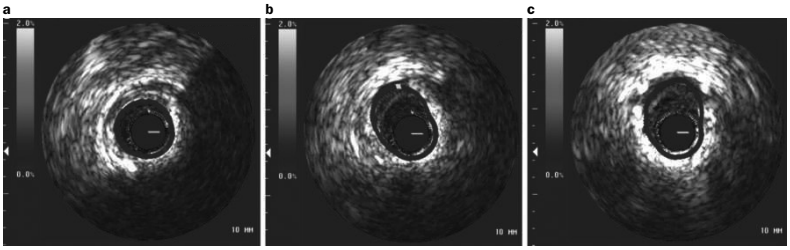

Figure 4 | Palpography of the intravascular-ultrasound-derived, thin-capped fibroatheroma. Palpography was performed **a** | before stenting with the vProtect® Luminal Shield, **b** | immediately after treatment with the vProtect® Luminal Shield, and **c** | at the 6-month follow-up appointment. The blue circle around the lumen indicates the absence of high strain areas.

Conclusions

The patient is enrolled in a prospective pilot trial (SECRITT I) aimed at evaluating the acute stabilization and long-term consequences of proactively stenting a vulnerable plaque. A patient with an IDTCFA was treated with a stent tailored for vulnerable plaques; data from the patient's 6-month follow-up appointment were very encouraging. Further follow-up of this and other patients will help determine if mechanical shielding of a vulnerable plaque is a feasible and safe treatment option.

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Chapter19

Comparison of acute vessel wall injury after self-expanding stent and conventional balloon-expandable stent implantation : a study with optical coherence tomography

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ABSTRACT

Background: The acute impact in vivo from a self-expanding stent on the vessel wall has not been sufficiently evaluated.

Objectives: We sought to compare acute in vivo injury on the vessel wall and clinical impact between a self-expanding coronary stent and conventional balloon-expandable stents immediately after stent implantation.

Methods: We included forty patients (45 vessels) with stable or unstable angina who were assigned to either the self-expanding stent (vProtect® Luminal Shield) group (n = 9; group 1) or the conventional balloon-expandable stent group (n = 36; group 2). Optical coherence tomography (OCT) was performed after stent deployment as were qualitative and quantitative assessments of tissue prolapse, intra-stent dissection, edge dissection, and incomplete stent apposition.

Results: Tissue prolapse was visible in all vessels in both groups. The corrected tissue prolapse area by stent length was larger in group 2 than group 1 (0.06 ± 0.06 vs. 0.02 ± 0.01 mm^2, p <0.001). Intra-stent dissection was more frequently seen in group 2 (33/36 vs. 4/9 vessels, p = 0.004) and the mean length of the dissection flap was greater in group 2 than in group 1 (277.6 ± 110.0 vs. 76.9 ± 103.7 μm, p<0.001). Although edge dissection was not detected in group 1, it was visible in 19/36 vessels (52.8%) in group 2. The frequency of incomplete stent apposition was not significantly different between group 2 and group 1 (23/36 vs. 7/9 vessels, p = 0.7) but the mean depth of incomplete stent apposition was greater in group 2 than in group 1(268.2 ± 72.1 vs. 178.2 ± 156.7 μm, p = 0.03).

Conclusions: A self-expanding stent was associated with less intra-stent dissection and edge dissection than conventional balloon-expandable stents with OCT.

INTRODUCTION

Although balloon-expandable stenting techniques with high pressure have proved to be useful for optimal stent implantation to reduce the risks of restenosis and subacute thrombosis, this stent deployment strategy may also increase the risk of creating vessel damage in the stented segment or at its edges 1. As a stent is expanded with high pressure, immediate injury occurs deep in the vessel wall within the stented segment as well as in the unscaffolded peristent margins 2. Importantly, several stent trials have drawn our attention to the problem of accelerated lumen loss at stent margins, which accounts for up to one-third of target-vessel revascularization in patients treated with balloon-expandable stents 3-5. On the other hand, a self-expanding stent allows deployment at lower pressures resulting in less intimal trauma. Late loss was significantly smaller at the peristent margins in the self-expanding stent than it was in the balloon-expandable stent 2.

Optical coherence tomography (OCT) is a high-resolution technique that allows very detailed assessment of the relationship between the stent and the vessel wall.

The objective of the present study was to qualitatively and quantitatively compare with OCT stent implantation-associated vessel wall injury between a self-expanding stent (vProtect® Luminal Shield) and conventional balloon-expandable stents, and to compare their clinical impacts during the hospitalization period.

METHODS

Study population

This study was conducted in single center of the Netherlands (Thoraxcenter, Erasmus MC). All consecutive 89 patients were performed OCT after stent implantation in native coronary arteries between May 2007 and March 2009 were included. Acute myocardial infarction and long lesion that needed over 50 mm of stent length (n = 33) were excluded. We also excluded 16 patients due to poor OCT images. Finally forty patients (45 vessels) with stable angina or unstable angina were included in the study. During the same period of time, nine patients enrolled in the SECRITT trial were included for evaluation of vProtect® Luminal Shield 6. All patients gave informed consent.

OCT acquisition

OCT acquisition was performed using a commercially available system for intracoronary imaging (LightLab Imaging Inc, Westford, MA, USA). In 5 cases, the occlusive technique was used in which a proximal, low-pressure (0.4 atm) occlusion balloon (Helios, Goodman Inc, Nagoya, Japan) was inflated with simultaneous distal flush delivery (lactated ringer; flow rate 0.8mL/sec) to remove blood from the vessel lumen. Images were acquired during a pullback rate of 1.0 mm/sec. In 40 cases, OCT was acquired with the non-occlusive technique. In this case, the Image Wire was positioned distal to the region of interest using a double-lumen catheter (Twin Pass catheter, Vascular Solutions Inc) that had been previously placed in the artery over a conventional guide wire. The automated pullback was performed at 3 mm/s (n = 39) or 20 mm/sec (n = 1,C7XR: LightLab Imaging Inc, Westford, MA, USA) while blood was removed by the continuous injection of iso-osmolar contrast (Iodixanol 370, Visipaque™, GE Health Care, Ireland) at 37° Celsius through the guiding catheter. Data were stored on CD for offline analysis.

Definitions of the acute impacts of stent implantation in OCT (Figure1)

Tissue prolapse was defined as protrusion of tissue between the stent struts without disruption of the continuity of the vessel luminal surface 7. Protrusion of tissue between struts was considered tissue prolapse only if the distance from the arc connecting adjacent stent struts to the greatest extent of protrusion was >50 μm 8. Intra-stent dissection was defined as disruption of the vessel luminal surface in the stent segment with a visible dissection flap 8.

Edge dissection was defined as disruption of the vessel luminal surface in the stent edge within the 5 mm proximal and distal segments. Incomplete stent apposition (ISA) was defined as at least one stent strut with detachment from the wall >1 thickness of the strut for the respective stent and unrelated with a side branch 9. Thrombus was defined as an irregular mass protruding into the lumen or an intraluminal mass unconnected from the surface of the vessel wall that had single-free shadowing in the OCT image 10.

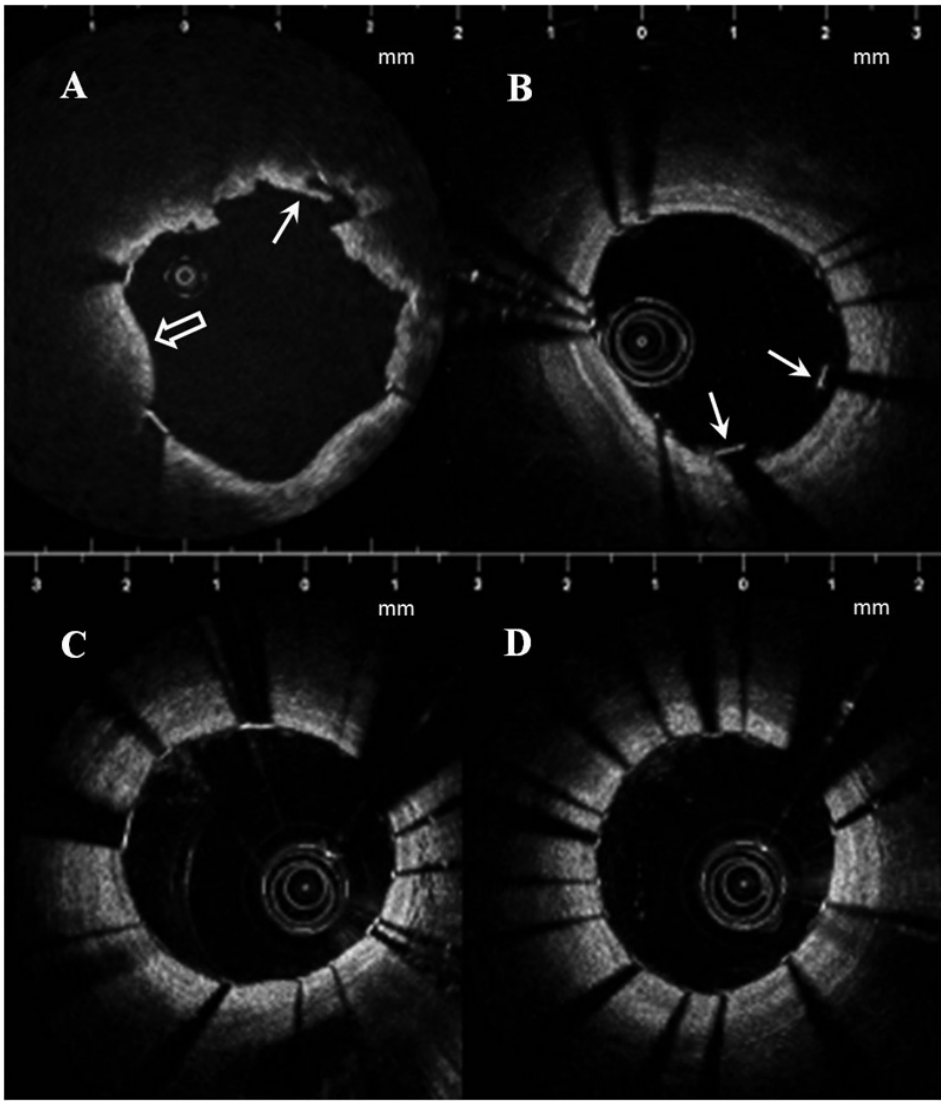

Figure 1. Various OCT images of acute impacts after stent implantation. (A) Tissue prolapse & intra-stent dissection; the white empty arrow points to an example of tissue prolapse with visible dissection flap (white arrow). (B) Edge dissection; a disruption of the vessel luminal surface in the edge regions within 5-mm proximal and distal to the stented region (white arrows). (C) Incomplete stent apposition; 3 stent struts are malapposed (white arrows). (D) Thrombus; an irregular mass protruding in the lumen accompanied by a shadow (white arrow).

Quantitative OCT analysis of the acute impacts of stent implantation 8

The analyzed region comprised the stented segment and the 5 mm proximal and distal peri-stent segments. The lumen and stent areas were measured at 1 mm intervals. In the case of tissue prolapse, the number of sites with tissue prolapse and the area were measured. Tissue

prolapse length was defined as the distance from the arc connecting adjacent stent struts to the greatest extent of protrusion. The area of tissue protruding between the stent struts was also measured. When there were signs of intra-stent dissection, the number of dissection flaps was counted and the length of the flap from its tip to the joint point with the vessel wall was measured. When edge dissection was present, the length of the dissection flap was measured in a similar way as described for the intra-stent dissection flap. At sites of ISA, maximum depth in single cut was measured and the average length is reported. The presence of thrombus was qualitatively assessed and maximum length of thrombus was measured. To account for differences in stent length, the number and total area of tissue prolapse and the number of dissection flaps were corrected according to the stent length and expressed on a per mm basis. Image analysts were blinded to the clinical and procedural characteristics.

Clinical follow-up

The presence of events (death, myocardial infarction, target lesion revascularization, target vessel revascularization and stent thrombosis) during the hospitalization period following stent implantation was registered in both groups. Myocardial infarction (MI) defined as chest pain together with ST-elevation or new left bundle branch block and an increase in cardiac enzymes (i.e. creatine kinase-MB fraction of 3 times the upper limit of normal) 8.

Statistical analysis

Continuous variables are expressed as mean± standard deviation. Categorical variables are expressed as percentages. Comparisons between groups were performed with the $\chi 2$ test for categorical variables. Continuous variables were compared with Student t test when they had a normal distribution and with nonparametric test (Mann-Whitney) when their distribution was not normal. A p value <0.05 was considered statistically significant.

RESULTS

Table 1 shows clinical and procedural characteristics. There were no significant differences between both groups. Group 2 had different stent types, 6 balloon-expandable bare-metal stents, 1 Paclitaxel-eluting stent, 3 Zotarolimus-eluting stents and 26 Everolimus-eluting stents. The frequency of ACC/AHA type B2 or C lesions was not significantly different, and the frequencies of pre-dilation and post-dilation did not differ significantly. However, stent length was significantly larger in group 2 than in group 1 (26.2 ± 8.8 and 17.1 ± 5.2 mm, respectively, $p = 0.001$).

Acute impacts of stent implantation assessed by OCT (Figure 2)

After stenting, the lumen area was 7.9 ± 2.3 mm^2 in group 1 and 7.3 ± 1.7 mm^2 in group 2 ($p = 0.3$). The mean and minimum stent areas were 8.0 ± 2.3 and 6.3 ± 2.3 mm^2 in group 1

Table 1. Clinical and pçrocedural characteristics of the self-expanding stent (vProtect® Luminal Shield; group 1) vs. the balloon-expandable stent (group 2).

