# CONTEMPORARY CORONARY INTERVENTION TRIALCONDUCT

ADDRESSING THE 4P'S: PATENCY, PERFUSION, PERFORMANCE AND PREVENTION

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Financial support for the publication of this thesis was generously provided by:
Harcentrum Hasselt, Belgium.
Cardialysis, Rotterdam.

# Contemporary Coronary Intervention Trial Conduct.

**Addressing the 4P's: Patency, Perfusion, Performance and Prevention.**

## Toegepast klinisch onderzoek in kransslagader lijden.

Oog voor de 4P's: doorgangkelijkheid (Patent), perfusie, performantie en preventie

**proefschrift**

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

Prof.dr. H.G. Schmidt

En volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op

door
Pascal Vranckx
Geboren te Leuven, België.

**PROMOTIECOMMISIE**

| | |
|---|---|
| Promotor: | Prof.dr. P.W. Serruys |
| | Prof.dr. F. Zijlstra |
| Overige leden: | Prof.dr. P.J. De Feijter |
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# General Introduction and Outline of This Thesis

## GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

### Introduction

Atherosclerosis and coronary artery thrombosis remains a major cause of premature death worldwide, and are an important source of loss of disability-adjusted life years. (1-3) Coronary artery disease (CAD) has no geographic boundaries and represents a global pandemic. Treatment goals for patients with CAD are improvement in survival and a reduction in the risk of myocardial infarction (MI) and symptoms of coronary disease. (4) Percutaneous coronary intervention (PCI) with stent implantation of obstructive coronary lesions that cause ischemia can improve a patient's functional status and outcome. (5-7) The expanding indications of PCI coupled with refinements in technology including the introduction of drug-eluting stents (DES) and more intensive adjunctive pharmacological treatment, resulted in treatment of increasingly complex lesions and patients with a history of established cardiovascular disease, coexisting morbidities, and/or complex coronary anatomy in recent years. (8) A substantial number of these patients were excluded from the initial coronary stent studies. However more recently, large 'all-comers' investigations of stents have been performed enrolling unrestricted patient populations.(9-11) These studies most closely reflect the routine clinical practice of PCI. (12)

Although PCI is highly effective for the management of obstructive CAD, it can potentiate an existing pro-thrombotic state around lesion areas and lead to ischemic complications. A certain level of anticoagulation is required to perform PCI safely and to minimize the peri-procedural risk of thrombosis and its attendant complications of death and myocardial infarction. Many different anti-thrombotic regimens have been investigated and are currently in use. The choice of the concomitant pharmacological environment (dual or even triple antiplatelet therapy and anticoagulants) proved critical, as is the dosage of the drugs.(13-14) The value of a peri-procedural antithrombotic regimen depends on the balance between prevention of ischemic complications and bleeding risk.(15)

In order to evaluate the effects of a particular treatment strategy on mortality and major morbidity within a disease entity, large, truly global clinical trial programs with relatively long-term clinical endpoints have become the accepted standard. The critical challenge in the conduct of endpoint trials, relates to the definition, collection and accurate assessment of endpoint data in a consistent timely manner.

Consensus on uniform definitions is required to enable meaningful, albeit informal and indirect, comparisons between clinical trials, and the ability to aggregate data across individual clinical trial(program)s, patient subgroups, or device models adds critical knowledge, particularly with regard to safety. The need for uniform endpoint

definitions and the harmonization of clinical event adjudication has been addressed by the Academic Research Consortium (ARC) group. The ARC-group proposed endpoints for uniform implementation in modern DES-versus-DES trials and on bleeding. (4, 16-17) The ARC consensus definitions were intended to be applied to relatively homogeneous populations with stable presentations of coronary disease. An important challenge in this process is to adapt the initial definitions, while maintaining accuracy and consistency across geographic areas and over the long course of the study. This may prove even more important while addressing minimally selected populations, including complex patients, reflecting routine clinical practice.

On this background the primary goal of this thesis were to:

I. Access the long-term stent and patient oriented composite outcome measures in all-comers undergoing PCI allowing the unrestricted use of 2nd generation DES.
II. Access the external validity of the actual proposed endpoints, and linked clinical event adjudication process, in contemporary all-comers stent trials allowing the unrestricted use of DES.
III. Access the impact of modified anti-thrombotic and anti-platelet regimens in patients undergoing PCI and stenting with regard to clinical outcomes.
IV. Assess the safety and tolerability and preliminary efficacy of hemoglobin-based oxygen carriers in patients suffering coronary artery disease.
V. Assess the prevalence of baseline demographic and the cardiovascular risk profile of patients included in coronary stent investigations.

The 4-P treatment concept, addressing coronary Patency, myocardial Perfusion, left ventricular Performance and 2nd Prevention for patients undergoing PCI, provided the framework to structure this thesis. In the summary and conclusion section we will focus on lessons learned important for future trial design.

**Part 1 (chapters 1.1-1.9)** of this thesis starts of (chapter 1.1) with a 'historical' device oriented outcome study testing, in a true global context the first indigenously designed and evaluated low cost DES from Asia to have obtained a Conformité Européenne (CE) quality certificate for commercialisation in Europe. Stable patients undergoing elective PCI for a single, de novo lesion of a native coronary artery were included.

With a quantum leap forward Chapter 1.2 contains the 2-year follow up data of the first randomised controlled coronary stent trial in an all-comers allowing the unrestricted use of 2nd generation DES.

Chapter 1.3-1.9 introduces the interested reader in specific aspects of All-comers trial methodology. In chapter 1.3-1.5 we scrutinize the issue of stent thrombosis and make

reference to the Resolute All Comers and ARTS-II trials. Stent thrombosis is a catastrophic complication of coronary stenting, presenting as sudden death or non-fatal myocardial infarction in almost all cases (Chapter 1.4-1.5, ).

In Chapter 1.6-1.7 we analysed evidence of myocardial injury due to PCI in the Resolute All Comers trial. We considered 3 different cardiac biomarkers and evaluated the differential implications of biomarker preference in MI-endpoint definitions on final outcome reporting and associated later case fatality. Clinical event committees (CEC) must be rigorous and consistent in their analysis of data to maximize the clinical and research value of clinical trial data. The quality of the CEC-process should be assessed on an on-going basis throughout a trial program via internal and/or external validation. The main findings and potential consequences on outcome reporting of an external validation of the CEC adjudication process applied to the Resolute All-comers trial are reported in chapter 1.8. Invasive coronary physiological studies have demonstrated favorable outcomes for decision-making in patients with intermediate single-vessel stenosis and have evident potential as an adjunct to QCA in the setting of clinical trials. Based on the value of FFR in terms of objective and clinically relevant information, we support its incorporation into clinical studies to establish standardized reporting of specific device-related angiographic and clinical events: chapter 1.9.

**Part-2 (chapters 2.1-2.6):** Deals with bleeding risk in cardiovascular intervention trials. chapter 2.1 addresses the issue whether the site of bleeding matters. Chapters 2.2-2.6 investigates into (pharmacologic) bleeding avoidance strategies. Intravenous direct thrombin inhibitors (DTIs) have emerged as potential alternatives to heparin. Bivalirudin, the most investigated intravenous DTI, consistently demonstrated a reduction in bleeding risk and its associated case fatality (Chapter 2.2-2.3). Dabigatran is a novel, oral, direct thrombin inhibitor, recently licensed in Europe for stroke prevention in atrial fibrillation. Patients on oral anticoagulation in the need for an (emergent) PCI represent a clinical conundrum, as management guidelines for revascularisation are based on clinical trials that have largely excluded patients who receive long-term anticoagulation therapy. The D-fine study (Chapter 2.4) is the first attempt to study whether Dabigatran provides sufficient antithrombotic effect to obviate the need for adjunctive heparin in case of a PCI and prevent effectively peri-procedural complications. For more than a decade, the mainstay of antiplatelet therapy has been the combination of the cyclo-oxygenase inhibitor aspirin, and the adenosine diphosphate (ADP)-receptor antagonist clopidogrel. Evidence has emerged, however, regarding the inherent limitations of clopidogrel. Approximately 15% to 48% of patients have a poor platelet inhibition response to clopidogrel, a factor that contributes to a high residual risk of recurrent events (19-20) chapters 2.5-2.6 includes a series of studies addressing the impact towards clinical outcome of

specific changes to the antiplatelet therapy in patients undergoing PCI with stenting. chapter 2.5 outlines the results of the 3T/2R study on tailored intensification of anti-platelet treatment based on individual response to aspirin and/or clopidogrel. chapter 2.6 challenges the assumed need for endless dual anti-platelet therapy, a 6 versus 12 months dual antiplatelet (DAPT)-regimen is compared. Safety towards bleeding was assessed based on both the Bleeding Academic Research Consortium (BARC, appendix 2.1) and The Thrombolysis In Myocardial Infarction (TIMI) criteria.

Moving forward, **Part 3 (chapters 3.1-3.3)** assessed the potential role of hemoglobin-based oxygen carrier solutions (HBOC, chapter 3.1) to reduce myocardial ischemia in post-stenotic areas that plasma, but not red blood cells, may be capable of reaching. chapter 3.2 evaluated the safety and tolerability of HBOC up to 230 ml in low to moderate risk cardiac patients scheduled for elective PCI, chapter 3.3 the potential of HBOC in preserving global left ventricular function, as a surrogate for myocardial oxygenation, using the angioplasty balloon inflation model of brief ischemia in humans. When anything can go wrong, fix it (dr. P. Safar ǂ 2003)(appendix 4.1).

**Part 4 (chapters 4.1-4.4)** addresses the implementation of portable left ventricular assist devices in the catheterisation laboratory setting. chapter 4.4 describes the use and the effect on haemodynamic variables of the Impella Recover LP2.5 axial flow pump, chapters 4.1-4.3 the use of the Tandemheart, a low-speed, centrifugal, continuous-flow pump in various indications. A true percutaneous insertion technique was introduced.

The final section **Part 5 (chapters 5.1-5.5)** addresses the impact of clinical and angiographic (risk) factors on outcome after PCI. Chapter 5.1 shows trends in the baseline demographic and cardiovascular risk profile of patients included in stent investigations over the last decades. Whilst, chapter 5.2 to 5.5 respectively addresses the impact of the (angiographic) syntax score alone and of either angiographic and/or clinical risk scores on long term (1-2 year) outcome.

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# PART 1

## PATENCY/MECHANICAL: THE ACADEMIC RESEARCH CONSORTIUM CONSENSUS DEFINITIONS IN CONTEMPORARY ALL-COMERS INVESTIGATIONS: LOST IN TRANSLATION?

# CHAPTER 1.1

## Biodegradable-polymer-based, paclitaxel-eluting Infinnium stent: 9 month clinical and angiographic follow-up results from the SIMPLE II prospective multi-centre registry study

Vranckx P, Serruys PW, Gambhir S, Sousa E, Abizaid A, Lemos P, Ribeiro E, Dani SI, Dalal JJ, Mehan V, Dhar A, Dutta AL, Reddy KN, Chand R, Ray A, Symons J.

*for the SIMPLE II study team EuroIntervention 2006,* ***3****:310-17.*
[**original research paper**]

EuroIntervention

# Biodegradable-polymer-based, paclitaxel-eluting Infinnium™ stent: 9-Month clinical and angiographic follow-up results from the SIMPLE II prospective multi-centre registry study

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*R. Chand and A. Ray are employees of Sahajand Medical Technologies,India. J. Symons is an employee of Cardialysis B.V.,The Netherlands. All other authors have no conflict of interest.*

**KEYWORDS**
*Angioplasty, coronary artery disease, restenosis, revascularisation*

## Abstract

**Background:** SIMPLE II was a multi-centre, prospective registry study aimed at investigating the safety and efficacy of the Infinnium™ (Sahajanand Medical Technologies Pvt. Ltd, India) paclitaxel-eluting stent for the treatment of single *de novo* lesions in the native coronary arteries.

**Methods:** One hundred and three patients with symptomatic coronary artery disease were treated for single *de novo* native coronary artery lesions using the Infinnium™ stent (paclitaxel concentration 1.4 mcg/mm$^2$ released over 48 days) in a multi-centre, prospective study performed on 3 continents (Asia, Europe and South America). The primary safety endpoint was major adverse cardiac events at 30 days (MACE 30d) and efficacy was assessed by in-stent binary restenosis as measured by quantitative coronary angiography (QCA) at six-month follow-up. A clinical follow-up was scheduled at nine months.

**Results:** The mean patient age was 58.5 years; 70.9% were males; 43.7% had unstable angina and 38.8% previous myocardial infarction. Risk factors included hypertension in 62.1%, hypercholesterolemia in 52.4%, current smoking in 32.0% and diabetes in 28.2%. Stent implantation was successful in all patients, with more than one stent being implanted in 9 patients (8.7%). Hierarchical MACE 30d was 2.9%. At nine months, 101 patients had clinical follow-up (1 patient had died and 1 refused). There was one death (1.0%), one Q-wave myocardial infarction (Q MI) (1.0%), three non-Q MIs (2.9%), one clinically-driven target lesion Coronary Artery Bypass Grafting (CABG) (1.0%), and one clinically-driven target lesion repeat percutaneous coronary intervention (re-PCI) (1.0%). The overall event-free rate at nine months was 93.2%. QCA revealed in-stent and in-segment late loss of 0.38±0.49 mm and 0.18±0.46 mm, resulting in binary restenosis rates of 7.3% and 8.3%, respectively. There was one case of late stent thrombosis in the patient experiencing the Q MI and subsequent re-PCI.

**Conclusions:** The Infinnium™ paclitaxel-eluting stent appears to be safe and efficacious for the treatment of single *de novo* lesions in coronary arteries in a patient population with symptomatic coronary artery disease (CAD).

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## Introduction

Although the immediate success and safety of coronary stenting has dramatically increased, in-stent restenosis has persisted as a limitation hampering the medium-term efficacy of coronary stenting.[1,2] The elucidation of the molecular and cellular mechanisms of inflammation and cellular proliferation in vascular injury and repair powered the development of site-specific and controlled release of therapeutic agents through the drug-eluting stent (DES) technology.[3,4,5,6] The cell cycle is a common hub of the different phases of the restenosis process.[7] Antiproliferative agents, such as sirolimus and paclitaxel have been coupled with polymers that elute or slowly release these inhibitors from the stent surface. Variations in pharmacological mechanisms and stent-coating technologies elicited different vascular reactions.[8,9,10,11,12,13,14]

Paclitaxel (Taxol; Bristol-Myers Squibb), a natural diterpenoid compound extracted from the Pacific yew tree Taxus brevifolia, has diverse mechanisms of action, including microtubule stabilisation, arrest of cell mitosis, retardation of cell migration and immunomodulation.[15,16,17,18,19,20,21] Paclitaxel is also highly lipophilic and poorly soluble in aqueous solution, making it an excellent candidate for sustained delivery from stents and prolonged deposition in atherosclerotic vessels. Stents coated with a polymer (lactide-co-Σ-caprolactone) to control the release of the drug have already proved effective in reducing late loss and restenosis in a series of clinical trials, the TAXUS studies.[9,22,23]

Many different platforms that use polymer coating or surface modifications to adhere paclitaxel onto the stents have been utilised over the past two years. The biodegradable-polymer-based, paclitaxel-eluting Infinnium™ stent (Sahajanand Medical Technologies Pvt. Ltd, India) is the first indigenously designed and evaluated DES from Asia.

The purpose of the present study was to assess the safety and efficacy of the Infinnium™ stent in single *de novo* native coronary artery lesions.

## Methods

### Selection of patients

The study was a non-randomised registry trial performed at 8 medical centres (with a maximum patient inclusion of 25 patients per site) on 3 continents (listed in the Appendix). This protocol was approved by the hospital ethics committees and is in accordance with the Declaration of Helsinki. All patients gave written informed consent.

Patients were eligible for the study if they were at least 18 years old, were not of child-bearing potential, and had received a diagnosis of symptomatic ischaemic heart disease: stable or unstable angina (CCS class 1-4, Braunwald class IB, IC, IIB, IIC, IIIB, IIIC)[24] and/or objective evidence of myocardial ischaemia.

Additional eligibility criteria were the presence of a single primary target lesion in a native coronary artery that was 2.5 to 3.5 mm in diameter and that could be covered by one single study stent; if the coronary artery lesion was ≤10 mm (visual estimate) it had to be covered with a 19 mm stent and if it was >10 mm and ≤15 mm, it had to be covered with a 23 mm stent aiming for a lesion/stent ratio of at least 1.6. The luminal diameter of the lesion had to have a stenosis of 51-99%, as estimated visually, and a flow rate grade of 1 or more according to the classification of the thrombolysis in myocardial infarction (TIMI) trial.

Patients were not eligible for enrolment if they had any significant medical condition which could interfere with the patient's optimal participation in the study, a life expectancy of less than 12 months, a Q-wave or non-Q-wave myocardial infarction within 72 hours preceding the index procedure (unless the CK and CK-MB enzymes were less than twice the Upper Normal Limit), other revascularisation procedures within the previous 6 months or prior stenting within 5mm of the target lesion, an unprotected left main coronary artery stenosis (≥50%), an ostial lesion, a calcified lesion that could not be completely dilated before stenting, proximal tortuosity, angiographic evidence of thrombus within the target lesion, pre-treatment with devices other than balloon angioplasty, total occlusion, bifurcations (potentially requiring stenting of the side branch); another stenosis of more than 50% proximal or distal to the target lesion or in an other vessel, poor distal run-off, a left ventricular ejection fraction ≤30%, or an intolerance to aspirin, clopidogrel, ticlopidine, heparin, nickel, or contrast material. Patients were not allowed to be participating in another investigational drug or device study.