	Group 1 (n = 9)	Group 2 (n = 36)	p
Demographics			
Age	68.4 ± 9.9	62.9 ± 10.0	0.15
Male	5 (55.6)	28 (77.8)	0.22
Hypertension	8 (88.9)	23 (63.9)	0.24
Diabetes Mellitus	0	7 (19.4)	0.32
Dyslipidemia	8 (88.9)	26 (72.2)	0.42
Smoker	2 (22.2)	9 (25.0)	1.0
Cardiac history			
Previous MI	5 (55.6)	16 (44.4)	0.71
Previous CABG	0	2 (5.6)	1.0
Previous PCI	4 (44.4)	16 (44.4)	1.0
Vessel			0.53
LAD	3 (33.3)	19 (52.8)	
LCX	1 (11.1)	5 (13.9)	
RCA	5 (55.6)	12 (33.3)	
Stent type			<0.001
BMS	9 (100)	6 (16.7)	
Paclitaxel-eluting stent	0	1 (2.8)	
Zotarolimus-eluting stent	0	3 (8.3)	
Everolimus-eluting stent	0	26 (72.2)	
Lesion type B2 or C	2 (22.2)	17 (47.2)	0.26
Stent length (mm)	17.1 ± 5.2	26.2 ± 8.8	0.006
Implantation pressure (atm)	0	16.3 ± 3.7	<0.001
Predilatation	2 (22.2)	18 (50.0)	0.25
Postdilatation	5 (55.6)	14 (38.9)	0.62

Values are presented as n (%) or mean ± SD. BMS: bare-metal stent

and 7.6 ± 1.9 and 6.0 ± 1.7 mm² in group 2, respectively. Although all vessels in both groups showed tissue prolapse, the corrected number of tissue prolapse and corrected area by stent length were larger in group 2 than in group 1 (Table 2). The vProtect® Luminal Shield had less intra-stent dissection than balloon-expandable stents and the corrected number of dissections and average length of intra-stent dissection flap were all lower (Table 2). In addition, there was no edge dissection in group 1, while in group 2 the distal and proximal edges presented edge dissection in 14/36 (38.9%) and 10/36 (27.8%) vessels, respectively. Among patients in group 2, five vessels (14%) showed both proximal and distal edge dissection. The average length of the dissection flap was 515 ± 403 µm. Regarding ISA, seven out of 9 vessels in group 1 and 23 out of 36 vessels in group 2, respectively, showed at least one malapposed stent strut; the maximum depth of ISA was 178 ± 156 µm in group 1 and 267 ± 72 µm in group 2 (p = 0.03). Images suggestive of thrombus were visible in 2 vessels in group 1 and 16 in group 2. Maximum length of visible thrombus was 131 ± 30 µm and 298 ± 122 µm, respectively.

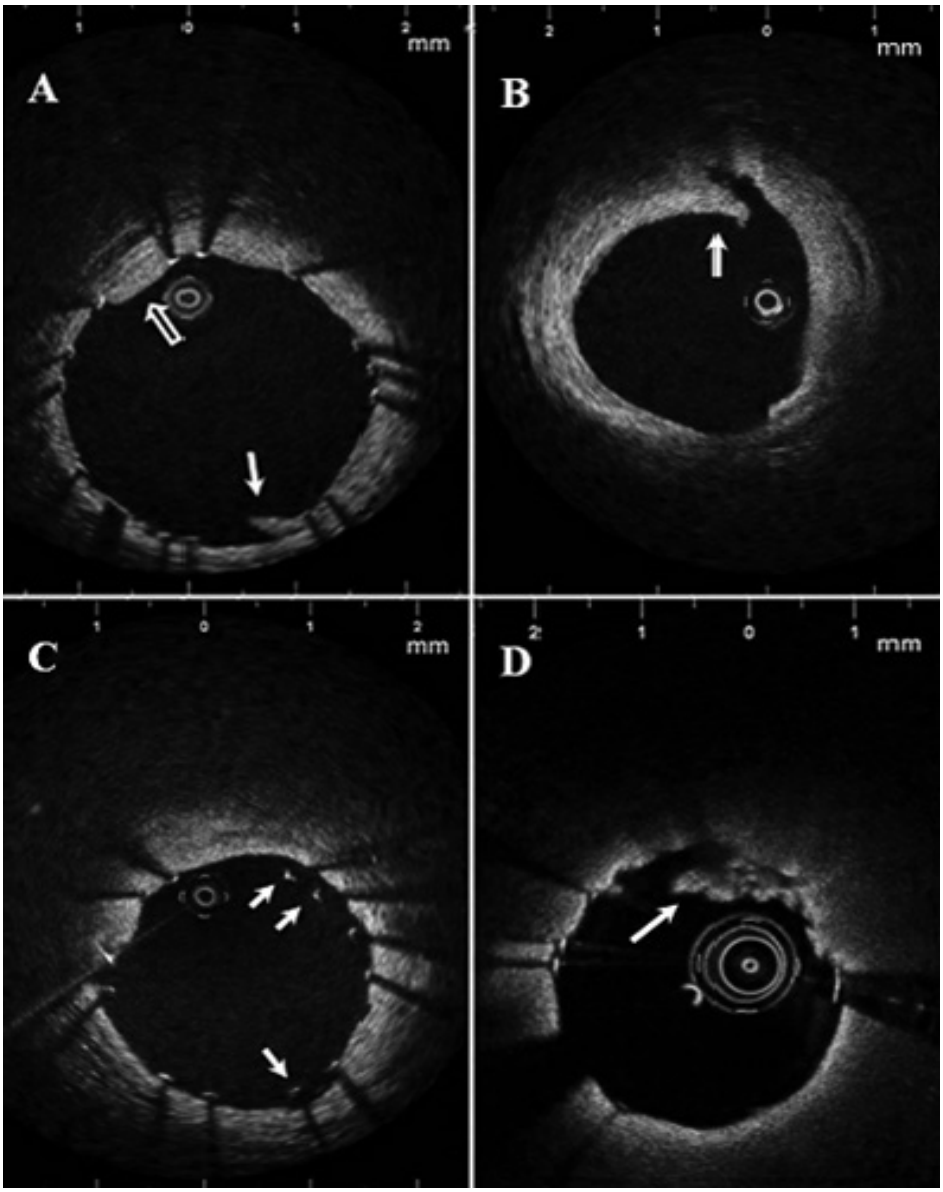

Figure 2. A and B show a case of balloon-expandable stent; tissue prolapse (A, white empty arrow) with intra-stent dissection (A, white arrow) and incomplete stent apposition (ISA) (B, two white arrows). C and D show a case of a self-expanding stent (vProtect® Luminal Shield); there are no tissue prolapse, intra-stent dissection and ISA.

In-hospital events

There were no events (death, MI, target-lesion revascularization, target-vessel revascularization or stent thrombosis) during the hospitalization period in both groups.

Table 2. Acute impacts of stent implantation on the vessel wall in the self-expanding stent (vProtect® Luminal Shield; group 1) vs. the balloon-expandable stent (group 2).

	Group 1 (n = 9)	Group 2 (n = 36)	p
Post-stenting measurement (mm^2)			
Lumen area	7.9 ± 2.3	7.3 ± 1.7	0.3
Stent area	8.0 ± 2.3	7.6 ± 1.9	0.6
Minimum stent area	6.3 ± 2.3	6.0 ± 1.7	0.7
Tissue prolapse			
Number of vessels with tissue prolapse	9 (100)	36 (100)	1.0
Number of tissue prolapse per mm	0.34 ± 0.34	0.64 ± 0.56	0.03
Average area (mm^2)	0.06 ± 0.03	0.13 ± 0.08	<0.001
Total area per mm (mm^2)	0.02 ± 0.01	0.06 ± 0.06	0.001
Intrastent dissection			
Number of vessel with intra-stent dissection	4 (44.4)	33 (91.7)	0,004
Number of dissected flaps per mm	0.06 ± 0.08	0.21 ± 0.18	0,003
Average length (μm)	79.6 ± 103.7	277.6 ± 110.0	<0.001
Edge dissection			
Proximal	0	10 (27.8)	0.17
Distal	0	14 (38.9)	0.04
Average length (μm)	0	515.2 ± 403.4	<0.001
Incomplete stent apposition			
Number of vessels	7 (77.8)	23 (63.9)	0.7
Maximum depth (μm)	178.2 ± 156.7	267.2 ± 72.1	0.03
Thrombus			
Number of vessels	2 (22.2)	16 (44.4)	0.28
Maximum length (μm)	131.4 ± 30.3	297.6 ± 121.5	0.08

Values are presented as n (%) or mean ± SD.

DISCUSSION

The present study is the first report comparing by OCT the acute impacts on the vessel wall between a self-expanding stent and balloon-expandable stents. The main findings are: 1) All stented segments showed tissue prolapse and a very high proportion of patients intra-stent dissection visible by OCT after stent implantation in both groups. Although the frequency of visible tissue prolapse was not significantly different between groups, average and corrected prolapsed area by stent length was larger in the balloon-expandable stent group. 2) Intra-stent and edge dissection was more frequently seen in balloon-expandable stents than in the self-expanding stent. 3) The frequency of ISA was not different in both groups but the maximum depth of ISA was greater in the balloon-expandable stent group. 4) The difference of acute impacts after stenting between two kinds of stent was not associated with clinical events during hospitalization.

According to OCT resolution, this technique has opened new possibilities for the evaluation of stents allowing a very detailed assessment of strut apposition 11, 12. Furthermore,

OCT allows not only qualitative but also quantitative evaluation of the acute in vivo injury after stenting. In a previously published pathological study, plaque compression by stent struts was observed in 94% patients and 91% arterial sections after stent implantation 13; while IVUS studies have reported plaque-prolapse frequencies ranging only from 18 to 35% 14. Our group has published the frequency of tissue prolapse by OCT, the tissue prolapse within the stented segment was visible in 97.5% of the cases 8. Similarly in the present study, even though the stent types were different, tissue prolapse was visible in all patients. However, in this study, no clinical events during hospitalization occurred even though the balloon-expandable stent group had visibly larger corrected number of tissue prolapse sites and area by OCT.

IVUS has inherent limitations to distinguish between intra-stent dissections and plaque prolapse, OCT can clearly differentiate those 2 entities 8. In our series, despite a high frequency of OCT-visible intra-stent dissections and edge dissections in the balloon-expandable stent group, no intra-hospital events were registered. In the literature, the relationship between these variables and clinical events at longer follow-up continues to be a matter of debate. On one hand, in a study of drug-eluting stents, 30% of proximal edge restenosis was developed after 6 months because of local injury outside the stent 15. But on the other hand, non-flow-limiting edge dissections detected by IVUS have not been associated with an increase in the rates of acute or long-term events or the development of restenosis 16-18. However, the long-term impact of the presence of intra-stent dissection on the incidence of restenosis or stent thrombosis is unknown.

As an alternative to balloon-expandable stents, self-expanding stents offer the potential advantages of less barotrauma to the vessel wall, differential expansion, and increased flexibility. Compared with balloon-expandable stents, self-expanding stainless steel stents, nitinol stents such as the vProtect® Luminal Shield stent may offer more accurate stent deployment through its use of thermal memory as the expansion mechanism. In native coronary arteries, studies have shown less vessel-wall injury and less edge dissection nitinol self-expanding stents 19, 20, which is in keeping with our present findings with OCT. Subgroup analysis in the SCORES trial revealed that lesions requiring higher pressure balloon inflation for implantation had higher rates of restenosis necessitating target lesion revascularization (TLR) than lesions requiring lower pressure balloon inflation 20. Another recent prospective randomized trial demonstrated that the incidence of procedural complications, such as slow flow, side branch occlusion, and edge dissection were significantly lower in the self-expanding stent group than in the balloon-expandable stent group and the occurrence of myocardial infarction tended to be lower in self-expanding stent group than in balloon-expandable stent group 12. In addition, the use of self-expanding stents with low-pressure dilatation instead of balloon-expandable stents could lead to lower incidences of periprocedural non Q-wave myocardial infarction. A high inflation pressure during PCI increases risk for periprocedural non-ST-segment elevation, myocardial infarctions, and increased systemic inflammatory state due to microembolization

21. This strategy of self-expanding stents could reduce directly the procedural risk by limiting the inflation pressure.

Limitations

This study has several limitations. 1) It is a non-randomised study, and a relatively small population was included in the self-expanding stent group. 2) The two study groups were not matched for lesion severity. Because target lesions were relatively simple in the self-expanding stent group and acute vessel injury might increase in the conventional balloon-expandable stent group, a large prospective study is needed to confirm our observations on the acute impact of self-expanding and balloon-expandable stents.

Conclusions

Although a very high proportion of patients showed tissue prolapse or intra-stent dissection visible by OCT after stent implantation in both groups, the self-expanding vProtect® Luminal Shield stent appears to be less frequently associated with intra-stent and edge dissection than conventional balloon-expandable stents. However, the latter vessel-wall injuries were not associated with in-hospital clinical events. OCT-detectable acute vessel-wall injury after stenting might therefore not be associated with early untoward early clinical safety events.

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Chapter 20

Plaque sealing and passivation with a mechanical self-expanding low outward force nitinol vShield device for the treatment of IVUS and OCT-derived thin cap fibroatheromas (TCFAs) in native coronary arteries. Report of the pilot study vShield Evaluated at Cardiac hospital in Rotterdam for Investigation and Treatment of TCFA (SECRITT).

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ABSTRACT

Background: High risk plaque (thin cap fibroatheroma, TCFA) is defined as a large lipid pool (within large plaque burden), thin cap (less than 65 μm) and macrophage dense inflammation, as well as positive remodeling. The majority of these plaques occur in the primal portion of the three major epicardial coronary arteries. Currently there are two strategies to manage patients with TCFA: medical therapy or mechanical plaque sealing.

Objective: The aim of the pilot SECRITT trial was to evaluate the safety and feasibility of sealing the high risk IVUS and OCT-derived TCFAs with a dedicated nitinol self-expanding vShield device.

Methods and results: After screening with angiography, FFR, IVUS-VH and OCT 23 patients met enrollment criteria (presence of non-obstructive VH-derived TCFA lesion with thin cap on OCT) and were randomized to vShield (n=13) versus medical therapy (n=10). Baseline percent diameter stenosis was 33%±14%,FFR was 0.93±0.06, baseline plaque burden was 61%±9%, percent necrotic core in contact with the lumen was 35%±6% and average MLA was 6.8±2.4 mm^2. At 6 months follow-up in shielded patients percent diameter stenosis further decreased to 19%±17% and FFR remained the same 0.93±0.05. Average late loss was 0.24 mm. Average baseline fibrous cap thickness was 48±12 μm. After shield placement at 6 months follow-up neo-cap formation was observed with average cap thickness of 201±168 μm. There were no dissections after shield placement and no plaque ruptures. In addition, mean stent area of 8.67 mm^2 increased to 9.44 mm^2, that is by 8.9% at 6 months follow-up. Number of malapposed struts decreased from 10.7% to 7.6% and the number of uncovered struts at 6 months was 8.1%. There were no device-related MACE events at 6 months follow-up.

Conclusion: High risk plaque passivation and sealing with v-Shield self expanding nitinol device appears feasible and safe. Long-term larger randomized study with streamlined screening criteria is needed to evaluate the efficacy of this approach over medical therapy.