### The Infinnium™ Paclitaxel-Eluting coronary stent

The active ingredient in the Infinnium™ stent is Paclitaxel. The paclitaxel concentration loaded on each stent was maintained to 1.4 µg/mm$^2$. The drug was applied to the surface of a stainless steel (slotted tube design), balloon-expandable stent (Matrix, Sahajanand Medical Technologies Pvt.Ltd.) using biodegradable polymers (Poly L-Lactide, 50/50 Poly DL-Lactide-co-Glycolide, 75/25 Poly L-Lactide-co-Caprolactone and Polyvinyl Pyrrolidone) in multiple layers. The drug is coated in 3 different layers of combination of drug and polymer. Each layer has a different release profile. The cumulative release of drug from the polymer is at 48 days after implantation (see Figure 1).

### Study procedures

Lesions were treated with the use of contemporary interventional techniques. Predilatation was advised but direct stenting was also allowed. The investigators used similar materials and techniques throughout the study to maintain consistency and standardisation of care.

The investigator determined the appropriate diameter (2.5, 2.75, 3.0 and 3.5 mm) of the Infinnium™ stent to be implanted aiming for a stent/vessel ratio of 1.1:1 prior to stent placement (using the nominal pressure). Two different stent lengths were recommended aiming for a lesion/stent ratio of at least 1.6. If the lesion was ≤10 mm, it had to be covered with a 19 mm stent, and if it was >10 mm and ≤15 mm, it had to be covered with a 23 mm stent. After the stent was implanted, further dilation was performed as necessary to ensure that the residual stenosis (by on-line QCA) was

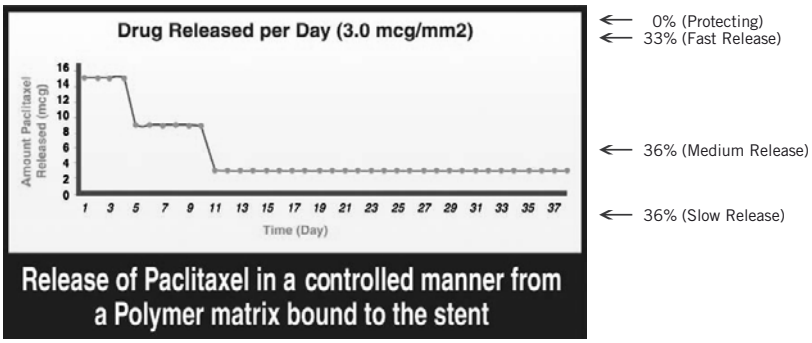


*Figure 1. The Infinnium™ paclitaxel-eluting coronary stent.*

≤20% and the mean reference diameter of the stent was >1.1 mm with respect to the reference diameter of the adjacent segments, with a TIMI grade III flow rate. In case of an edge dissection, an additional 11 or 16 mm Infinnium™ stent could be deployed adjacent to the first stent in order to cover the dissection.

Intravenous boluses of heparin were administered to maintain an activated clotting time that exceeded 250 seconds during the procedure and were discontinued immediately following the index PCI procedure in order to allow for sheath removal. Treatment with aspirin, at a dose of 160-500 mg (when the patient was not already on aspirin), was begun 12 hours before the procedure and continued indefinitely. A loading dose of (at least) 300 mg of clopidogrel was administered optimally 48 hours before the index procedure with a minimum of 4 hours, followed by (at least) 75 mg daily for 6 months. Alternatively, treatment with ticlopidine, at a dose of 250 mg twice daily, was begun one day before the procedure and continued for 6 months. The administration of a glycoprotein IIb/IIIa inhibitor was optional and left to the investigator's discretion according to clinical practice.

## Follow-up

Patients were evaluated at 30 days (±7 days) and at 6 and 12 months (±30 days). They were asked specific questions about the interim development of angina, according to the Canadian Cardiovascular Society classification of stable angina[25] and the Braunwald classification of unstable angina.[26] The patients were also monitored for major cardiac events and for the need for additional revascularisation of the index target lesion. An electrocardiogram was obtained at each visit, and an angiographic study was performed at a mean (±SD) of 183±19.3 days. A 6-month post-procedure follow-up angiography – independent of the clinical status – was requested per protocol. Other studies and tests were performed at the discretion of the investigators at the participating centres.

The decision to perform further revascularisation of the target lesion or vessel after the six-month angiographic study was based on clinical justification (see definition of clinically driven target lesion revascularisation under "Study endpoints").

## Quantitative Coronary Angiographic (QCA) evaluation

Coronary angiograms were obtained in multiple views after the intracoronary injection of nitrates. Quantitative analyses of all angiographic data before, during, and after the procedure were performed by an independent core laboratory (Cardialysis, Rotterdam, The Netherlands) with the use of edge detection techniques (CASS II, Pie Medical).[27] Visual assessments included TIMI flow, calcification, thrombus, lesion length, AHA/ACC classification, dissection grade and aneurysm. Interpolated reference diameter, minimal luminal diameter, and diameter stenosis were measured before dilation, at the end of the procedure, and at six months. Restenosis was defined as stenosis of ≥50% of the luminal diameter and was classified as in-stent if inside the stent or in-segment if located within the stented segment plus the 5-mm segments distal or proximal to the stent margins.[28] Late luminal loss was calculated as the difference between the minimal luminal diameter immediately after the procedure and the diameter at six months.

## Study endpoints

The primary goal included a reduction in the in-stent binary restenosis rate (luminal narrowing of ≥50%) at 6 months follow-up, as determined by quantitative angiography (QCA). Secondary goals included angiographic and procedural success, and a number of in-stent and in-segment (stent +5 mm proximal and 5 mm distal) vessel parameters derived by off-line QCA: acute gain, the minimal luminal diameter (MLD), the percentage of stenosis of the luminal diameter (% DS) and the mean lumen diameter.

The primary goal in this study also included a reduction of the composite of major adverse cardiac events (MACE) until 30 days, defined as cardiac death, Q-wave or non-Q-wave myocardial infarction, coronary artery bypass grafting (CABG) and clinically driven target lesion revascularisation (TLR). The secondary clinical endpoints were MACE until 9 months, device-related serious adverse events (DSAEs) until 9 months, and angiographic stent thrombosis (subacute: until 30 days, and late: until 9 months).

A non-Q-wave myocardial infarction was defined by an increase in the creatine kinase level to more than twice the upper limit of the normal range, accompanied by an increased level of creatine kinase MB, in the absence of new Q waves on the surface electrocardiogram. Angiographic success was defined as a successful delivery and deployment of the study stent – without the use of a device outside the study treatment strategy – and a final residual stenosis of ≤20% (by off-line QCA) with TIMI 3 post-procedure. Procedural success was defined as angiographic success in the absence of MACE during hospital stay. Target lesion revascularisation was defined as a repeat intervention (surgical or percutaneous) to treat a luminal stenosis within the stent or in the 5-mm distal or proximal segments adjacent to the stent. A TLR/TVR was considered clinically driven (retrospective adjudication by the clinical event committee) if the diameter stenosis at the time of angiography was ≥50% and at least one of the following criteria was present: a history of recurrent angina pectoris presumably related to the target vessel, objective signs of ischaemia at rest (ECG changes) or during exercise test (or equivalent) presumably related to the target vessel, abnormal results of any invasive functional diagnostic test (e.g. Doppler flow velocity reserve, fractional flow reserve). A TLR/TVR with a diameter stenosis ≥70% in the absence of the above- mentioned ischaemic signs or symptoms was also considered clinically driven. Thrombotic stent occlusion was angiographically documented as a complete occlusion (TIMI flow 0 or 1) or a flow-limiting thrombus (TIMI flow 1 or 2) of a previously successfully treated artery. The endpoints were adjudicated by an independent clinical event committee (CEC). In addition, an independent data and safety monitoring board (DSMB) that was not affiliated with the study sponsor reviewed the event data to identify any safety issues related to the study (see Appendix 1 for members of the CEC and DSMB).

### Statistical analysis

This is an observational, prospective, non-randomised registry. No formal power calculation was performed. The primary analysis was carried out according to the intention-to-treat principle.

Descriptive statistics was performed for all relevant variables. Count variables were summarised by the count and the percentage. Various continuous variables were summarised by the mean, standard deviation, minimum and maximum. The event variables, such as MACE, were also summarised as time-to-event variables and presented using the Kaplan-Meier method.

If a revascularisation procedure involving the treated lesion was performed before the planned 6-month repeat angiography, the last angiogram obtained before the re-intervention was used for the angiographic endpoint evaluation. The MACE per patient was ranked according to the highest category on a scale ranging from (1) cardiac death, (2) MI, (3) CABG to (4) TLR. Only events adjudicated by the clinical event committee were taken into account in the analysis of MACE.

All listed authors participated in the study design, enrolment of patients, and/or data interpretation. The data was processed and analysed by Cardialysis B.V., an independent clinical research organisation in Rotterdam, The Netherlands. The authors of this manuscript had full access to the data.

## Results

### Baseline and procedural characteristics

Between 3 July 2004 and 7 January 2005, one hundred and three patients were enrolled in the study. Baseline and procedural characteristics are shown in Table 1 and Table 2. Overall, 71% of the patients were men, and the mean age was 58.5 years, with the expected prevalences of dyslipidaemia, diabetes, hypertension, and current tobacco use. Stenting was performed because of unstable angina in 43.7% of the patients (7% had post infarct angina). The target vessel was the left anterior descending coronary artery in 54.4% of the patients, the right coronary artery in 24.3%. Nearly all the treated lesions were class B1 or B2 according to the American College of Cardiology/American Heart Association classification. None were type C lesions. Although all the target index lesions were primary lesions, 1.9% of the patients had undergone previous coronary artery surgery and 5.8% had undergone previous percutaneous interventions for the treatment of other lesions.

The angiographic success rate was 90.3%. Eight percent (n=8) of the patients with unsuccessful angiographic success had a final residual stenosis > 20% (by off-line QCA) and 2% (n=2) needed more than one study stent. The procedural success rate was 87.4% as 3 patients experienced a MACE during hospital stay; all were related to peri-procedural myocardial necrosis (non-ST-segment elevation ACS). There were no cases of a clinically driven target lesion revascularisation procedure (CABG or PCI). No patient needed a platelet glycoprotein IIb/IIIa inhibitor during peri-procedural treatment at the index hospitalisation.

**Table 1. Baseline clinical characteristics (n = 103)**

| | | |
|---|---|---|
| Male (%) | | 70.9 |
| Age (years) | | 58.5±10.7 |
| Previous MI (%) | | 38.8 |
| Previous CABG (%) | | 1.9 |
| Previous PCI (%) | | 5.8 |
| Diabetes mellitus (%) | | 28.2 |
| Hypercholesterolaemia (%) | | 52.4 |
| Hypertension (%) | | 62.1 |
| Current smoker (%) | | 32.0 |
| Unstable angina (%) | | 43.7 |
| Braunwald classification (%) | IB | 8.7 |
| | IIB | 15.5 |
| | IIIB | 12.6 |
| | IC | 1.0 |
| | IIC | 5.8 |
| Stable angina (%) | | 47.6 |
| CCS classification (%) | 1 | 4.9 |
| | 2 | 34.0 |
| | 3 | 6.8 |
| | 4 | 1.9 |
| Silent ischaemia (%) | | 8.7 |

Plus-minus values are means ±SD

**Table 2. Baseline angiographic and procedural characteristics (n= 103)**

| | | |
|---|---|---|
| Location of lesion (%) | LAD | 54.4 |
| | RCA | 24.3 |
| Lesion classification (%) | Type A | 3.0 |
| | Type B1 | 42.6 |
| | Type B2 | 54.5 |
| | Type C | 0.0 |
| Reference diameter of the vessel (mm) | | 2.59±0.44 |
| Length of lesion (mm) | | 10.0±4.6 |
| Accessibility *f* (%) | Readily | 95.0 |
| | Moderate | 5.0 |
| | Excessive | 0.0 |
| Calcification (%) | Little or none | 74.0 |
| | Moderate to heavy | 26.0 |
| Lesion angulation | None | 97.0 |
| | Moderate | 3.0 |
| Angiographic success (%) | | 90.3 |
| Stenosis > 20% post procedure (QCA) (%) | | 7.8 |
| Other stent implanted in addition to study stent (%) | | 1.9 |

Plus-minus values are means ±SD

*f* The classification of the American College of Cardiology-American Heart Association was used

LAD = left anterior descending coronary artery; RCA = right coronary artery

## Quantitative Coronary Angiographic (QCA) analysis

Figure 2 shows the cumulative frequency of stenosis immediately after the index procedure and at six months. Angiographic measurements are shown in Table 3. Angiographic follow-up at 6 months was obtained for 96 patients (93%), at a mean of 183±19.3 days (ranging from 119 to 296 days, including early symptomatic interventions).

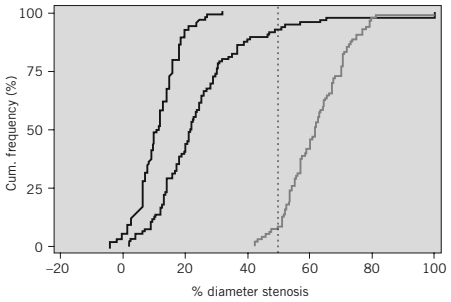


*Figure 2. Cumulative frequency of % diameter stenosis.*

QCA revealed in-stent and in-segment late loss of 0.38±0.49 mm and 0.18 ± 0.46 mm, resulting in binary restenosis rates of 7.3% and 8.3%, respectively.

## Major adverse cardiac events (MACE)

Ninety-eight percent of the patients completed nine months of clinical follow-up. One patient died and one patient refused further follow-up. Major adverse cardiac events (MACE) and other safety data are listed in Tables 4 (hierarchical count) and 5 (total count). The Kaplan-Meier estimate of event-free survival is shown in Figure 3. The overall event-free rate (based on hierarchical MACE) at nine months was 93.2%, i.e. the overall rate of major cardiac events was 6.8%. There was one case of cardiac death: A 61 year old female patient suffered a cardiac arrest during transportation to the hospital with complaints of sudden breathlessness, general discomfort

**Table 3. Results of the sub-segmental Quantitative Coronary Angiographic (QCA) analysis (n=96)**

| | In-stent | In- segment | Proximal edge | Distal edge |
|---|---|---|---|---|
| Mean lumen diameter (mm) | | | | |
| Before procedure | | 2.28±0.37 (total vessel) | | |
| After procedure | 2.82±0.38 | 2.74±0.39 | 2.82± 0.53 | 2.39± 0.46 |
| At 6 months | 2.65±0.45 | 2.62±0.43 | 2.75± 0.55 | 2.43± 0.47 |
| Minimal luminal diameter (mm) | | | | |
| Before procedure | | 0.97±0.29 (total vessel) | | |
| After procedure | 2.40±0.37 | 2.05±0.45 | 2.55± 0.53 | 2.11± 0.47 |
| At 6 months | 2.02±0.59 | 1.87±0.54 | 2.42± 0.66 | 2.09± 0.57 |
| Stenosis (% of luminal diameter) | | | | |
| Before procedure | | 62±10 (total vessel) | | |
| After procedure | 11±7 | 22± 9 | 14±11 | 19±10 |
| At 6 months | 25±17 | 29±16 | 15±16 | 19±16 |
| Absolute gain | 1.43±0.42 | 1.07 ±0.49 | NA | NA |
| Late loss (mm) | 0.38±0.49 | 0.18±0.46 | 0.13±0.52 | 0.02±0.41 |
| ≥ 50% restenosis (% of patients) | 7.3 | 8.3 | 3.1 | 2.1 |

The data is represented as mean values with ±Standard Deviation.

Late loss = the difference between the minimal luminal diameter (MLD) immediately after stent implantation and at six months.

Absolute gain = the difference between the MLD immediately after stent implantation and before stent implantation (pre-procedure).

Matched results = the analysis only includes patients for whom both post-procedural and follow-up QCA data are available.

NA = Not available

**Table 4. Major adverse cardiac events (MACE)* at 30 days, 6 months and 9 months - hierarchical¶**

| | 30 days N (%) (n= 103) | | 180 days N (%) (n= 103) | | 270 days N (%) (n= 103) | |
|---|---|---|---|---|---|---|
| Cardiac death | 0 (0.0) | | 1 (1.0) | | 1 (1.0) | |
| Myocardial infarction | | | | | | |
| Q-wave | 0 (0.0) | | 0 (0.0) | | 1 (1.0) | |
| Non-Q wave | 3 (2.9) | | 3 (2.9) | | 3 (2.9) | |
| Target lesion revascularisation (TLR) | *Clinically driven TLRs only* | *All TLRs* | *Clinically driven TLRs only* | *All TLRs* | *Clinically driven TLRs only* | *All TLRs* |
| Surgical (CABG) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.0) | 2 (1.9) |
| Percutaneous (re-PCI) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.0) | 1 (1.0) | 3 (2.9) |
| Event-free survival | 100 (97.1) | 100 (97.1) | 99 (96.1) | 98 (95.1) | 96 (93.2) | 93 (90.3) |
| MACE | 3 (2.9) | 3 (2.9) | 4 (3.9) | 5 (4.9) | 7 (6.8) | 10 (9.7) |

* MACE as defined in the protocol is a composite of cardiac death, myocardial infarction and clinically driven target lesion revascularisation. To compare the results with some other trials, we have calculated the MACE rate with all target lesion revascularisations.