INTRODUCTION

Our current understanding of the pathogenesis of acute coronary syndrome, the progression of coronary artery disease and sudden death is that patients with atherosclerosis and fatal myocardial infarction 70% of the time incur plaque rupture of the so-called thin cap fibroatheroma and in the rest of the cases pathology reveals plaque erosion or calcified nodule.(1-3) Many of these plaques have gone undetected by conventional coronary angiography because the underlying lesion was non-obstructive (<50% diameter stenosis) due to the so-called Glagov effect (positive remodeling at the site of large plaque burden). High risk plaque is defined as a large lipid pool (within large plaque burden), thin cap (less than 65 μm) and macrophage dense inflammation, as well as positive remodeling.(2, 4-6) The majority of these plaques occur in the primal portion of the three major epicardial coronary arteries(7, 8). It is also becoming clear that obstructive plaques (with minimal luminal area < 4mm^2) can also be high risk and identify a patient at risk of future events. In fact these plaques have been shown to result in the highest number of events in the PROSPECT trial, (9) the first prospective natural history study of atherosclerosis using multimodality imaging. Currently there are two strategies to manage patients with thin cap fibroatheromas: 1) conservative medical therapy based on the premise that none of the imaging modalities to-date have been able to identify reliable features of the plaque that render it prone to major adverse cardiac events, and 2) focal treatment to seal and passivate the plaque. The latter approach has been recently demonstrated in the VELETI trial to prevent progression of disease in vein grafts with non-obstructive lesions.(10) The SECRITT trial is a randomized, controlled pilot study that evaluates the safety and feasibility of sealing the high risk IVUS and OCT-derived TCFAs with a dedicated nitinol self-expanding vShield device. As such it is the first such trial in native coronary arteries of a dedicated device for treatment of "vulnerable plaque".

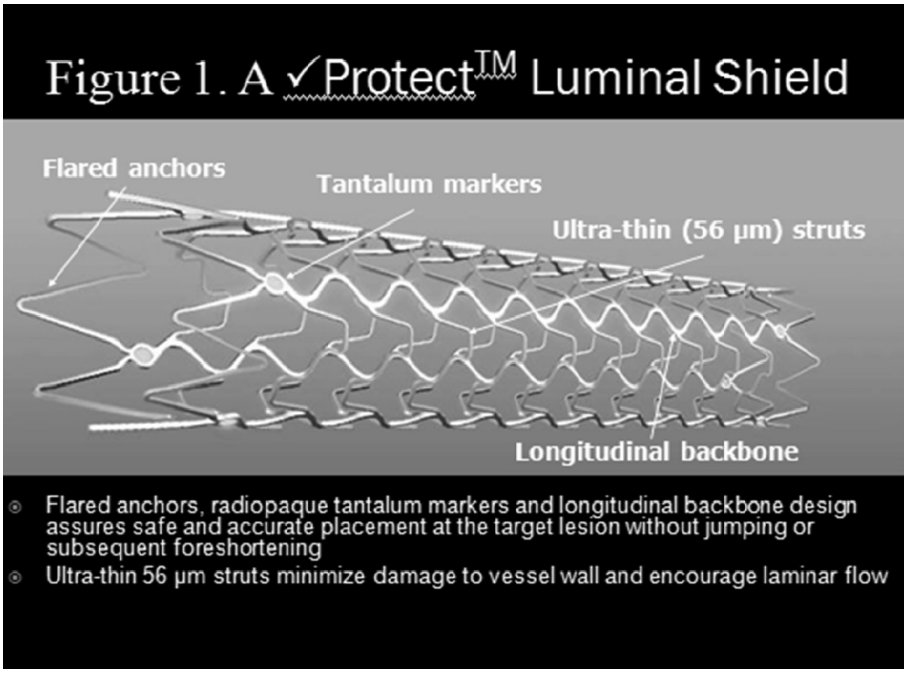
METHODS

Device description:

The vProtect™ luminal shield system consists of the self expanding (Nitinol) vascular shield (Figure 1A) and a rapid exchange delivery system. The delivery system is compatible with .014" guidewires and 6 Fr Guiding catheters. The delivery system consists of a distal outer sheath that houses the luminal shield and an inner body with radiopaque markers at the distal and proximal ends of the Shield. The luminal shield is constructed from a nickel-titanium alloy with an austenetic finish. The shield has a wall thickness that is less than 70 μm and has been designed with the objective to match the elastic properties of the TCFA. The shield is available in 3.5 mm, 4.0 mm and 4.5 mm diameter with length of 15 mm for all the diameters. This allows vessels 2.75 mm to 4.0 mm to be treated. The distinctive feature of the shield is the hysteresis between the inward radial resistive force and the outward force exerted on the vessel wall. The latter is very low not exceeding 100 mm Hg (Figure 1B) thereby minimizing the trauma to the vessel wall and potential for plaque rupture during the deployment.

Study design and patient population:

SECRITT is a clinical prospective pilot, open, single center randomized study assessing the safety and feasibility of shielding the non-obstructive IVUS-derived TCFAs, and the effects on the prevention of plaque progression at 6 months follow-up. Patients over the age of 18 admitted with stable or unstable coronary syndromes (including Non-ST elevation myocardial infarction) and an angiogram demonstrating the need for PCI in one or more lesion, and concomitant presence of angiographically and hemodynamically non-obstructive IVUS-derived TCFA were eligible for the study. After obtaining informed consent and successful treatment of the culprit lesion (Flow chart 1) patients were randomized 1:1 to treatment with the shield device or medical therapy. Exclusion criteria were as follows: acute myocardial infarction, prior CABG, significant left main disease, cardiogenic shock, renal insufficiency (cr > 1.5 mg/dL), resuscitation or intubation, cerebrovascular event within the last 30 days, major bleeding event within the last 30 days, severe hypertension refractory to medical therapy, history of significant trauma or surgery within the last 6 weeks, know nickel allergy, allergy to aspirin or clopidogrel that cannot be treated, pregnancy, coexisting condition with life expectancy < 12 months and vessel diameter on angiography or < 2.5 or > 4.0 mm. All patients in the study were on aspirin therapy and received clopidogrel loading dose (600 mg) or were on maintenance clopidogrel dose. Anticoagulation during the procedure was achieved with heparin (with goal ACT > 300 msec). After the procedure all patients received aspirine and clopidogrel. All patients were treated with anti-cholesterol medications with the goal low-density lipoprotein < 70 mg/dL. The study protocol was approved by the institutional ethics committee and all patients provided signed informed consent.



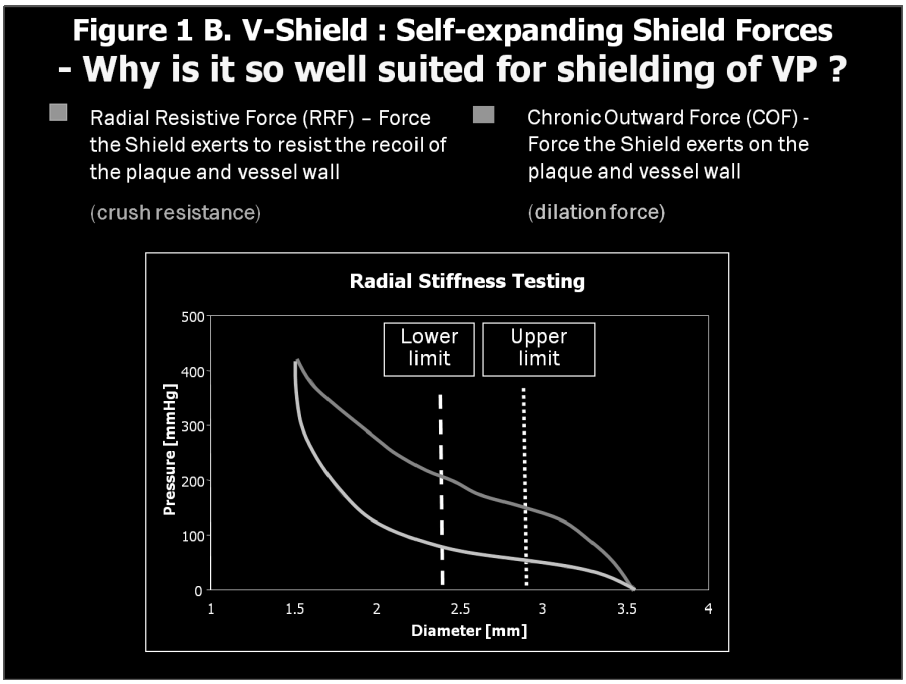


Figure 1 A. Device design and structure highlighting the ultra-thin struts and tantalum markers to allow for positioning. 1B. Hysteresis curve between radial resistive force and chronic outward force (COF) exerted by the device on the vessel wall. In the case of the V-shield COF is around 100 mmHg minimizing vessel trauma and allowing for gentle continued expansion over time (9% at 6 months).

Study lesion definition:

Lesions qualified as study lesions if (1) they were angiographically intermediate with 40-50% diameter stenosis and (2) had an FFR of more than 0.75 (Pathway B in the flow chart) and (3) fulfilled the criteria for IVUS-derived TCFA. Cap thickness and presence of the lipid pool was also documented by OCT.

Quantitative angiography:

The target coronary segment was be filmed in 2 orthogonal planes that have been prescribed after viewing of the preceding angiogram. QCA was performed following administration of 100-200 micrograms of Nitroglycerin to assess the proper length and diameter of the vessel. A final angiogram was made under the same rotation and skew angles following intracoronary Nitroglycerine administration. A QCA off-line using CMS-Medis quantitative angiography (Medis, Leiden, Netherlands) was made to quantify the final result. The following measures were obtained for each lesion: minimal luminal diameter, reference vessel diameter and percent diameter stenosis. Late loss was calculated from the difference between minimal luminal diameter immediately post shielding and at 6 months follow-up. Restenosis was defined as the presence of in-lesion > 50% diameter stenosis at follow-up.

Fractional flow reserve assessment:

Fractional flow reserve was measured with a sensor-tipped 0.014" angioplasty guidewire (WaveWire/WaveMap, Volcano Therapeutics, Inc, Rancho Cordova, CA or PressureWire, Radi Medical Systems, Uppsala, Sweden). After crossing the target lesion with the wire, hyperemia was induced with intravenous infusion of 140 µg/kg/min of adenosine (Adrecar, Sanofi, Munich, Germany) for a total of 2 minutes. The maximum pressure gradient used to calculate *FFR* was defined as the ratio of the mean post-stenotic pressure to the mean aortic pressure, measured by the guiding catheter, during maximal hyperemia. FFR of ≥0.75, was considered functionally not significant and constituted the enrollment criterion. Exact FFR measurement at baseline and at 6 months follow up was recorded.

IVUS-VH acquisition and analysis:

Details regarding the validation of the technique, have previously been reported.(11, 12) Briefly, IVUS-VH uses spectral analysis of IVUS radiofrequency data to construct tissue maps that are correlated with a specific spectrum of the radiofrequency signal and assigned color codes [fibrous (labeled green), fibrolipidic (labeled greenish-yellow), necrotic core (labeled red) and calcium (labeled white)].

IVUS-VH data was acquired using either the In-Vision Gold console (in the same pullback as palpography) or the S5 imaging system, and a 20 MHz eagle Eye Gold catheter (Rancho Cordova, CA, USA). The IVUS-VH sampling rate during pullback is gated to peak R-wave and is therefore dependent on heart rate.

IVUS B-mode images were reconstructed from the RF data by customized software (IVUS Lab Version 4.4, Volcano Therapeutics, Rancho Cordova, CA). Semi-automated contour detection of both lumen and the media-adventitia interface was performed and the RF data was normalized using a technique known as "Blind Deconvolution", an iterative algorithm that deconvolves the catheter transfer function from the backscatter, thus accounting for catheter-to-catheter variability. Compositional data obtained for every slice was expressed as mean percent for each component.

Pullback of 40 mm was performed after administration of 100-200 micrograms of intracoronary nitroglycerine and incorporated the segment at least 5 mm proximal and distal to the region of interest. Pullback speed was 0.5 mm/sec.

Online analysis was performed to look for ID-TCFA (enrollment criterion). The analysis was subsequently repeated off-line by two independent observers blinded to patient clinical data and randomization to verify the presence of ID-TCFA. After tracing the lumen and external elastic membrane diameters, plaque, lumen and total vessel area and volumes were computed for the segment of interest. The three consecutive cross-sections with >40% plaque burden, >10% necrotic core in contact with the lumen were identified and their quantitative characteristics and measurements were recorded. In addition, minimal luminal area (MLA) was measured.

IVUS-Palpography acquisition and analysis:

Intravascular ultrasound palpography is a technique that allows the assessment of local mechanical tissue properties. At a defined pressure difference, soft tissue (*e.g.*, lipid-rich) components will deform more than hard tissue components (*e.g.*, fibrous-calcified).(13-15) In coronary arteries, the tissue of interest is the vessel wall, while the blood pressure with its physiologic changes during the heart cycle is used as the excitation force. Radiofrequency data obtained at different pressure levels are compared to determine the local tissue deformation.

Each palpogram represents the strain information for a certain cross section over the full cardiac cycle. Palpograms will be acquired using a 20-MHz phased-array IVUS catheter (EagleEye™ Volcano Therapeutics, Rancho Cordova, USA). Cine runs, before and during contrast injection were performed to define the position of the IVUS catheter. Digital radiofrequency data was acquired using a custom-designed workstation.

During the recordings, data was continuously acquired at a pullback speed of 0.5 mm/s using an automated pullback device (Track Back II, Volcano Therapeutics, Rancho Cordova, USA) with simultaneous recording of the ECG and the aortic pressure. The data was stored on a DVD and sent to the imaging core lab for offline analysis (Cardialysis BV, Rotterdam, The Netherlands).

The local strain was then calculated from the gated radiofrequency traces using cross-correlation analysis and displayed color-coded, from blue (for 0% strain) via red through to yellow (for 2% strain). This color-coded information was superimposed on the lumen vessel boundary of the cross-sectional IVUS image.

Using previously described methodology, plaque strain values were assigned a Rotterdam Classification (ROC) score ranging from 1 to 4 (ROC I = 0-0.5 %; ROC II = 0.6- <0.9 %; ROC III = 0.9- 1.2 %; ROC IV = > 1.2 %). A CSA was defined as a high-strain when it had a high strain region (ROC III-IV) that spanned an arc of at least 12° at the surface of a plaque (identified on the IVUS recording) adjacent to low-strain regions (<0.5 %). The highest value of strain in the cross section is taken as the strain level of the CSA.

Highest strain value pre and post-shielding and was recorded and colocalization with the IVUS-VH derived TCFA performed using time stamps.