¶ If a patient had more than one event, only the highest-ranking (worst) event was counted.

**Table 5. Major adverse cardiac events (MACE*) and other safety data at 30 days, 6 months and 9 months - non-hierarchical¶**

| | 30 days N (%) (n= 103) | 180 days N (%) (n= 103) | 270 days N (%) (n= 103) |
|---|---|---|---|
| Death | | | |
| Cardiac | 0 (0.0) | 1 (1.0) | 1 (1.0) |
| Non-cardiac | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Myocardial infarction | | | |
| Q-wave | 0 (0.0) | 0 (0.0) | 1 (1.0)§ |
| Non-Q wave | 3 (2.9) | 3 (2.9) | 3 (2.9) |
| CABG | | | |
| Target lesion (TL) | 0 (0.0) | 0 (0.0) | 2 (1.9) |
| Target vessel (non-TL) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Non-target vessel | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Re-PCI | | | |
| Target lesion (TL) | 0 (0.0) | 1 (1.0) | 4 (3.9)§ |
| Target vessel (non-TL) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Non-target vessel | 0 (0.0) | 0 (0.0) | 3 (2.9) |
| Late angiographic stent thrombosis# | 0 (0.0) | 0 (0.0) | 1 (1.0)§ |

* MACE as defined in the protocol is a composite of cardiac death, myocardial infarction and *clinically driven* target lesion revascularisation. To compare the results with some other trials, we have calculated the MACE rate with *all* target lesion revascularisations.

¶ All events are counted individually (i.e. there is no hierarchy as in Table 4).

# There were no cases of subacute stent thrombosis.

§ The late stent thrombosis, Q-wave MI and a target lesion re-PCI all occurred in one patient.

and diarrhoea. Three patients had a non-ST-segment elevation myocardial infarction at the time of stenting, resulting in a procedural success rate of 87.4% and a hierarchical MACE at 30 days of 2.9%. One patient suffered an ST-segment elevation myocardial infarction due to a late stent thrombosis 14 days after stopping clopidogrel and while on aspirin anti-platelet treatment only and underwent a successful primary repeat percutaneous coronary intervention (non-clinically driven re-PCI). In addition to this clinically-driven target lesion re-PCI, there was one clinically-driven target lesion coronary artery bypass grafting (CABG).

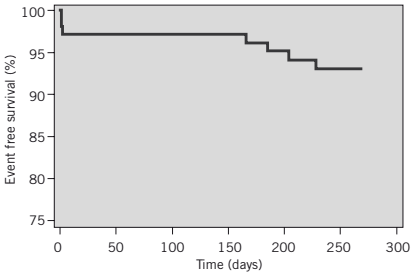


*Figure 3. Kaplan-Meier estimate of the MACE-free survival rate.*

To compare the MACE results with those of some other trials, the MACE rate was also calculated with all target lesion revascularisations, clinically driven or not. Up to 270 days, three patients experienced a non-clinically driven TLR. This resulted in an overall event-free MACE rate of 90.3% at 9 months, i.e. a MACE rate of 9.7% (see also Tables 4 and 5).

## Discussion

This multi-centre, prospective registry study reported on the efficacy and safety of the Infinnium™ stent for the treatment of single *de novo* lesions in a low to moderate risk CAD patient population. The concordant improvements in angiographic and clinical indices of restenosis at 6 months follow-up provide proof of principle that the current biodegradable-polymer-based Infinnium™ stent assembly reduces neointimal hyperplasia after coronary stent implantation, resulting in reduced rates of target lesion revascularisation. The QCA results at 6 months reveal a late loss that is in line with the observations in TAXUS I, II and IV trials.[16,17] The MACE rate including all target lesion revascularisations of 9.7% at 9 months is acceptable and comparable with similar DES systems.[16,17,29] The MACE included one case of cardiac-related death (at day 167) and one case of repeat PCI for an acute myocardial infarction due to late stent thrombosis (1%), 14 days after stopping clopidogrel and while the patient was on aspirin.

The achievement of a hospitable relationship between stent, coating matrix, drug, and vessel wall is extremely challenging. The long-term outcome of treatment with Infinnium™ paclitaxel-eluting coronary stent will reflect the response to all three components. The platform release kinetics are crucial. The hydrophobic properties of paclitaxel and its narrow toxic-therapeutic window require tightly controlled drug release. In the Infinnium™ paclitaxel-eluting stent, the drug is blended into a unique biodegradable polymeric matrix which is easily degraded into $H_2O$ and $CO_2$ and readily eliminated from the body providing excellent biocompatibility. The concentration of drug on each stent was maintained at 1.4 µg/mm$^2$ (versus 1.0 mm for the Taxus stent). Three different layers of combined drug and biodegradable polymers, each with a different release profile, were coated on the stent (coating thickness 4-5 µm), showing a bimodal release pattern with 50% drug release after 9 days, 90% after 38 days and 100% after 7 weeks.

The Infinnium™ is the first indigenously designed and evaluated "low cost" DES from Asia to have obtained a *Conformité Européenne* (CE) quality certificate for commercialisation in Europe. It holds strong promise for improving outcomes while limiting health care expenditure in CAD patients.

Limitations of the present study evaluating the Infinnium™ stent are the need for longer-term follow-up and the focus on standard-risk, focal, *de novo* lesions that may not reflect the more complex lesions and patients encountered in real-world practice. Whether the positive results in these patients can be expected across the full spectrum of patient complexity remains to be determined.

In conclusion, in patients with symptomatic ischaemic heart disease, treated for single, primary lesions in native coronary arteries, the low cost Infinnium™ stent system proved both effective in reducing restenosis at 6 months and safe with an acceptable rate of cardiac events at 9 months.

## Appendix

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***Funding/Support***

This work was supported by a grant from Sahajanand Medical Technologies Pvt. Ltd.

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# CHAPTER 1.2

## Clinical Relevance of Patient-related versus Stent-related Outcome: Two-year Comparison of the Unrestricted Randomized Use of Two Newer Generation Drug-eluting Coronary Stents

Silber S, Windecker S, Vranckx P, Serruys PW,

*On Behalf of the RESOLUTE All Comers Investigators.* *The Lancet* 2011;**377**:1241-47 [**original research paper**]

# Unrestricted randomised use of two new generation drug-eluting coronary stents: 2-year patient-related versus stent-related outcomes from the RESOLUTE All Comers trial

*Sigmund Silber, Stephan Windecker, Pascal Vranckx, Patrick W Serruys, on behalf of the RESOLUTE All Comers investigators*

## Summary

**Background** **In the RESOLUTE All Comers trial, the Resolute zotarolimus-eluting stent was non-inferior to the Xience V everolimus-eluting stent for the primary stent-related endpoint of target lesion failure (cardiac death, target vessel myocardial infarction, and ischaemia-driven target lesion revascularisation) at 1 year. However, data for long-term safety and efficacy from randomised studies of new generation drug-eluting coronary stents in patients treated in routine clinical practice are scarce. We report the prespecified 2-year clinical outcomes from the RESOLUTE All Comers trial.**

**Methods** **In 2008, patients with at least one coronary lesion 2·25–4·0 mm in diameter, with greater than 50% stenosis, were randomly assigned to a Resolute zotarolimus-eluting stent or a Xience V everolimus-eluting stent at 17 centres in Europe and Israel. Randomisation was by an interactive voice response system stratified by centre. Study investigators were not masked to treatment allocation; but those who did data management and analysis, and patients were masked. There were no restrictions as to the number of vessels or lesions treated, or the number of stents implanted. We assessed prespecified safety and efficacy outcomes at 2 years with specific focus on patient-related composite (all death, all myocardial infarction, all revascularisation) and stent-related composite outcomes. Analyses were by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00617084.**

**Findings** **1140 patients were assigned to the zotarolimus-eluting stent and 1152 to the everolimus-eluting stent; 1121 and 1128 patients, respectively, completed 2-year follow-up. The patient-related outcome (231 [20·6%] zotarolimus *vs* 231 [20·5%] everolimus; difference 0·1%, 95% CI −3·2 to 3·5; p=0·958) and stent-related outcome (126 [11·2%] *vs* 121 [10·7%]; difference 0·5%, −2·1 to 3·1; p=0·736) did not differ between groups, although rates of the stent-related outcome were substantially lower than were those for the patient-related outcome. Three patients in each group (0·3%) had very late (after 1 year) stent thrombosis.**

**Interpretation** **Similar safety and efficacy outcomes were sustained between two new generation drug-eluting stents at 2-year follow-up. The greater number of patient-related than stent-related events in patients with complex clinical and lesion characteristics emphasises that during long-term follow-up, the optimisation of secondary prevention is at least as important as the selection of which new generation drug-eluting stent to implant in a specific lesion.**

**Funding** **Medtronic (USA).**

Published Online
April 3, 2011
DOI:10.1016/S0140-6736(11)60395-4

See Online/Comment
DOI:10.1016/S0140-6736(11)60468-6

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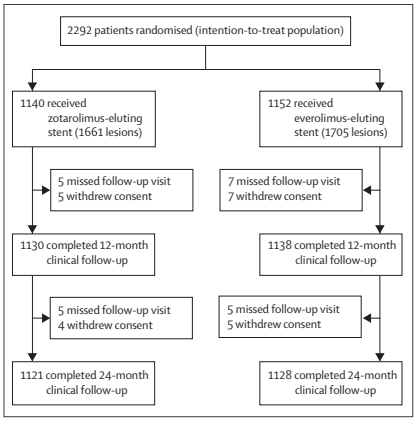
## Introduction

Early generation drug-eluting stents were better than bare-metal stents in reducing the need for repeat revascularisation for the treatment of obstructive coronary artery disease.[1,2] However, much of this initial evidence was based on patients with single, uncomplicated lesions and without serious comorbidities.[1–3] Over time, their use extended to patients with more complex lesions and clinical characteristics.[3] In 2006, after concerns about late (after 30 days) and very late (after 1 year) safety outcomes, the US Food and Drug Administration convened a special assembly of the Circulatory System Device Panel and concluded that the use of drug-eluting stents in study-defined patient cohorts did not increase risk of death or myocardial infarction.[4] Additionally, the Panel noted that data were insufficient in patients with more complex lesions and recommended that trials of drug-eluting stents should study patients with characteristics more likely to be encountered in routine clinical practice.[3,4] These patients often have an increased risk of adverse events when presenting with acute coronary syndromes in the presence of complex comorbidities such as diabetes mellitus and renal failure. Therefore, study endpoints should focus not only on stent-related parameters but also measure patient-related events to improve assessment of overall cardiovascular outcomes.[5]

At the same time, new stent technologies were developed with modified stent designs, improved delivery systems, altered polymers, and new drugs,[6] subsequently leading to the use of these new generation drug-eluting stents in patients with more challenging characteristics who more closely resemble those treated in routine clinical practice.

RESOLUTE All Comers was a randomised controlled trial to compare two new generation drug-eluting stents

in an unrestricted patient population. The Resolute zotarolimus-eluting stent (Medtronic, Santa Rosa, CA, USA) was non-inferior to the Xience V everolimus-eluting stent (Abbott Vascular, Santa Clara, CA, USA) for the primary composite stent-related endpoint of target lesion failure at 1 year.[7] Whether the similarity between these two stents is sustained beyond 1 year is unknown. We report the prespecified 2-year clinical outcomes from the RESOLUTE All Comers trial with specific focus on patient-related and stent-related outcomes.




See Online for webappendix

***Figure 1:*** **Trial profile**

| | Zotarolimus-eluting stent (N=1140) | Everolimus-eluting stent (N=1152) |
|---|---|---|
| Age (years) | 64·4 (10·9) | 64·2 (10·8) |
| Men | 874 (76·7%) | 889 (77·2%) |
| Diabetes mellitus | 268 (23·5%) | 270 (23·4%) |
| Insulin treated | 96 (8·4%) | 82 (7·1%) |
| Hypertension | 811 (71·1%) | 821 (71·3%) |
| Hyperlipidaemia | 730 (64·0%) | 780 (67·7%) |
| Current smoker | 302 (26·5%) | 305 (26·5%) |
| Previous myocardial infarction* | 323 (28·8%) | 341 (30·4%) |
| Acute myocardial infarction (within 72 h) | 330 (28·9%) | 332 (28·8%) |
| Stable angina | 382 (33·5%) | 416 (36·1%) |
| Unstable angina | 221 (19·4%) | 218 (18·9%) |
| Left ventricular ejection fraction <30%† | 17 (2·8%) | 13 (2·1%) |
| SYNTAX score‡ | 14·8 (9·3) | 14·6 (9·2) |
| Complex§ | 764 (67·0%) | 756 (65·6%) |
| Target vessel | | |
| Left main | 25 (2·2%) | 29 (2·5%) |
| Left anterior descending | 600 (52·6%) | 560 (48·6%) |
| Left circumflex | 376 (33·0%) | 379 (32·9%) |
| Right coronary | 425 (37·3%) | 476 (41·3%) |
| Bypass graft | 28 (2·5%) | 28 (2·4%) |
| Stents per patient¶ | 1·9 (1·2) | 2·0 (1·3) |
| Total stent length (mm)¶ | 34·4 (24·5) | 37·0 (26·5) |
| Reference vessel diameter (mm) | 2·63 (0·57) | 2·63 (0·58) |

Data are mean (SD) or number (%). *Data available for 1122 patients in the zotarolimus group and 1120 in the everolimus group. †Data available for 610 patients in the zotarolimus group and 608 in the everolimus group. ‡Data available for 1008 patients in the zotarolimus group and 1025 in the everolimus group. §See methods section for definition. ¶Patient level.

***Table 1:*** **Baseline patient and lesion characteristics at 2 years**

## Methods

### Study design and patients

The design, detailed methods, and endpoint definitions of the RESOLUTE All Comers trial have been previously described.[7] Briefly, the RESOLUTE All Comers trial is a prospective, randomised, single-blind, non-inferiority study in which patients with chronic stable angina, or acute coronary syndromes who qualified for percutaneous coronary intervention, were recruited from 17 centres in Europe and Israel (webappendix). Patients were enrolled between April 30, 2008, and Oct 28, 2008. Final 5-year follow-up is expected in November, 2013, with available data anticipated from January, 2014. Eligible patients had at least one coronary artery stenosis greater than 50% with a reference diameter of 2·25–4·0 mm by visual estimation. Key exclusion criteria were limited to study medication intolerance, stent component allergies, or necessary surgery within the 6 months after the index procedure. There were no restrictions as to the number, severity, or location of lesions, or number of stents used. Patients who met all eligibility criteria, and for whom written informed consent was obtained, were randomly assigned to receive either the Resolute zotarolimus-eluting stent or the Xience V everolimus-eluting stent. Randomisation was by an interactive voice response system stratified by centre. Study investigators were not masked to treatment allocation; however, those who did data management and analysis, and patients were masked.

Every centre's ethics committee approved the study protocol, all patients signed informed consent before intervention, and this study complied with the declaration of Helsinki. All case report forms were verified at the study site by an independent monitoring provider (Premier Research Group, Yverdon, Switzerland).

### Study endpoints and procedures

The primary trial endpoint was stent-related target lesion failure, a composite of cardiac death, target vessel myocardial infarction, or ischaemia-driven target lesion revascularisation at 1 year. Any death of unknown cause was classified as cardiac. Secondary endpoints included the 2-year outcomes for the composite endpoints of target lesion failure, and the patient-related endpoint, including all deaths, all myocardial infarctions (Q wave or non-Q wave), and any revascularisation. Any revascularisation included all target lesion revascularisation (ischaemia-driven and non-ischaemia-driven), all target vessel revascularisation (ischaemia-driven and non-ischaemia-driven), and any non-target vessel

revascularisation by percutaneous or surgical means. Additional secondary endpoints included the composite major adverse cardiac events (any death, any myocardial infarction, emergent coronary bypass surgery, and any target lesion revascularisation); and definite, probable, possible, and overall stent thrombosis. Stent thrombosis was classified according to the Academic Research Consortium (ARC) definition.[5]

Patients with complex lesions were defined as having at least one of the following characteristics: serum creatinine concentration of 140 µmol/L or more; left ventricular ejection fraction less than 30%; an acute myocardial infarction within the previous 72 h; more than one lesion per vessel; two or more vessels treated with a stent; a lesion longer than 27 mm; or bifurcation, bypass graft, in-stent restenosis, unprotected left main coronary artery, presence of thrombus, or total occlusion. A complete list of study-related definitions has been previously published.[7]

All patients were prescribed lifelong daily aspirin (≥75 mg) and daily clopidogrel (75 mg) for at least 6 months. Follow-up was done in clinic at 30 days and 1 year, and by telephone at 2 years, which will be repeated every year for 5 years. An independent Clinical Events Committee, consisting of members masked to treatment assignments for the duration of the trial, adjudicated all clinical events for analysis.

### Statistical analysis

All analyses were done by intention to treat. Published studies[8,9] that included an unrestricted patient population provided the basis for a predicted 1-year rate for the stent-related endpoint (target lesion failure) of 8% for both treatment groups. On the basis of a non-inferiority margin of 0·035 (3·5%) as the acceptable difference between the two groups to declare the zotarolimus-eluting stent to be non-inferior to the everolimus-eluting stent, and with a one-sided type I error of 0·05, 2300 patients (1150 patients in each group) would yield at least 90% power to detect non-inferiority.[10]

Categorical variables were reported as numbers and percentages of patients, and continuous variables as means and SD. Differences between treatment groups with 95% CIs and p values, on the basis of the Fisher's exact test for categorical outcomes, and two-sample *t* test for continuous outcomes are reported. Time-to-event analysis was assessed with the Kaplan-Meier method, with differences between groups compared with the log-rank test. A two-sided p value of less than 0·05 was regarded as significant.