TD and OFDI-OCT acquisition and analysis:

The OCT M3 (TD-OCT) and C7 (OFDI-OCT) systems used in this study (LightLab Imaging Inc., Westford, MA, US) have been described previously (16-21). Briefly, a TD or an OFDI-OCT catheter was advanced distal to the stented lesion over a conventional coronary guide wire in the case of C7 system or, in the case of M3 system, OCT imaging wire (ImageWire™) was directly advanced past the lesion. The OCT catheter was then withdrawn proximal to the stented segment and the lesion visualized using an automated pullback system at 20 mm/sec in the case of C7 system and 3.0mm/sec in the case of M3 system. During image acquisition, coronary blood flow is replaced by continuous flushing of contrast at 3.0-4.0 ml/sec using a power injector (Mark V ProVis, Medrad, Inc. Indianola, PA, US) at 300 psi. Cross sectional images are acquired at 100 frames/sec for C7 and 20 frames/sec for M3. During the baseline study documentary OCT was performed to measure and record the thickness of the fibrous cap overlying the lipid pool corresponding to the area of the ID-TCFA. The thinnest cap measurement was recorded. The assessment of the shield with OCT post implantation was used to assess procedure related trauma to the vessel wall (plaque prolapse, presence of filling defects, proximal and distal edge dissection), and at 6 months follow-up to assess shield strut apposition and tissue coverage and to measure the thickness of neo-cap. The thickness of the cap was measured every 1 mm within the shielded segment (15 frames per shield) using 360 degree analysis off-line software. In addition, shield areas were measured immediately post-shielding and at 6 months follow up to assess the degree of continued shield expansion with OCT.

Measurements were repeated off-line by two independent observers using Lightlabs imaging software.

Follow-up and study endpoints:

The primary end-point of the study was the acute change in lesion strain pattern immediately after shielding and acute device and angiographic success. Secondary end-points of the study included: 1) change in the fibrous cap thickness from baseline to 6 months post-shielding, 2) change in the stent area, 3) percent diameter stenosis at baseline and at follow-up, late loss and binary re-stenosis rate, and 4) cumulative incidence of major adverse cardiac events (death, MI

and revascularization) at 6 months follow-up. Stent thrombosis occurrence was defined and classified according to the ARC criteria.(22)

Sample size calculation and statistical analysis:

The study population was statistically based on the change in study lesion strain patterns immediately post-stenting as noted in the ABSORB trial.(23) In this trial the mean of the maximal strain/crossection /patient decreased from 0.44 ± 0.25 to 0.00 ± 0.01. Based on the assumptions for these the sample size was calculated as detailed below.

Assumptions for the sample size calculation using a paired t-test:

- mean difference between pre and post equal to zero;
- alpha = 0.05;
- mean pre = 0.4;
- mean post = 0.0;
- SD of difference pre-post = 0.3;
- 90% power.

To assess the change in strain observed on palpography post-treatment, paired (pre-and post-) data of 9 patients would have been needed. However, in order to account for the patient loss to follow-up, we aimed to enrol a total of 15 patients in each arm of the trial.

Discreet variables are presented as counts and percentages. Continuous variables are expressed as means $\pm$ standard deviation.

RESULTS

Patient enrollment : From June 2008 through February 2010 over 100 patients were approached for participation in the trial, 48 signed informed consent but only 23 patients met inclusion and enrollment criteria (including presence of ID-TCFA) and were enrolled in the trial. Thirteen patients were randomized to shield device and 10 randomized to medical therapy but with one patient crossing over to the shield arm. Baseline clinical characteristics of the patients enrolled are summarized in Table 1. Notably 24% of the patients were diabetic and 65% had multivessel disease. Of the 13 shielded patients 11 completed full angiographic and imaging follow-up. Of the 10 control patients only 5 completed full angiographic and imaging follow-up.

Angiographic and FFR analysis: In 24% of the case proximal or mid LAD was the site of the TCFA treated, in 24% LCX and in 52% cases the RCA. Baseline percent diameter stenosis was 33%$\pm$14% with MLD of 2.01$\pm$0.39 mm and lesion length of 14 mm (Table 2). Baseline FFR was 0.93$\pm$0.06. Post-stenting percent diameter stenosis decreased to 21%$\pm$11% in the shielded patients and MLD increased to 2.43$\pm$0.44 mm. At 6 months follow-up in shielded patients

Table 1. Baseline clinical characteristics for the overall population

Characteristic	N=23
Age	67 (range 50-82)
Gender (male)	76%
Current smoking	18%
Hypertension	71%
Hypercholesterolemia	76%
Diabetes melitus	24%
Prior MI	41%
Prior PCI	58%
Angina type:	
Stable	76%
Unstable	24%
Multivessel disease	65%
Non-culprit vessel (TCFA vessel)	
LAD	24%
LCX	24%
RCA	52%

Table 2. Angiographic and FFR assessment

Parameter	Pre-stenting (n=11)	Post-stenting (n=11)	6 months follow-up (n=11)
MLD (mm) RVD (mm)	2.01+0.39 2.95+0.39	2.43+0.44	2.19+0.33
% Diameter Stenosis	33.2+13.5%	21.0+10.7%	18.7+16.9%
FFR	0.93+0.06		0.93+0.05
Late loss (mm)			0.24

percent diameter stenosis further decreased to 19%$\pm$17% with MLD of 2.19$\pm$0.33 mm and FFR remained the same 0.93$\pm$0.05. Average late loss was 0.24 mm.

IVUS-VH analysis and palpography: At the site of the TCFA lesion baseline plaque burden was 61%$\pm$9%, percent necrotic core in contact with the lumen was 35%$\pm$6% averaged over three consecutive frames. Average MLA was 6.8$\pm$2.4 mm^2 (Table 3 and Figure 2). At follow up the the 5 control patients no increase in plaque burden (66%) or necrotic core (33% down to 26% with some patients showing a decrease and some an increase) was observed over time and no MLA decrease (6.2 mm^2 at both baseline and follow-up) (data not shown).

Table 3. IVUS VH and palpography baseline and acute data summary

Parameter	(n=23)
MLA mm2	6.8 + 2.4
% plaque burden	60.6 + 8.8
%Necrotic core	34.7 + 6.3
Strain pre-shield	0.71%+0.53%
Strain post-shield	0.1%+0.09%

Average strain before shield placement was 0.71%±0.53% (ROC score of II on average). This decreased acutely post-shield placement to 0.1%±0.09% (ROC score of I).

OCT analysis and data: As previously reported by our group,(24) deployment of the self-expanding shield resulted in minimal trauma to the vessel wall, particularly when compared to the balloon-expandable devices. There were no proximal or distal edge dissections and no filling defects. Length of intrastent dissections was also minimal.

Average baseline fibrous cap thickness was 48±12 μm with a range of 30-70 μm. After shield placement at 6 months follow-up neo-cap formation was observed with average cap thickness of 201±168 μm (range 50-608 μm) (Table 4). The patient with 608 μm of neo-cap formation at baseline had adjacent calcifications which required high pressure (16 atms) post-dilation of the shield with resultant barotrauma and more exuberant healing response.

In addition, mean stent area of 8.67 mm^2 increased to 9.44 mm^2, that is by 9% at 6 months follow-up (Table 4 and Figure 3). Number of malapposed struts decreased from 10.7% to 7.6% and the number of uncovered struts at 6 months was 8.1%.

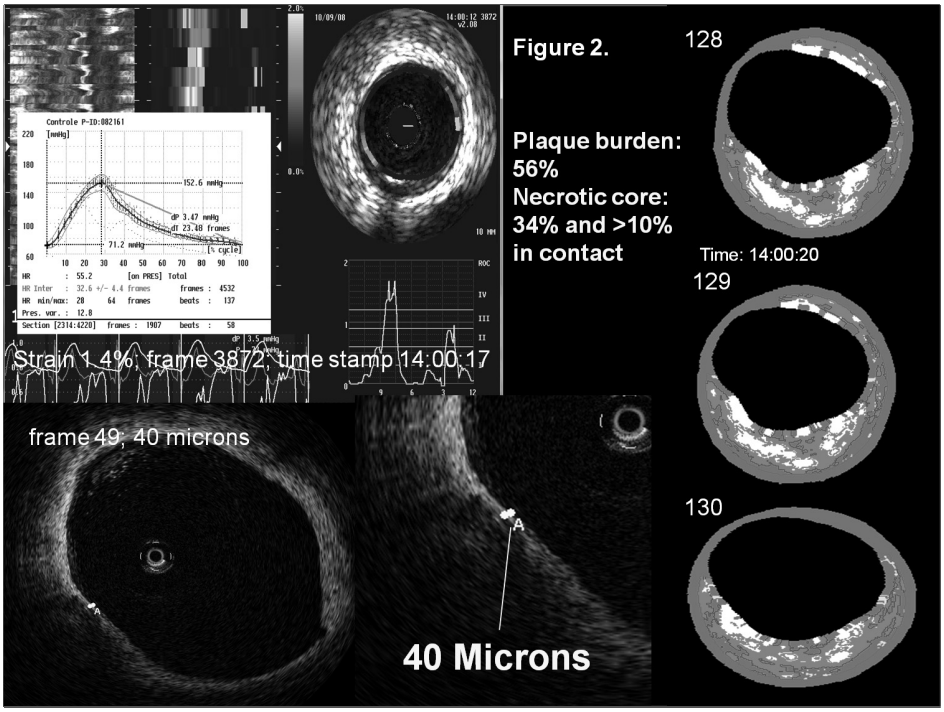


Figure 2. Example of baseline imaging for one of the enrolled patients. A. In the upper left, Palpogram showing stain value of 1.4% (ROC III-IV), B. In the upper right corresponding matched TCFA on IVUS VH analysis with plaque burden of 56% and necrotic core of 34% in three consecutive frames, and C. In lower left corner, matched OCT frame showing cap thickness of 40 μm.

Detailed per strut analysis: Total of 11 stents were evaluated at baseline. Total length of stents evaluated at baseline was 127.15 mm. Mean lumen area was 9.03±2.29 mm2 and mean stent area was 8.67±2.16 mm2. In two patients there was high degree of malaposition due to undersizing of the device. Mean ISA area was 0.36±0.47 mm2. Mean prolapse area was 0.009±0.17 mm2. Of the 1,721 stent struts counted at baseline 1,521 were well apposed, 185 (10.7%) were malapposed and 15 were in front of side branches. There were no dissections seen. Mean thrombus area was 0.015 mm2.

At 6 month follow up 12 stents were evaluated with a total length of 142.95 mm. Mean lumen area was 8.36±2.87 mm2 (decreased by 7.4%), with late loss of 0.13 mm. There were no binary restenosis events. Mean stent area increased to 9.45±2.30 mm2 (by 8.9%), implying continued stent expansion. Mean ISA area was 0.88±0.85 mm2. Of the total of 2072 struts

Table 4. Optical coherence tomography at baseline, post-shield and at 6 months follow-up

	Pre-shield/acute post-shield	6 months follow-up
Cap thickness (μm)	48 + 12 (range 30-70)	201 + 168 (range 50-608)
Presence of lipid pool	100%	
Mean lumen area mm2	9.03	8.36
Mean stent area mm2	8.76	9.44 (9% increase)
Minimum lumen area mm2	7.23	6.12
Malapposed struts	10.7%	7.6%
Uncovered struts		8.1%

evaluated, 1910 were well apposed, 159 were malapposed (7.6%; decrease from baseline), and 3 were in front of a side-branch. 8.1% of all struts were non-covered. Of the well-apposed struts 93.2% were covered, while of the malapposed struts 78% were covered.

Clinical events: There were no device-related MACE events (Table 5). One of the control (non-shielded) patients returned within two weeks of the procedure with an unstable coronary syndrome and crossed over to the shield arm. There were no stent thrombosis events. Lastly, non-invasive assessment of shield patency with MSCT appears feasible owing to its thin nitinol struts (Figure 4).

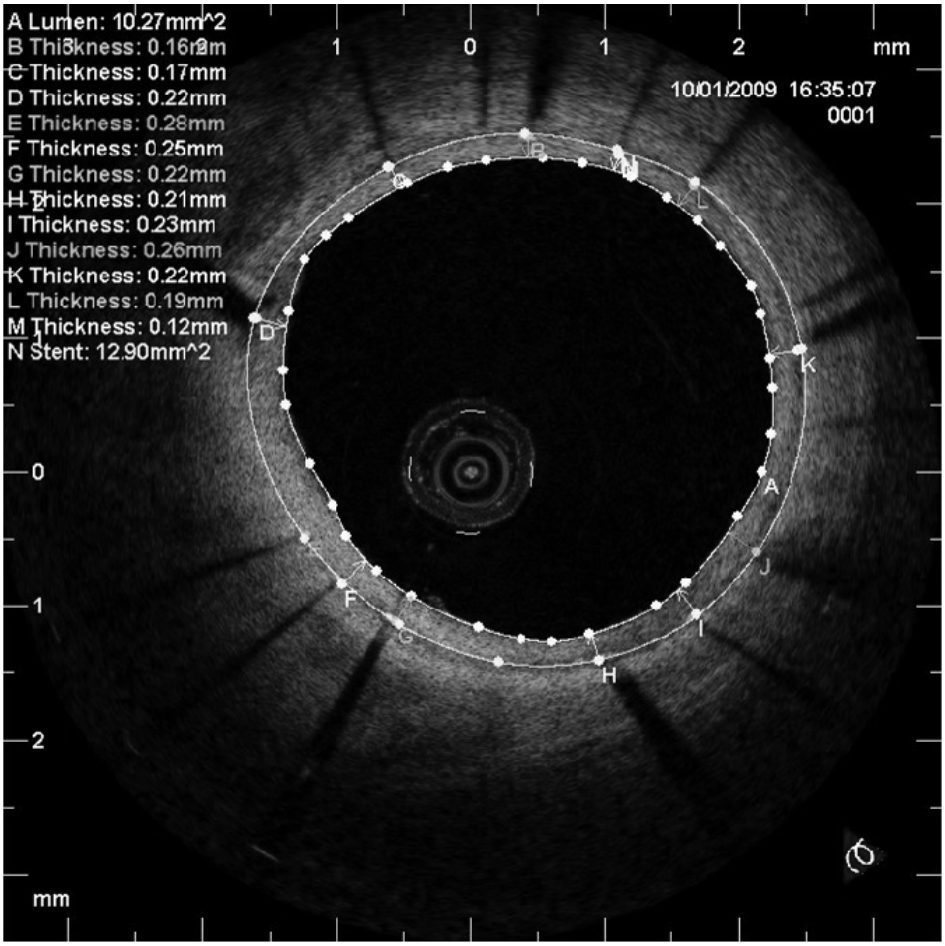


Figure 3. Example of per-strut OCT analysis and appearance of V-shield at 6 months follow-up with uniform strut coverage of around 200 μm and no malapposition.