This study is registered with ClinicalTrials.gov, number NCT00617084.

| | Zotarolimus-eluting stent (N=1121) | Everolimus-eluting stent (N=1128) | Difference (95% CI) | p value |
|---|---|---|---|---|
| Patient-related outcome* | 231 (20·6%) | 231 (20·5%) | 0·1% (−3·2 to 3·5) | 0·958 |
| Stent-related outcome† | 126 (11·2%) | 121 (10·7%) | 0·5% (−2·1 to 3·1) | 0·736 |
| Any death | 36 (3·2%) | 45 (4·0%) | −0·8% (−2·3 to 0·8) | 0·366 |
| Cardiac death | 29 (2·6%) | 25 (2·2%) | 0·4% (−0·9 to 1·6) | 0·584 |
| Any MI‡ | 62 (5·5%) | 56 (5·0%) | 0·6% (−1·3 to 2·4) | 0·571 |
| Q wave | 15 (1·3%) | 7 (0·6%) | 0·7% (−0·1 to 1·5) | 0·091 |
| Non-Q wave | 48 (4·3%) | 49 (4·3%) | −0·1% (−1·7 to 1·6) | 1·000 |
| Target-vessel MI‡ | 53 (4·7%) | 51 (4·5%) | 0·2% (−1·5 to 1·9) | 0·841 |
| Q wave | 11 (1·0%) | 6 (0·5%) | 0·4% (−0·3 to 1·2) | 0·235 |
| Non-Q wave | 43 (3·8%) | 45 (4·0%) | −0·2% (−1·8 to 1·4) | 0·914 |
| Non-target-vessel MI‡ | 10 (0·9%) | 5 (0·4%) | 0·4% (−0·2 to 1·1) | 0·207 |
| Q wave | 4 (0·4%) | 1 (0·1%) | 0·3% (−0·1 to 0·7) | 0·217 |
| Non-Q wave | 6 (0·5%) | 4 (0·4%) | 0·2% (−0·4 to 0·7) | 0·547 |
| Cardiac death or target-vessel MI‡ | 78 (7·0%) | 71 (6·3%) | 0·7% (−1·4 to 2·7) | 0·553 |
| Any death or any MI‡ | 93 (8·3%) | 95 (8·4%) | −0·1% (−2·4 to 2·2) | 0·939 |
| All revascularisations | 174 (15·5%) | 156 (13·8%) | 1·7% (−1·2 to 4·6) | 0·258 |
| Re-PCI | 156 (13·9%) | 139 (12·3%) | 1·6% (−1·2 to 4·4) | 0·288 |
| CABG | 27 (2·4%) | 22 (2·0%) | 0·5% (−0·7 to 1·7) | 0·474 |
| Ischaemia-driven TLR | 64 (5·7%) | 58 (5·1%) | 0·6% (−1·3 to 2·4) | 0·577 |
| Re-PCI | 56 (5·0%) | 48 (4·3%) | 0·7% (−1·0 to 2·5) | 0·423 |
| CABG | 12 (1·1%) | 12 (1·1%) | 0·0% (−0·8 to 0·9) | 1·000 |
| Non-ischaemia-driven TLR | 26 (2·3%) | 25 (2·2%) | 0·1% (−1·1 to 1·3) | 0·888 |
| Re-PCI | 22 (2·0%) | 23 (2·0%) | −0·1% (−1·2 to 1·1) | 1·000 |
| CABG | 4 (0·4%) | 2 (0·2%) | 0·2% (−0·2 to 0·6) | 0·451 |
| Target-vessel revascularisation | 112 (10·0%) | 103 (9·1%) | 0·9% (−1·6 to 3·3) | 0·519 |
| Re-PCI | 99 (8·8%) | 90 (8·0%) | 0·9% (−1·4 to 3·1) | 0·494 |
| CABG | 18 (1·6%) | 18 (1·6%) | 0·0% (−1·0 to 1·0) | 1·000 |
| Non-target-vessel revascularisation | 87 (7·8%) | 84 (7·4%) | 0·3% (−1·9 to 2·5) | 0·812 |
| Re-PCI | 73 (6·5%) | 68 (6·0%) | 0·5% (−1·5 to 2·5) | 0·664 |
| CABG | 19 (1·7%) | 17 (1·5%) | 0·2% (−0·8 to 1·2) | 0·740 |
| Target-vessel failure§ | 141 (12·6%) | 138 (12·2%) | 0·3% (−2·4 to 3·1) | 0·848 |
| Major adverse cardiac events¶ | 140 (12·5%) | 146 (12·9%) | −0·5% (−3·2 to 2·3) | 0·752 |
| ARC definite and probable stent thrombosis | 21 (1·9%) | 11 (1·0%) | 0·9% (−0·1 to 1·9) | 0·077 |
| Early (0–30 days)‖** | 12 (1·1%) | 6 (0·5%) | 0·5% (−0·2 to 1·3) | 0·164 |
| Late (31–360 days)** | 7 (0·6%) | 2 (0·2%) | 0·4% (−0·1 to 1·0) | 0·108 |
| Very late (361–720 days) | 3 (0·3%) | 3 (0·3%) | 0·0% (−0·4 to 0·4) | 1·000 |
| ARC definite and probable stent thrombosis and any death | 53 (4·7%) | 52 (4·6%) | 0·1% (−1·6 to 1·9) | 0·921 |

Data are number (%), unless otherwise indicated. MI=myocardial infarction. PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. TLR=target lesion revascularisation. ARC=Academic Research Consortium. *Patient-related outcome included any death, any MI, or any revascularisation. †Stent-related outcome (target lesion failure) included cardiac death, target-vessel MI, or ischaemia-driven TLR. ‡Medtronic extended historical definition. §Target-vessel failure included cardiac death, target vessel MI, or ischaemia-driven target-vessel revascularisation. ¶Major adverse cardiac events included any death, Q wave or non-Q wave MI, emergent coronary bypass surgery, or repeat TLR (ischaemia-driven) by percutaneous or surgical methods. ‖One patient in the zotarolimus group had a probable stent thrombosis event on day 0 and a definite stent thrombosis event on day 5. **One patient in the zotarolimus group had a definite stent thrombosis event on day 4 and day 31.

*Table 2:* **Overall patient-related and stent-related composite and detailed clinical outcomes at 2 years**

### Role of the funding source

The sponsor of the study participated in the trial design and aided in the management of data collection. The sponsor funded an independent data management and analysis centre (Cardialysis, Rotterdam, Netherlands) for database management and all statistical analyses, and an independent provider to perform study site monitoring (Premier Research Group, Yverdon,

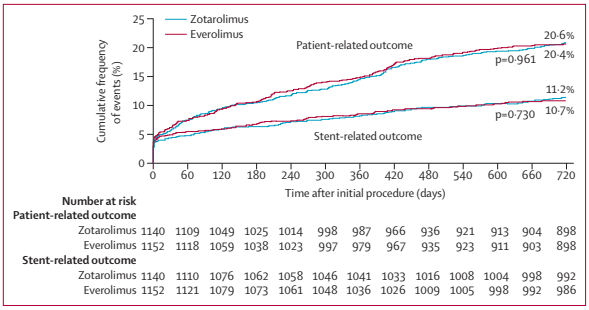



***Figure 2:*** **Cumulative frequency of patient-related and stent-related* outcomes up to 2 years**
The difference between patient-related and stent-related outcomes continues to diverge over time. *Target lesion failure.

| | Days after procedure | Clinical event | Antiplatelet drug at event |
|---|---|---|---|
| **Zotarolimus-eluting stent** | | | |
| Probable | 376 | MI | Aspirin; clopidogrel stopped same month as event |
| Definite | 572 | MI, TLR | Aspirin and clopidogrel |
| Definite | 656 | Q-wave MI, TLR | Aspirin; clopidogrel stopped 16 months before event |
| **Everolimus-eluting stent** | | | |
| Definite | 408 | TLR | Aspirin and clopidogrel |
| Definite | 486 | TLR | Aspirin; clopidogrel stopped 3 months before event |
| Definite | 613 | MI, TLR | Aspirin; clopidogrel stopped 7 months before event |

ARC=Academic Research Consortium. MI=myocardial infarction. TLR=target lesion revascularisation.

***Table 3:*** **Timing and event details for the six patients who had an ARC definite or probable stent thrombosis event in year 2**

Switzerland). All authors had full access to the study data. The corresponding author had full responsibility for the decision to submit the report for publication.