DISCUSSION

In this First in Man experience with shielding of vulnerable plaque (thin cap fibroatheroma) using self-expanding nitinol shield, we demonstrate the feasibility and preliminary efficacy of the approach. The device delivery was successful in all 13 patients who were randomized to the shield and there were no MACE events related to the shield device treatment at 6 months of follow up. The treatment strategy employed in this protocol is based on the fact that most myocardial infarctions (MI) result, not from a critical blockage, but from lesions that are non-flow limiting.(25-30) In individuals that have undergone angiography in the months preceding myocardial infarct the culprit lesions most often show <50% diameter stenosis. (27) Moreover, only approximately 15% of acute MIs arise from lesions of <60% stenosis on a

Table 5. Cummulative incidence of MACE rate at 6 months follow up

	Shield arm (n=13)	Medical therapy arm (n=10)
MACE	0	1
Death	0	0
MI	0	0
Clinicaly driven Revascularization	0	1 (cross-over to shield)
Revascularization related to the target lesion/shielded vessel	0	0

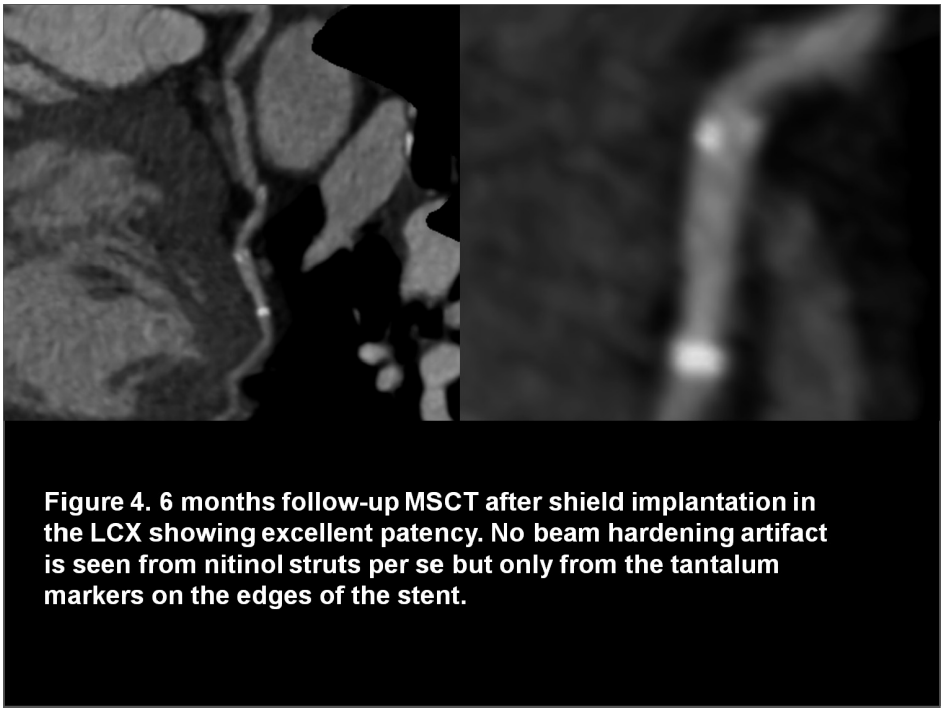


Figure 4. MSCT image of V-shield at 6 months. There is no beam-hardening artifact from nitinol struts (except for tantalum markers at the edges) allowing for good non-invasive evaluation of patentcy.

previous angiogram (11). These lesions, however, have a substantial plaque volume/percent plaque burden. The coronary flow is not obstructed because of outward (positive) remodelling. Longer term prognosis of a patient might depend on far more detailed plaque assessment than angiography and on adequate treatment of plaques at risk to rupture.

The use of IVUS-VH to identify vulnerable plaques (IDTFCA) is well documented and is comparative to what has been demonstrated from documented plaque ruptures. IDTCFA is currently defined as a lesion fulfilling the following criteria in at least 3 consecutive cross-sectional areas (CSA): 1) necrotic core ≥10% without evident overlying fibrous tissue, 2) lumen obstruction ≥ 40 %. In addition, the IDTCFA must also demonstrate positive remodeling by having a remodeling index (RI) $\geq$ 1.05. In a study population of 21 patients Garcia-Garcia (12) found in 13 patients 42 IDTCFA that fulfill the IVUS-VH criteria. This meant that on average there are approximately 3 IDTCFA per patient. Documented plaque ruptures were reported by Rioufol(31) in 2002 in 24 patients referred for PCI after a first ACS with a troponin I elevation. He found that there were 50 plaque ruptures corresponding to 2.08 vulnerable plaques per patients presenting with an ACS which is in accordance with Garcia-Garcia's IVUS-VH findings. Interestingly plaque rupture on the culprit lesion was found only in 9 patients (37%). In 19 patients (79%) at least 1 plaque rupture was found somewhere other than the culprit lesion, in a different artery in 70% and in both other arteries in 12.5% of the patients. This reinforces the importance of identifying and treating vulnerable plaques and the fact that they can be remotely associated from the culprit lesion causing the presenting symptom. This also constitutes the rationale for the treatment of intermediate non-flow limiting lesions with signs of vulnerability. Accuracy of thin cap atheroma detection can be further increased by combining IVUS-VH imaging with OCT imaging of the lesion which due to its micron resolution can allow to measure the thickness of the fibrous cap. Sawada and Garcia-Garcia(32) have shown that out of 126 lesions examined with two modalities only 28 (22%) fulfill thin cap fibroatheroma criteria by both IVUS-VH and OCT with thin cap defined as < 65 micron. For these reasons, we have chosen in this study to perform very detailed multimodality examination of plaque before enrolling the patient in the study. The examination that each patient underwent were 1. Angiography, 2. FFR, 3. Palpography (off-line), 4. IVUS-VH and 5. OCT online at baseline. This was followed by post-shielding assessment with 1. Angiography, 2. Palpography and 3. OCT. At 6 months follow-up the assessment included: 1. Angiography, 2. FFR, 3. Palpography/IVUS and 4. OCT. With such extensive examination and procedure times which was challenging for both patients, personel and operators enrollment in the study was rather slow (23 patients in under 2 years), and several patients (particularly in the control arm) were unwilling to participate in the follow-up catherization. While using stringent criteria for enrollment was justified in this pilot study, the protocol may have been more successful had we used a simple combination of non-invasive coronary MSCT assessment (for positive remodeling, plaque burden, 3D strain and flow) combined with intraprocedural OCT (to measure cap thickness and show presence of a lipid pool). In the future, angiography,

FFR and IVUS/palpography assessment should be replaced by MSCT examination which can provide equivalent information before the start of the invasive procedure. (33-35)

We have been able to demonstrate here that the self-expanding device is ideally suited for treatment of thin-cap fibroatheromas. Self-expanding nature of the device causes minimal trauma to the vessel wall minimizing the risk of thin cap rupture and necrotic core embolization. We had no per-procedural MIs in this patient cohort. Furthermore, the device is well apposed and continues to expand gently by 9% over 6 months minimizing the risk of having malapposed and uncovered struts. While there is no drug coating and the device is bare metal, the combination of thin nitinol struts and lack of traumatic balloon expansion, result in minimal neo-intimal formation. 8% of the struts were still uncovered at 6 months with average neo-cap of 201 μm and late loss of 0.13 mm which is comparable to some of the state of the art drug eluting stents. There were no stent thrombosis events. The continued gentle expansion of the device is similar to that observed by Granada et al. in the First in Human trial of the vShield device in moderate stable lesions completed recently(36) and also comparable to the results achieved with the Stentys stent in the Apposition study.(37)

The number of patients enrolled and lack of events made it impossible to determine whether placement of the shield and plaque passivation demonstrated by OCT offered an advantage over standard medical therapy with aspirin, clopidogrel and statins. Such ability to prevent plaque growth and disease progression to a significant lesion was demonstrated recently in the VELETI trial of paclitaxel eluting stent treatment versus medical therapy in graft disease.(10)

Limitations: This is an exploratory analysis with all its inherent limitations. The greatest limitation was failure to complete the full projected study enrollment and lack of angiographic/imaging follow-up in a large proportion of non-shielded control arm patients.

Conclusion: Passivation of the thin cap fibroatheroma with self-expanding nitinol vShield device appears to be safe and feasible. Larger cohort study with long-term follow-up will be needed to evaluate this device as a treatment for necrotic core rich lesions.

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Chapter 21

First Clinical Evaluation of a Luminal Self-Expanding Shield in Patients with Intermediate Coronary Lesions

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ABSTRACT

Background: The mechanics of expansion of balloon-expandable stents are complex and usually result in under-deployment and malapossition. An emerging new generation of self-expanding coronary stents promises to improve some of the limitations of balloon-based technologies. This first-in-human study aimed to evaluate the safety and feasibility of a new generation low pressure self-expanding luminal Shield (LS; vProtect™, Prescient Medical, Doylestown, PA) for the treatment of intermediate coronary lesions.

Methods and Results: A total of 29 patients with evidence of myocardial ischemia and intermediate de novo coronary lesions were included in the study. All target lesions were pre-dilated under low dilatation pressures. Following LS deployment, post-dilatation was allowed if the residual angiographic %DS was ≥30%. Angiographic and IVUS follow-up were performed at 9 months following LS implantation. In all patients %DS <30% was achieved and device success was 100%. No patient required bailout stenting. The mean lumen area was 6.11 ± 1.23 mm^2 following LS implantation and post-dilatation and 7.00 ± 1.41 mm^2 at 9 months follow up. The cumulative MACE event rate at 9 months was 10.3% and was related to target lesion revascularizations. There were no cases of death, myocardial infarction or stent thrombosis. Angiographic follow up showed an in-stent lumen loss of 0.50±0.30 mm and a binary restenosis rate of 10.3%.

Conclusions: In patients undergoing intervention of intermediate de novo coronary lesions the implantation of the LS was safe, feasible and displayed a low restenosis rate. IVUS analysis showed favorable mechanical properties of the LS as compared to previous generation self-expanding stents.

Key words: self-expanding shield, percutaneous coronary intervention, intermediate coronary lesion

Balloon-expandable stent (BES) technologies are the standard of care for the interventional therapy of obstructive atherosclerotic coronary lesions (1). Due to its mechanism of expansion, BES typically exerts an unpredictable pattern of mechanical stress to the vessel wall leading to variable degrees of vascular injury and restenosis (2). In addition, due to the fact that BES relies on the plastic deformation of its structure via balloon dilatation, these devices are frequently associated to acute under-deployment and late malapossition, especially in situations in which the vessel lumen can not be accurately determined (i.e., STEMI) (3).

A new generation of self-expanding coronary stents displaying more stable biomechanics (lower chronic expansive forces) are under development (4). It has been hypothesized that these devices may improve clinical outcomes by providing suitable outward forces enabling proper vessel wall apposition and controlled luminal gain yet reducing the amount of vascular injury and resulting neointimal formation (5). In this first-in-human study, we aimed to evaluate the safety and feasibility of implantation of a new generation low pressure self-expanding luminal shield device (vProtect™, Prescient Medical Inc., Doylestown, PA, USA) among patients with de novo intermediate coronary lesions.

METHODS

Device Description

The vProtect™ luminal shield is a self expanding Nitinol-based device originally designed to achieve the mechanical stabilization of non-obstructive, thin-cap fibro-atheromas in the coronary territory. The biomechanical behavior of the device shows lower chronic outward forces compared to previously designed self-expanding stents while maintaining a stable radial force (crush-resistant), thus avoiding collapse following implantation. The device consists of self expanding luminal shield and a rapid exchange delivery system. This system is compatible with 0.014" guidewires and 6 Fr Guiding catheters. The shield has a strut thickness of ~57 microns and has a vessel surface area coverage from 13% to 15% in 2.5 to 3.0mm vessels (4).

Study Design

The current study was designed as a non-randomized, single-arm, single center (Corbic Research Institute, Corbic Institute, Envigado, Colombia) prospective trial to evaluate the safety and feasibility of implantation of the luminal shield among patients with evidence of myocardial ischemia and intermediate de novo coronary lesions. The study was approved by the Institutional Ethics Committee. All patients provided written informed consent for participation in the trial. The study case reports were verified by independent study monitors (Clinlogix, North

Wales, PA). All potential adverse events were independently adjudicated by an independent clinical event committee and reported to the ethics committee.

Inclusion and Exclusion Criteria

Patients aged 18 years or older presenting symptoms of coronary artery disease were eligible if they had single, non-calcified target lesion by angiography of ≤ 15 mm in length with a diameter stenosis of ≥50% (by visual assessment) that was suitable for stent implantation in a vessel with a reference diameter ranging from 2.75 to 3.5mm in diameter. Baseline IVUS examination was mandatory in order to exclude lesions with a calcium arc greater than 90 degrees. Only one luminal shield was permitted to be implanted per lesion in every single patient. Other lesions could be treated with other clinically approved devices.

The principal exclusion criteria were known allergy or sensitivity to Nitinol or its components; known hypersensitivity or contraindications to anticoagulant or antiplatelet therapies; history of bleeding or known coagulopathy; major surgery within the past 30 days; lesions that were severely calcified based on IVUS imaging defined as a ring of calcium occupying more than 90 degrees of the visual field; left main coronary disease; previous stent placement or angioplasty in the target vessel; ST segment elevation myocardial infarction; lesions involving a side branch of ≥ 2.0mm in diameter or side branches < 2.0mm with the presence of occlusive ostial disease or plaque shifting following balloon dilatation of the main vessel lesion; unsuitable coronary anatomy; females who were pregnant; participation in another investigational device or drug trial.

Procedural Description

All patients received 600mg of Clopidogrel and 300mg of Aspirin (or 100mg if they were already taking daily chronic dose) at least 2 hours before the angioplasty procedure. Following the procedure Clopidogrel was maintained at a dose of 75mg for at least 4 weeks and Aspirin was administered in a dose of 300mg for at least 1 month. Aspirin was continued indefinitely at a dose of at least 100mg daily. Intravenous unfractionated heparin was administered during the procedure in doses sufficient to achieve and maintain an Activated Coagulation Time (ACT) between 250 to 350 seconds. The use of glycoprotein IIb/IIIa antagonists was left at the discretion of the operator. Percutaneous coronary intervention was performed using standard techniques. After angiography images were obtained intravascular ultrasound (IVUS) imaging was performed to determine the presence or absence of calcified lesions according to the inclusion criteria. A description of the procedural methodology is shown in Figure 1. All target lesions were pre-dilated with a 2.5mm balloon that was inflated at 1-ATM increment ("stepwise fashion") until complete balloon dilatation was achieved. Then, the target diameter of the luminal shield was selected based on the QCA measurements. The luminal shield was available in diameters of 2.75 to 4.0 mm and in a single length of 15 mm. Size selection was performed by selecting half a size above the vessel reference diameter (3.0 diameter for a ~2.5 mm vessel reference diameter). The luminal shield was deployed aiming to cover the borders

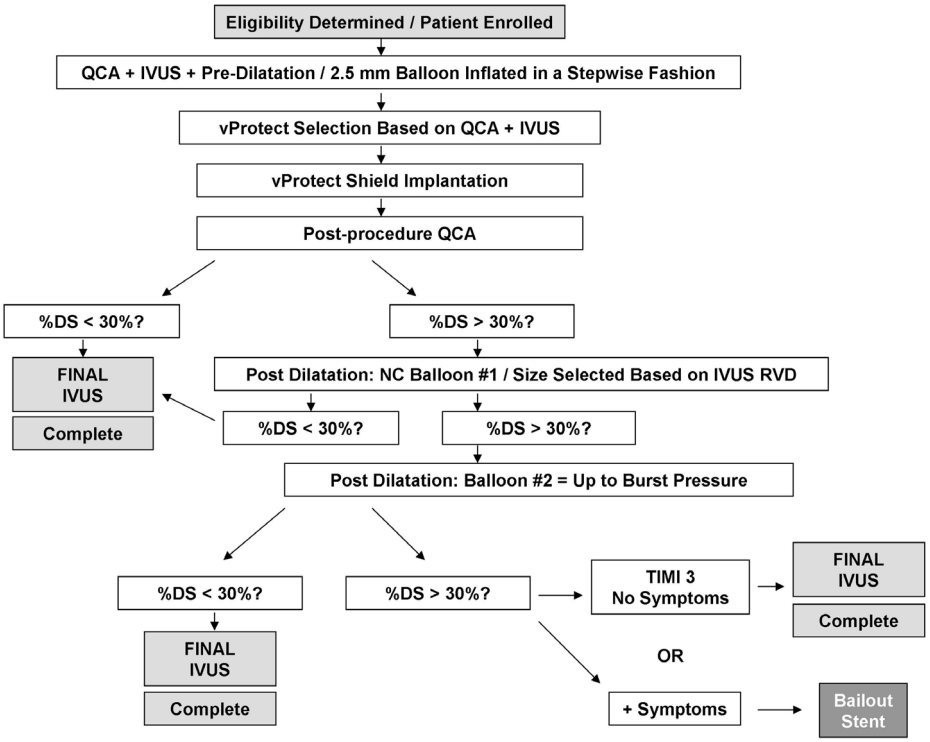

Figure 1. Flow chart of study design.

of the previously dilated lesion. Post-dilatation, using a non-compliant balloon usually shorter than the total length of the luminal shield was allowed when the residual on-line angiographic %DS was ≥30%. The procedure was terminated if the angiographic %DS was <30% and if a final TIMI III flow was reached. In the case two consecutive balloon inflations failed to reduce the angiographic %DS to ≤ 30% or the presence of altered coronary flow or dissections were noted, bailout stenting was indicated. At the end of the procedure, final IVUS imaging was performed. A 12-lead electrocardiograph was obtained before the procedure, within 24 h after and in case of suspected acute ischemia. Cardiac enzymes were monitored through the entire hospitalization.

Study End-Points

Angiographic follow-up was performed in all patients at 9 months following the procedure. Clinical follow-up was performed immediately after the procedure, prior to hospital discharge, at 30 days and at 6, and 9 months post procedure. The primary endpoints of the study were defined as post-procedural angiographic %DS ≤ 30%, IVUS mean lumen area ≥ 4mm^2 and in-hospital and 30 days major adverse cardiac event (MACE) rate defined as cardiac death, myocardial infarction (MI) and target lesion revascularization (TLR). Secondary endpoints

included 6 month MACE and 9 month angiographic restenosis rate, TLR, target vessel revascularization (TVR), target vessel failure (TVF) and MACE. TLR was defined as revascularization (any percutaneous intervention or bypass surgery) performed on the target lesion due to a stenosis including 5mm margins (proximal and distal to the stent) at any time after the index procedure; TVR was defined as revascularization performed on the target vessel at any time after the index procedure; TVF was defined as TVR, myocardial infarction, or death that could not be clearly attributed to a vessel other than the target vessel. A revascularization procedure was adjudicated as "clinically indicated" if the stenosis of the treated lesion was at least 50% of the lumen diameter on the basis of QCA in the presence of ischemic signs or symptoms, or if the diameter stenosis was at least 70% irrespective of the presence or absence of ischemic signs or symptoms. Device success was defined as attainment of ≤ 30 % residual stenosis immediately following the procedure of the target lesion using only the assigned device. Procedural success was defined as attainment of a ≤ 30% residual diameter stenosis of the target lesion and freedom from in-hospital MACE.

Imaging Analysis

Angiographic and IVUS data were analyzed by an independent core laboratory (Cardialysis, Rotterdam, Netherlands). The QCA analysis was performed with the CAAS II analysis system (Pie Medical BV, Maastricht, the Netherlands). All angiographic measurements were obtained within the stented segment (in-stent) and over the entire segment consisting of the stent and its 5mm proximal and distal margins (in-segment). Acute gain was calculated as a difference between minimal lumen diameter (MLD) after the procedure and MLD at baseline. Late lumen loss (LL) was a difference between MLD after the procedure and MLD at follow-up. Percent diameter stenosis (%DS) was defined as ([reference vessel diameter – minimal lumen diameter] / reference vessel diameter) x 100%. The case was classified as a binary restenosis when percentage diameter stenosis was equal or greater than 50% in the target lesion. The CURAD QCU Analysis Software (Curad B.V., Wijk bij Duurstede, the Netherlands) was used to analyze the IVUS images obtained immediatelly after stents implantation and at 9-month follow-up. Analysis was performed at the target segment (stent ± 5mm) to measure and calculate the lumen, vessel, plaque and stent volumes. In addition, mean stent symmetry, in-stent obstruction volume (%) and number of patients with mean lumen area ≥ 4.0mm^2 were analyzed.

RESULTS

Study Population

A total of 33 patients were screened and 4 were not finally included in the study population due to procedurally-related exclusion criteria. The baseline clinical variables are shown in Table 1. The mean age of all 29 included patients was 60 years of whom almost 59% were male.

Table 1. Baseline demographic characteristic

	n=29
Age (years)	60.2 (7.6)
Male sex	17 (58.6%)
Diabetes	12 (41.4%)
Insulin-requiring	3 (10.3%)
Hypertension	18 (62.1%)
Hyperlipidemia	19 (65.5%)
Current smoker	7 (24.1%)
Renal insufficiency	0 (0%)
Family history of CAD	3 (10.3%)
Prior myocardial infarction	10 (34.5%)
Prior percutaneous coronary intervention	6 (20.7%)
Prior coronary-artery bypass grafting	0 (0%)
Stable angina pectoris	9 (31%)
Unstable angina pectoris	20 (69%)
Coronary artery disease	
1 - vessel	11 (38%)
2 - vessel	14 (48%)
3 - vessel	5 (17%)
Baseline ejection fraction (%)	57.6 (±8.4%)

Demographic features were similar to other published stent studies except for a slightly higher number of diabetic patients (41%, 10.3% requiring insulin therapy). Almost one third of all patients had a history of prior myocardial infarction, 21% had previous percutaneous revascularization and more than 50% presented two or three coronary vessel disease.

In-Hospital Outcomes

Procedural characteristics including baseline lesion characteristics and distribution as well as procedural data are presented in the Tables 2 and 3. The mean baseline vessel diameter was 2.94 ± 0.34 mm and % DS was 53.97 ± 11.11 % which decreased to 35.9 % ± 8.2% immediately following pre-dilatation and luminal shield implantation and further decreased to 16.71% ± 6.53% after final balloon post-dilatation. Post-dilatation was performed in 93% of patients achieving an average in-stent acute gain of 1.09 mm. In all patients %DS <30% was achieved and device success was 100%. No patient required bailout stenting. There were no peri-procedural complications and no incidents of MACE, repeat revascularization or stent thrombosis during hospitalization period.

IVUS Analysis of Luminal Shield Mechanics

IVUS analysis revealed that the average minimal lumen area before intervention was 2.75 ± 0.74 mm^2. Immediately following low pressure balloon-dilatation and luminal shield implantation the average minimal lumen area increased to 4.49 ± 1.20 mm^2 (63.3 % increase from baseline). Following final balloon post-dilatation of the luminal shield, all patients reached a

Table 2. Angiographic characteristics of the target lesions.

	n=29
Target lesion coronary artery	
Left anterior descending	8 (27.6%)
Left circumflex	8 (27.6%)
Right	12 (41.4%)
Ramus intermediate	1 (3.4%)
Lesion length (mm)	11.20 (±3.89)
Reference vessel diameter (mm)	2.94 (±0.34)
Minimum lumen diameter (mm)	1.35 (±0.31)
% Diameter stenosis	53.97 (±11.11)
Baseline TIMI flow = 3	29 (100%)

Table 3. Procedural characteristics.

Mean stent diameter (mm)	3.88 ±0.29
Stent length (mm)	15.0
Predilatation	29 (100%)
Balloon diameter (mm)	2.5
Mean pressure (atm.)	7.66 ±2.21
Post dilatation	27 (93.1%)
Balloon diameter (mm)	3.28 ±0.25
Mean pressure (atm.)	10.3 ±3.8
Number of patients requiring post-dilatation	27 (93%)
Patients requiring bailout procedure	0
Device success	29 (100%)
Procedural success	29 (100%)
Geographic miss	1 (3.4%)
No of patients with post-procedural %DS < 30%	29 (100%)
Final TIMI flow = 3	29 (100%)

post-procedural mean shield lumen area ≥ 4.0 mm^2 (mean shield area post procedure = 6.11 ± 1.23 mm^2) and all had mean shield symmetry index ≥ 0.7 (0.87 ± 0.04). However, commonly the lumen area tended to be slightly lower in the center of the device where the plaque burden was the highest (Figure 3). Overall, the net acute volumetric luminal gain at the end of the procedure was 15% (Figure 4).

Long-Term Outcomes

Clinical, angiographic and IVUS follow up was completed in all enrolled patients. During 9 month follow-up no case of death, myocardial infarction or stent thrombosis occurred. In total, there were 3 cases of MACE, all caused by TLR. Two patients with TLR presented with symptoms of unstable angina 2 and 7 months following luminal shield implantation. In all these patients there was angiographic evidence of in stent re-stenosis and all the patients were successfully treated with drug eluting stent (DES) implantation. These two cases were qualified as a clinically-driven TLR. The third patient with TLR underwent successful PCI with DES implantation after

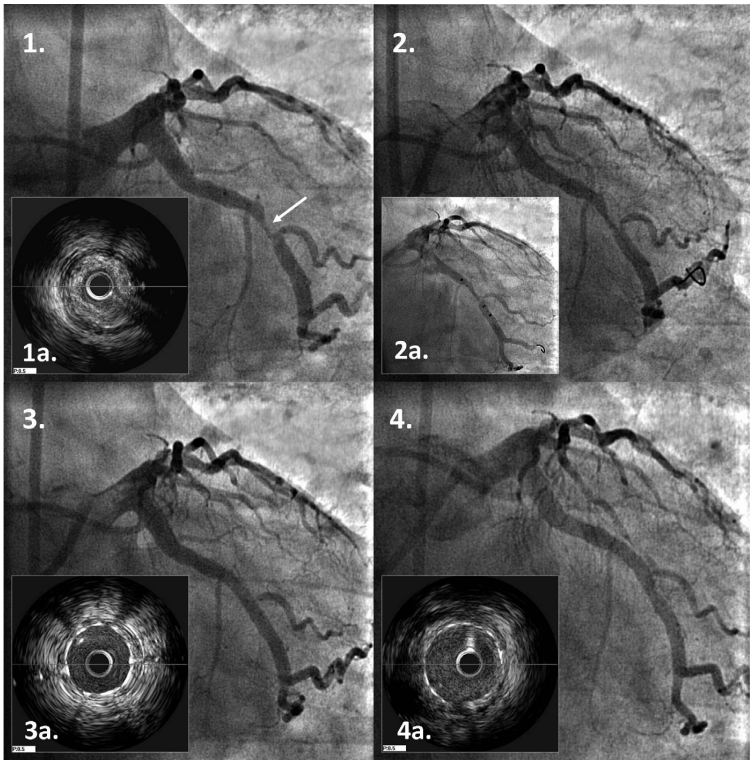

Figure 2. vProtect luminal shield placement in the left circumflex (LCX) artery (LAO 0, CAU 20) of a patient undergoing PCI. (1). Baseline angiography presenting lesion in a mid LCX (%DS = 68%); (1a). IVUS cross sectional view. (2). Effect after balloon pre-dilatation (balloon 2.5 x 9mm; max. pressure: 12 atm); (2a). vProtect Luminal Shield (4.0 x 15mm) positioning. (3). Final effect after vProtect placement and balloon post-dilatation (balloon 3.5 x 8mm; max. pressure: 12 atm); (3a). IVUS cross sectional view of the final effect. (4). Angiographic results at 9-months follow-up; (4a). IVUS cross sectional view at 9 month follow-up. Image courtesy of Corbic Research Institute, Envigado, Colombia.

the planned 9-month control angiography revealed significant in-stent restenosis. The average in-stent LL at 9 month follow-up was 0.50 mm, mean in-stent % DS was 28.3% and the total binary restenosis rate was 10.3%.

IVUS Analysis of Vascular Remodeling

At 9 months, IVUS volumetric analysis displayed an additional 13% increase in the total shield volume compared to the post-implantation values (total increase in shield volume over time of 28%). The mean shield area at 9 months was 7.00 ± 1.41 mm^2 (additional 14.6 % increase). In addition, the volumetric analysis showed that there was a slight increase (5%) in total vessel volume over time (figure 4). The resulting in-stent obstruction volume was 19.8% and the mean stent symmetry index was 0.89.

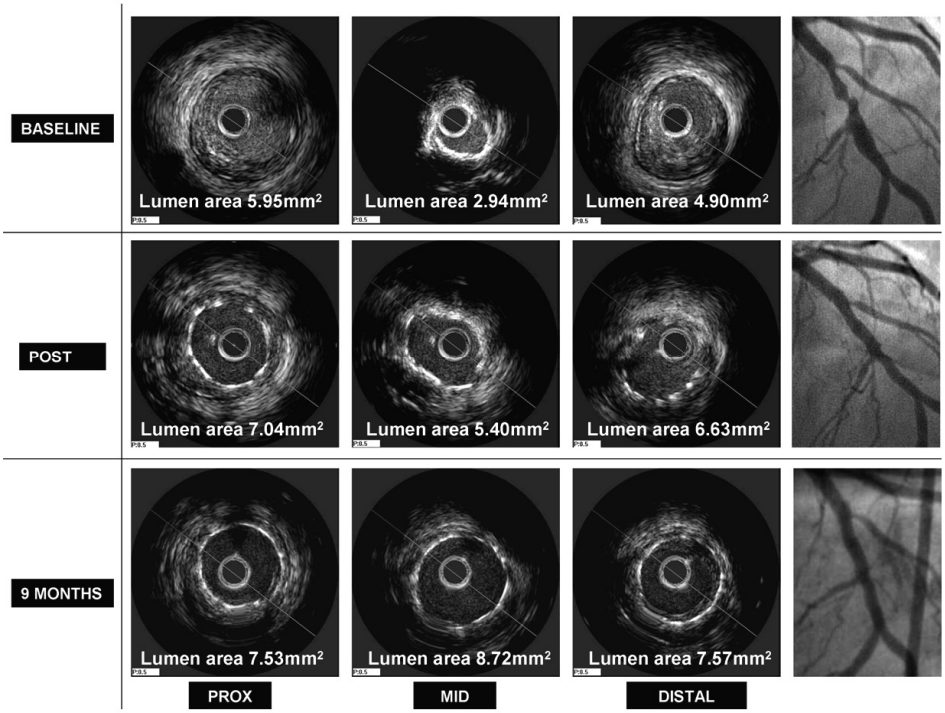

Figure 3. IVUS analysis of vessel remodeling at proximal, mid and distal segments of shield at different time points. Immediately following shield implantation the average lumen area was slightly lower in the center of the device where the plaque burden was the highest. During the next 9 months the shield continued to enlarge resulting in a final lumen area comparable to what has been reported in BES studies with optimal device symmetry.

DISCUSSION

Clinically available coronary stent technologies base their mechanism of expansion on the plastic deformation of its metallic structure via balloon inflation (6, 7). This mechanism of stent delivery elicits an unpredictable degree of mechanical injury to the vessel wall typically resulting in an injury-dependent pattern of vascular healing and restenosis (5). Similarly, due to its limited capability of expansion, stent malapossition is a common phenomenon seen following BES deployment especially in clinical circumstances in which the lumen of the vessel can not be accurately determined (i.e., STEMI) (3). Due to their intrinsic mechanical properties and material composition, self-expanding stent technologies have the potential to improve some of these limitations (6). Specifically, self-expanding stent platforms have the ideal mechanical characteristics for the treatment of coronary lesions in which either high-radial expansive forces are not required (i.e., non-calcific), stent-wall apposition is highly desirable (i.e., STEMI) or the potential for distal embolization during PCI is likely (i.e., large necrotic cores) (2).

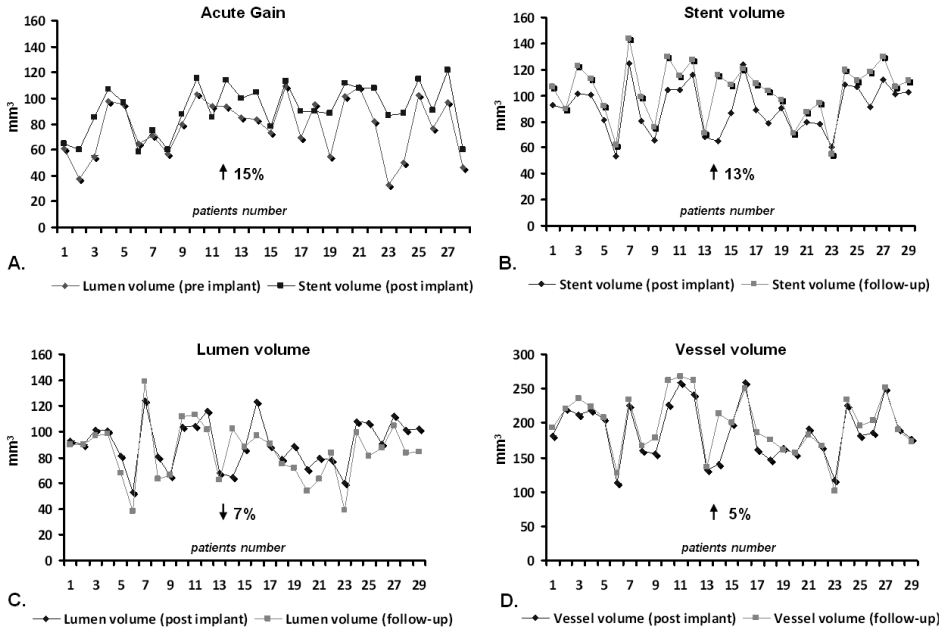

Figure 4. Mechanical behavior of the vProtect™ luminal shield and its influence on vessel and lumen remodeling based on IVUS calculations. (A). Acute gain (calculated as a difference between shield volume post-procedure minus lumen volume measured at baseline); (B). Stent volume change (difference between stent volume post-procedure and stent volume at 9 month follow-up); (C). Lumen volume change (difference between lumen volume post-procedure and lumen volume at 9 month follow-up); (D). Vessel volume change (difference between vessel volume post-procedure and vessel volume at 9 month follow-up).

In this study, we evaluated the safety and efficacy of implantation a new self-expanding (SE) luminal shield (vProtect™ Luminal Shield, Prescient Medical, Doylestown, PA) for the therapy of intermediate lesions in patients scheduled for PCI with evidence of myocardial ischemia. The device utilized in this study is structurally and mechanically different to previous generations of SE stent technologies. The luminal shield is characterized by maintaining lower and more stable chronic outward expanding forces over time thus resulting in lower degree of vascular injury (4, 8). Previous biomechanical testing has shown that the luminal shield posses 50% less chronic outward forces than the previously clinically tested Radius™ stent (Boston Scientific, Natick, MA), however, maintaining a similar radial resistance force at the same dilation diameters (2). Preliminary animal data demonstrated proper vascular healing and no evidence of chronic over-expansion over 180 days in normal porcine coronary arteries (9).

In this study, we used a very specific pre-dilatation technique aiming to facilitate the analysis of the biomechanical behavior of the luminal shield. Following shield implantation, IVUS analysis showed that the final mean lumen area achieved (6.11 ± 1.23 mm^2) was slightly lower than the average mean lumen areas reported in clinical trials of contemporaneous BES technologies (range from 6.5 to 9.3mm) (3, 10, 11) and first generation SES (7.7 ± 2.1 mm^2, Radius

Table 4. Clinical outcomes.

In-hospital and through 30 days post-procedural events	N (%)
MACE (all)	0
Cardiac death	0
Myocardial infarction (Q-wave and non-Q-wave)	0
TLR	0
Events at 6 months	
MACE (all)	1 (3.4%)
Cardiac death	0
Myocardial infarction (Q-wave and non-Q-wave)	0
TLR	1 (3.4%)
Events at 9 months	
MACE (all)	3 (10.3%)
Death (cardiac and non-cardiac)	0
Myocardial infarction (Q-wave and non-Q-wave)	0
Clinically-indicated TLR	2 (6.9%)
Any TLR	3 (10.3%)
Clinically-indicated TVR	2 (6.9%)
Any TVR	3 (10.3%)
Any TVF	3 (10.3%)
Stent thrombosis	0

Table 5. Procedural and 9 months angiographic analysis.

	Mean (n=29)
Post procedure	
Acute gain in-stent (mm)	1.09 (±0.33)
Acute gain in-segment (mm)	0.93 (±0.36)
Reference vessel diameter (mm)	2.85 (±0.35)
Minimum lumen diameter in-stent (mm)	2.44 (±0.24)
Minimum lumen diameter in-segment (mm)	2.28 (±0.30)
% Diameter stenosis in-stent (mm)	16.71 (±6.53)
% Diameter stenosis in-segment (mm)	19.79 (±7.05)
9 months follow-up	
In-stent % diameter stenosis	28.34 (±12.13)
In-segment % diameter stenosis	28.38 (±12.31)
In-stent minimum lumen diameter (mm)	1.95 (±0.41)
In-segment minimum lumen diameter (mm)	1.91 (±0.40)
Reference vessel diameter (mm)	2.66 (±0.36)
In-stent lumen loss (mm)	0.50 (±0.30)
In-segment lumen loss (mm)	0.38 (±0.31)
Binary restenosis (all)	3 (±10.3%)
Clinically driven	2 (±6.9%)
Angiographic	1 (±3.4%)

stent, Boston Scientific, Natick, MA) (11). These changes are reflected on the ~16% residual angiographic diameter of stenosis typically not seen in BES trials following immediate stent implantation. IVUS analysis showed that the device was always apposed to the vessel wall and

Table 6. Intravascular Ultrasound (IVUS) analysis.

	Mean (n=29)
Post procedure	
Luminal volume (mm3)	90.39 (±18.76)
Vessel volume (mm3)	188.3 (±41.10)
Stent volume (mm3)	90.53 (±18.79)
Total Plaque Volume (mm3)	97.93 (±26.64)
In-stent plaque volume (mm3)	0.15 (±0.33)
Plaque behind stent volume (mm3)	97.78 (±26.71)
In-Stent obstruction volume (%)	0.17 (±0.36)
Mean stent symmetry	0.87 (±0.04)
No of patients with stent symmetry index ≥ 0.7	29 (100%)
No of patients with mean lumen area ≥4.0mm2	29 (100%)
9 months follow-up	
Luminal volume (mm3)	83.99 (±22.49)
Vessel volume (mm3)	197.8 (±42.67)
Stent volume (mm3)	104.2 (±21.70)
Total Plaque Volume (mm3)	113.8 (±26.05)
In-stent plaque volume (mm3)	20.30 (±8.02)
Plaque behind stent volume (mm3)	93.54 (±26.21)
In-Stent obstruction volume (%)	19.81 (±8.29)
Mean Stent symmetry	0.89 (±0.02)
No of patients with stent symmetry index ≥ 0.7	29 (100%)

conformed to the different degrees of plaque burden, displaying lower luminal areas at places in which the plaque burden was the highest. In addition, the shield had a good post-procedure symmetry index, demonstrating a homogeneous distribution of the radial force and no localized stent recoil.

The acute deployment of the shield and resulting mechanical behavior was not associated to any in-hospital or short-term clinical adverse events. The primary endpoint of this study, a combination of a post-procedural %DS ≤ 30%, an IVUS mean lumen area ≥ 4mm^2 and in-hospital through 30 days major adverse cardiac event (MACE) rate showed that the use of the shield was safe and feasible. At 9 months of clinical follow-up, there was no incidence of death, myocardial infarction or stent thrombosis. The total incidence of MACE was 10.3% (3 patients) and was related to target lesion revascularizations. Two of these patients classified as undergoing a clinically-indicated PCI as they presented symptoms of unstable angina at 2 and 7 months of follow-up respectively. In all cases, follow up angiography revealed in-stent restenosis which were successfully treated with DES implantatiThe long term IVUS analysis displayed very interesting findings in regards to the biomechanics of the device and its impact on vascular remodeling. In contrast to what has been previously published with previous generations of SE stent platforms (11), the luminal shield did not "over expand" over time. Instead, following device implantation, the shield starts off with a lumen area lower than previously reported, then the device continues to enlarge and finally achieves an additional 13% of area gain over 9 months

resulting in a final area comparable to what has been reported in BES studies (mean 7.55 mm; range: 6.5 – 9.4) (10-12). Interestingly, this increase in shield areas was not related to an increase in the total vessel dimensions (~5% increase of vessel volume; figure 4). Instead, the remodeling effect appeared to be related to plaque remodeling occurring over time throughout the length of the device. Conversely, previous data suggests that the Radius stent achieved stent areas comparable to BES almost immediately following stent implantation and then over-expansion occurred (20% to 40% in stent areas) over time (11, 13, 14). This relatively high increase of the Radius stent volume over time may have been responsible for additional injury to the vessel wall resulting in a higher restenosis rate (24%) and late lumen loss (0.82 – 0.98mm) at 6 month follow-up compared to our study (13-15). In the present study, although the lower restenosis rate may have been related to the mechanical properties of the device itself, it is possible that the technique employed for plaque and device dilatation ("gentle balloon dilatation") may have played a role in the lower restenosis rate found in this study. It is important to highlight that one case of restenosis found in the present study was most probably related to stent misplacement ("geographical miss") leading to edge restenosis rather than to a "classic" biological response of the vessel wall to a stent. Also, the control angiography and IVUS imaging were performed at 9 month follow-up as opposed to most previously published clinical trials evaluating the first generation SES at 6 month follow-up which further underline the value of our results.

The main limitation of the present study is the sample size and the highly selected population that was included in the study. Secondly, although the target lesions were defined as non-calcified we did not specify the type and morphology of underlying plaques which potentially may influence the results. Is summary, our study demonstrated that the implantation of an innovative luminal shield for the treatment of intermediate coronary lesions is safe and feasible. The device maintains its mechanical integrity following implantation and is capable to resists plaque compression forces. It induces progressive but well controlled vascular remodeling overtime, which is far less than originally reported with first generation self expanding stents. Due to its intrinsic mechanical properties, this device may improve the outcomes of PCI by inducing less injury at the time of implantation. Thus, this device could be indicated in specific patient subsets such as acute coronary syndromes if long-term data in a larger population subset is obtained.

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Disclosures

Authors: Juan F. Granada, Krzysztof Milewski, Maria Paola Uribe, Miguel Moncada, Andres Fernandez, Guillermo Blanco, Greg L. Kaluza, Joanna J. Wykrzykowska, Patrick W. Serruys, Gregg Stone and Juan A. Delgado have no conflict of interest.

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Chapter 22

Summary and conclusions.
Samenvatting en conclusie.

SUMMARY AND CONCLUSIONS.

While we are fully aware that the drug eluting stents still face challenges in complex patient populations, the first two "all-comers" studies comparing the first generation permanent polymer and new generation biodegradable polymer drug stent (LEADERS) and two new drug eluting permanent polymer stents (RESOLUTE) could only demonstrate non-inferiority but failed to demonstrate superiority of one device over the other, despite the fact that they had enrolled close to 80% of off-label indication cases. However, when the LEADERS patient population was further analyzed in sub-studies focusing on subgroups known to be particularly challenging to interventional cardiologists advantage of the new generation biodegradable polymer device over the first generation permanent polymer device could be demonstrated (Chapters 5, 7, 8, 9).

First and foremost, we have demonstrated for the first time that risk stratification scores such as SYNTAX score and ACEF score can be applied to the "all comers" PCI patient population and allow for meaningful risk assessment not only in patients with multivessel disease (Chapter 2 and 3). Further we showed that in the highest tertile of the SYNTAX score within this "all-comers" group, the two devices and their performance can be separated, with the new generation biodegradable polymer device being superior in primary clinical endpoints such as cardiac mortality (Chapter 5). Other challenging subgroups in which a distinction could be made between the devices are also studied in this thesis: small vessels (Chapter 7), long lesions (Chapter 8) and bifurcation lesions (Chapter 9, 10, 11). Furthermore, a demonstration was made that while superiority end-points are not reached at short term follow-up of 9 months, separation of clinical outcomes occurs at longer term follow-up of 3 years (Chapter 13). Whether the superior performance of the biodegradable polymer device has to do with its better strut coverage as demonstrated at 1 and 2 year follow-up by optical coherence tomography or other factors such as better profile of the device has still not been directly proven but the former is suggested by the results from our group. This issue of stent strut coverage also raises the question of the ability to stop the dual antiplatelet therapy sooner without increasing the pro-inflammatory markers as occurs in the case of many first generation devices (Chapter 16) and exposing the patient to higher risk of stent thrombosis. We have shown that patients within the highest tertile SYNTAX score treated with the biodegradable polymer device have lower stent thrombosis rates than patients treated with the permanent polymer first generation devices (Chapter 5).

The ultimate solution to the greatest remaining challenge of metallic devices, namely stent thrombosis, may potentially be the fully biodegradable scaffolding device (Chapter 17). This has been heralded as the 4th revolution in interventional cardiology, balloon angioplasty being the1st, metallic bare metal stent being the 2nd and metallic drug eluting stents being the 3rd. Again, performance of these devices in the most challenging lesion subsets and patient populations will determine if these devices/scaffolds will be the future of our clinical practice. We have started to formulate the plan to further explore the issues of prediction and prevention of

stent thrombosis in the synopsis of the European Union grant proposal (Chapter 17; full grant text available electronically on demand).

Lesions at high risk of causing an acute coronary syndrome such as non-obstructive thin cap fibroatheromas (Chapter 15) may also benefit from a dedicated device such as a gentle outward force self-expanding rather than balloon-expandable device. The former would reduce the trauma to the vessel wall but passivate the plaque and induce protective fibrous cap formation as is suggested by the pilot SECRITT trial and its companion vPROTECT first in man study (Chapter 18-21). The ultimate challenge of treating these high risk lesions at risk of rupture, however, remains their appropriate diagnosis of the patient and identification of the lesion whether with biomarkers and/or intravascular imaging methods (Chapter 14 and 15). As we have shown in IBIS-1 proteomic analysis and in a substudy of the PROSPECT trial aiming at establishing whether thin cap fibroatheroma lesions tend to be more proximally distributed and therefore more easily accessible to focal treatment, diagnosis of truly "vulnerable patient and plaque" still remains elusive.

Last but not least in this thesis we explored the performance of bare metal stents, drug eluting stents versus coronary artery bypass surgery in diabetic patients at 5 years follow up within the ARTS studies population showing that while the safety of the drug eluting stents at five years at long term follow-up is equivalent to CABG, the efficacy remains better for CABG (Chapter 1 and 12). Bare metal stent treatment in patients with diabetes is unsafe. We have summarized the state of the art knowledge of multivessel disease treatment in a book chapter that serves as an introduction to this thesis (Chapter 1).

SAMENVATTING EN CONCLUSIE.

Het gebruik van drug eluting stents in complexe patiëntenpopulaties staat nog steeds voor grote uitdagingen. De eerste twee "all-comers" studies LEADERS, waarbij de eerste generatie duurzame polymere stents werden vergeleken met nieuwe generatie stents met oplosbaar polymeer, de zogenaamde biodegradables, en RESOLUTE, waarbij twee verschillende nieuwe drug eluting met duurzaam polymeer vergeleken werden, toonden beide studies non-inferioriteit aan, maar slaagden ze er niet in om superioriteit van de ene stent boven een andere aan te tonen, waarbij aangetekend dat er bijna 80% van de patiënten waren geïncludeerd met een off-label indicatie. Wanneer de LEADERS patiëntenpopulatie echter in bepaalde subgroepen, die als moeilijk behandelbaar te boek staan, werd onderverdeeld bleek er wel degelijk voordeel te kunnen worden aangetoond van de nieuwe generatie biodegradable stents ten opzichte van de eerste generatie duurzame polymere stents (hoofdstukken 5, 7,8 en 9).

Wat we vooral en als eerste hebben aangetoond is dat het gebruik van risico stratificatie scores zoals de SYNTAX of de ACEF scores toepasbaar zijn op alle patiënten die percutane coronaire interventie ondergaan en dus niet alleen bij patiënten met meervatslijden (Hoofdstuk2). Daarbij toonden we aan dat in het hoogste tertiel van de SYNTAX score van deze all-comers groep een verschil is tussen de twee soorten stents en hun prestaties, waarbij de nieuwe biodegradable stent superieur was in primaire klinische eindpunten zoals cardiale mortaliteit (Hoofdstuk 5). Andere moeilijk behandelbare subgroepen waarbij eventuele verschillen tussen de verschillende stents zou kunnen worden aangetoond zijn ook onderzocht in dit proefschrift, zoals kleine vaten (Hoofdstuk 7), lange laesies (Hoofdstuk 8) en bifurcatie laesies (Hoofdstukken 9, 10 en 11). Bovendien werd aangetoond dat de uitkomsten, hoewel nog niet verschillend na korte follow-up van 9 maanden, na een langere follow-up van 3 jaar wel verschillend werden tussen de verschillende stents (hoofdstuk 13). Of het superieure resultaat van de biodegradable stent te verklaren valt uit een betere bedekking van de struts van de stent zoals aangetoond werd met behulp van optical coherence tomography na 1 en 2 jaar follow-up of verklaard kan worden door andere factoren zoals een beter profiel van de stent is nog niet direct bewezen, maar de resultaten van onze onderzoeksgroep ondersteunen de eerste verklaring. Betere strut bedekking zou eventueel ook de mogelijkheid scheppen om de dubbele antiplaatjes therapie eerder te stoppen zonder dat de pro-inflammatoire markers stijgen zoals bij veel eerste generatie stents het geval is (Hoofdstuk 16) en waarbij de patiënt aan een hoger risico van stent trombose wordt blootgesteld. We hebben laten zien dat patiënten binnen het hoogste tertiel van de SYNTAX score die behandeld zijn met biodegradables een lagere stent trombose hebben dan patiënten die met een eerste generatie duurzame polymere stent behandeld is (Hoofdstuk 5).

De ultieme oplossing voor de grootste overgebleven uitdaging van metalen stents, namelijk stent trombose, zou potentieel de volledig oplosbare devices, oftewel de fully biodegradable scaffolding devices, kunnen zijn (Hoofdstuk 17). Dit wordt binnen de interventiecardiologie,

na de introductie van ballonangioplastiek, bare metal stents en de drug eluting stents aangekondigd als de vierde revolutie. De uitkomsten van het gebruik van deze nieuwe devices in moeilijk behandelbare laesies en patiëntenpopulaties zullen bepalen of deze devices in de toekomst in de kliniek gebruikt zullen gaan worden. In de samenvatting van de aanvraag voor de Europese Unie beurs hebben we een plan geformuleerd om voorspelling en preventie van stent trombose nader te onderzoeken. (Hoofdstuk 17; volledige tekst van de beursaanvraag is op aanvraag elektronisch verkrijgbaar).

Laesies met hoog risico voor het veroorzaken van een acuut coronair syndroom zoals een niet obstructieve fibroatheroom met dunne kap (Hoofdstuk 15) zouden ook kunnen profiteren van speciaal voor het type laesie ontworpen stents, zoals een zichzelf ontvouwende stent in plaats van een stent die zich ontvouwd met hulp van een ballon. De eerste zou schade van de vaatwand laten afnemen, terwijl de plaque bedekt wordt en de formatie van een beschermende kap wordt geïnduceerd zoals gesuggereerd wordt in de pilot SECRITT trial en de gerelateerde vPROTECT first in man study (Hoofdstukken 18-21). De ultieme uitdaging van de behandeling van laesies met verhoogde kans op rupturatie blijft echter het herkennen van dergelijke laesies met behulp van biomarkers en/of intravasculaire beeldvormende methodes (Hoofdtukken 14 en 15). Zoals we in de IBIS-1 proteomic analyse en in een substudie van de PROSPECT trial, waarbij werd beoogd om aan te tonen of fibroatherome laesies met dunne kap meer geneigd zijn om meer proximaal gelegen te zijn en zodoende makkelijker bereikbaar voor focale behandeling, hebben aangetoond blijft de diagnose van de "kwetsbare patient en plaque" ongrijpbaar.

Tot slot hebben we de resultaten onderzocht van bare metal stents versus drug eluting stents versus coronaire arteriële bypass chirurgie (CABG) in patiënten met diabetes na 5 jaar follow-up in de patiëntenpopulatie van de ARTS studies. Daarbij werd aangetoond dat, hoewel de veiligheid gelijk was, CABG betere uitkomsten liet zien ten opzichte van de drug eluting stents (Hoofdstukken 1 en 12). Bovendien bleek behandeling met bare metal stenst in patiënten met diabetes bleek niet veilig. Ten slotte hebben we de state-of-the-art kennis over behandeling van meervatslijden in een hoofdstuk voor een boek samengevat dat tevens dient als een introductie van dit proefschrift (Hoofdstuk 1).

Chapter 23

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My deepest thanks for this thesis and all the guidance and friendship go, of course, to my mentor, Professsor Patrick Serruys. I remember meeting Professor Serruys for the first time at the Interventional cardiology course in Snowmass, Colorado. I was a second year cardiology fellow at Harvard Medical School and was presenting an abstract based on some pre-clinical work on a new cell therapy technology that I had done (now published in *Circulation*). Although the presentation was before the main session Professor Serruys was there listening attentively and asking very challenging questions. His comments and talks were the highlight of that meeting. It was probably at that time that I decided to apply for a fellowship position with Professor. Starting from the interview day where I was able to observe very educational cases and joined the Eurointervention Journal meeting, it was a challenge and an adventure. I will never forget the live cases we did together where I received the best instruction ever, and learned from both the criticism of my wiring technique to compliments on perfect stent deployment. Professor's enthusiasm for angioplasty and the new technologies was infectious. I think the best quote that I still have on tape was at the end of a two hour bifurcation case: "This is fun angioplasty." I learned from the easiest and the most complex cases. I learned to identify new research questions while doing cases in the cath lab. I learned watching him talk to patients with great sympathy and understanding. At the end of that same long bifurcation case, Professor asked the patient whether she'd like to have her simple RCA stented now or was she tired and would prefer to come back at a later date. She was tired. And the Professor said to her: "Me too.". That honesty was disarming. What was also remarkable is his ability to be your real "guardian angel" during the cases and knowing exactly when to let you proceed on your own with a tough case while he read over his email in the back and when to scrub in. He demanded discipline and high standards, of course, and taught you to carefully look at angiograms and anticipate problems. I am sure that what I learned at Tuesday morning meetings helped me avoid many of the "booby traps". And it is the hands-on learning in those last two years that now earns me compliments and trust of patients and colleagues at AMC and allows me at times to make people better. Most importantly, I am grateful for the guidance in research and all the opportunities, from multiple papers, challenging large projects such as Atheroremo and SECRITT, opportunity to participate in writing the two grants and developing my own ideas. Whether it was discussions at Cardialysis, in your attic at home on the weekend or over a glass of wine after a murderous game of tennis, these were all precious learning moments.

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Chapter 24

Curriculum Vitae

CURRICULUM VITAE

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Education:

2008-2010	PhD candidate in Interventional Cardiology, Thoraxcentrum, Erasmus MC, Rotterdam NL
2002 MD	Harvard Medical School and Massachusetts Institute of Technology, Boston MA
1996 BA	Smith College, Biochemistry (with High Honors), Northampton MA
1993	Marymount International School, International Baccalaureate, London UK

Postdoctoral Training:

4/2010-9/2010	Cardiology fellowship training (ECHO and ICU), Thoraxcenter, Erasmus MC, Rotterdam, NL (towards Dutch MSRC registration in Cardiology)
5/2008-4/2010	Interventional Cardiology Clinical Fellowship under Patrick W. Serruys (more than 500 primary operator cases), Thoraxcentrum, Erasmus MC, Rotterdam, NL
2005-2008	Cardiology Fellowship, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA (American Board Certification in Cardiovascular Medicine)
2002-2005	Internship and Residency in Internal Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA (American Board Certification in Internal Medicine)

Hospital or Affiliated Institution Appointments:

10/2010	Interventional Cardiologist, Academic Medical Center, Amsterdam, NL
2008-2010	Interventional Cardiology Clinical and Research Fellow, Thoraxcentrum, Erasmus MC, Rotterdam, NL
2005-2008	Clinical Fellow in Cardiology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
2002-2005	Clinical Fellow in Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Major Committee Assignments:

2008-2010	Vulnerable plaque meeting organizing committee
2008-2010	Associate Editor, Editorial Board of Eurointervention Journal
2006- 2008	Medical Advisory Board for the Goodwin Group Int. (Medical publishing group – MD Connect Express)
1998-2000	Admissions Committee, Harvard Medical School

Professional Societies:

2008	Fellow of the American College of Cardiology
2006-present	Harvard Stem Cell Institute
2006-present	Working group for the Interventional Section (European Society of Cardiology)
2006-present	American Heart Association
2005-present	American College of Cardiology
1998-present	Massachusetts Medical Society

Honors and Awards:

2008	**American Heart Association M. Leon/J&J Cordis Interventional**
2008	**American College of Cardiology Merck Research Fellowship in Cardiovascular Disease and Metabolic Syndrome (awarded)**
2008	**SCAI GE Fellowship (awarded)**
2006	**Richardson Fellowship/Research Grant** from the Harvard Medical School Alumni Association
2006/2007	**Finalist for the Massachusetts Technology Transfer Office Award:** Myotissue catheter design and Pericardial sail – cardiac restraint device for treatment of heart failure
2000	American Diabetes Association Physician Scientist Training Award (awarded)
1996	Howard Hughs travel award recipient
1996	Sigma Xi, Associate Member
1994	Albert Blakeslee Fund for Genetic Research Summer Research Award
1995-1995	Dean's List and First Group Scholar
1995-1995	National Dean's List, Multiple Year Award