## Results

2292 patients were enrolled and randomly assigned to treatment with the zotarolimus-eluting stent (n=1140) or the everolimus-eluting stent (n=1152). 1121 (98·3%) of zotarolimus patients and 1128 (97·9%) of everolimus patients completed follow-up at 2 years (figure 1). Table 1 summarises the baseline demographics and the clinical and angiographic characteristics of all patients.

At 2 years, a patient-related outcome occurred in 231 patients in each group (table 2); the number of stent-related outcomes events was substantially lower, but did not differ between groups (table 2). Kaplan-Meier analyses showed no differences between the two groups in the incidence of patient-related or stent-related endpoints (figure 2). Furthermore, we noted no differences between the two stent groups for any major clinical event (table 2).

1520 of 2292 (66·3%) patients were classified as complex (table 1). At 2 years, the zotarolimus and everolimus patient groups had similar outcomes irrespective of complexity. For the complex group, a patient-related outcome occurred in 162 of 752 (21·5%) patients in the zotarolimus group versus 166 of 738 (22·5%) in the everolimus group (difference –1·0%, 95% CI –5·2 to 3·3; p=0·662) and stent-related outcomes in 91 of 752 (12·1%) versus 93 of 738 (12·6%) patients (difference –0·5, –3·8 to 2·8; p=0·813). For the simple group (patients not meeting complex criteria), patient-related outcomes occurred in 69 of 369 (18·7%) patients in the zotarolimus group versus 65 of 390 (16·7%) in the everolimus group (difference 2·0%, –3·4 to 7·4%; p=0·505) and stent-related outcomes in 35 of 369 (9·5%) versus 28 of 390 (7·2%) patients (difference 2·3%, –1·6 to 6·2; p=0·293).

At 1 year, 933 of 1110 (84·1%) patients in the zotarolimus group and 929 of 1108 (83·8%) in the everolimus group were taking dual antiplatelet therapy (p=0·908). After 2 years, 201 of 1080 (18·6%) zotarolimus patients and 195 of 1076 (18·1%) everolimus patients were still on dual antiplatelet therapy (p=0·781). Three patients in each group (0·3% for both) had an ARC definite or probable stent thrombosis event during the second year (ie, very late stent thrombosis), with no associated mortality (table 3, figure 3).

## Discussion

The RESOLUTE All Comers trial compared two new generation drug-eluting stents: the Resolute zotarolimus-eluting and the Xience V everolimus-eluting stents. The safety and efficacy of these two drug-eluting stents are clinically equivalent, even after 2 years in a mostly complex population. Our results accord with two post-hoc analyses[11,12] showing similar clinical outcomes between the two stents irrespective of complexity. Between year 1 and 2, six patients (three in each group) had an ARC definite or probable stent thrombosis, representing a very late stent thrombosis rate of 0·3% for each stent group (figure 3, tables 2 and 3).

The multicentre LEADERS trial[13,14] showed that over 3 years there is an increasing divergence in outcomes between early generation and new generation drug-eluting stents, in favour of the new stent. The same finding was detected in the single-centre COMPARE trial[15] that also compared a new generation drug-eluting stent with an early generation drug-eluting stent. Thus, LEADERS, COMPARE, and now the RESOLUTE All Comers trials suggest that new generation drug-eluting stents help to improve clinically important outcomes, especially in complex patient and lesion subsets (panel).[13–16] Our results are not comparable with the SORT OUT III study,[17] which compared an earlier generation zotarolimus-eluting stent (Endeavor, Medtronic) with an

early generation sirolimus-eluting stent, although as in our study the patient population was unrestricted. The Resolute zotarolimus-eluting stent is similar to its predecessor (Endeavor), but the drug release is sustained over a longer period (180 days *vs* 14 days).[18,19]

Composite endpoints in cardiovascular trials include a wide range of events, from patient-related death from any cause to so-called pure stent-related events, such as stent thrombosis. Comparison of composite endpoints can be difficult because of the lack of consensus definitions, and overlap between composite endpoint components. The difference between the patient-related and stent-related outcomes from the RESOLUTE All Comers trial included any non-cardiac death, any myocardial infarction not related to the target vessel, and any revascularisations not related to the target vessel. The differences between stent-related and patient-related events can be regarded as more indicative of the patients' underlying global disease,[20] rather than related to the specific localised coronary obstruction treated with the study stents. One example of the differences between patient-related and stent-related outcomes is shown by analysis of the mortality rates from our study: of 16 non-cardiovascular deaths, 13 were due to various carcinomas (three in zotarolimus group; ten in everolimus group), contributing to a substantial difference between patient-related and stent-related outcomes (table 2, figure 2). Any death of unknown cause was by default classified as a cardiac death, even if it was a non-cardiac death.

We recorded a substantial and surprisingly high numerical difference between patient-related and stent-related outcomes, with an approximate doubling of event rates for patient-related outcomes (table 2, figure 2). This finding emphasises the importance of stent-independent comorbidities in consideration of the prognosis of patients indicated for percutaneous coronary intervention with stenting, because these comorbidities exacerbate the underlying lesion-related coronary artery disease over time. Drug-eluting stents are able to perform the function for which they are designed; however, the patient's underlying disease affects long-term outcomes to a greater extent than does the need for repeat revascularisation or stent thrombosis of the initially treated lesion (figure 2). Thus, optimisation of secondary prevention and overall medical management during long-term follow-up seems to be more important than the initial choice between advanced, new generation drug-eluting stents. However, we should note that any comparisons between the stent-related and patient-related outcomes are hypothesis generating and were not prespecified. Our finding could be attributable to the pathophysiology of coronary artery disease, such that about half of the coronary events are attributable to so-called non-culprit lesions.[21]

Although drug-eluting stents do not generally increase mortality,[22] valid concerns about early (less than 30 days), late (31 days to 1 year), and very late (after 1 year) stent thrombosis persist. In our study, two patients (one in each group) with very late stent thrombosis were still on dual antiplatelet therapy (table 3). Overall, 18% of our patients were still on dual antiplatelet therapy after 2 years, compared with 13% from COMPARE[16] and 23% from LEADERS trials.[14] Although the rate of very late stent thrombosis of 0·3% recorded in our study is lower than the 0·6% per year described for early generation drug-eluting stents,[23] each very late stent thrombosis is a crucial event with potentially high mortality.[24] In our study, none of the six patients with very late stent thrombosis events died (table 3). We did not record any differences at 2 years between the two stent groups for any myocardial infarction or cardiac death (table 2). Despite the abundance of evidence supporting drug-eluting stents, whether prolonged dual antiplatelet use (beyond 12 months) can reduce the likelihood of very late stent thrombosis is unclear.[25]

Our analysis was limited to 2 years. This study's powered primary endpoint of stent-related target lesion failure outcome was at 1 year; however, the prespecified secondary endpoints included yearly reporting up to 5 years of all clinical outcomes, with each event adjudicated by the independent Clinical Events Committee. Since results of safety and efficacy of randomised trials can change substantially during long-term follow-up,[14,16,26] randomised trials of drug-eluting stents should report long-term follow-up results up to 5 years.[27]

An ideal study should include all patients presenting for percutaneous coronary intervention at the investigational

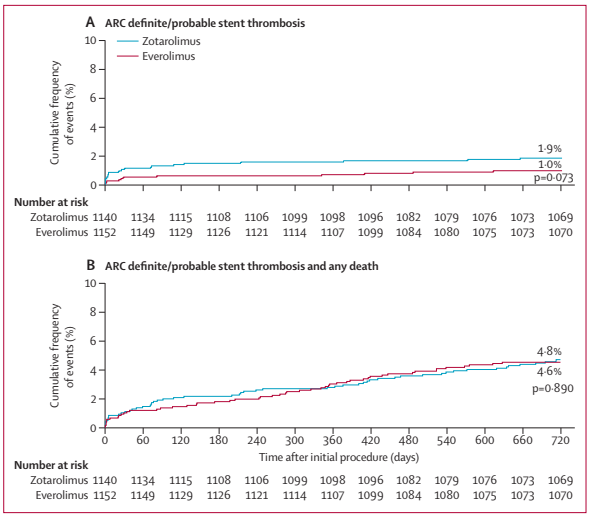



***Figure 3*: Cumulative frequency of ARC definite and probable stent thrombosis (A), and composite of ARC definite and probable stent thrombosis and any death (B), up to 2 years**
ARC=Academic Research Consortium.

*Panel:* **Research in context**

**Systematic review**

We searched PubMed from January, 2007, to January, 2011, for complete reports of randomised trials comparing new generation drug-eluting stents with unrestricted use in all patient populations. We identified only the LEADERS and the COMPARE trials, which compared different generations of drug-eluting stents.

**Interpretation**

Our study showed that the two new generation Xience V and Resolute drug-eluting stents were clinically equivalent in all outcomes in a diverse patient population. When comparing the results from the RESOLUTE All Comers trial and the LEADERS and COMPARE trials, caution is needed. Nevertheless, we viewed target lesion revascularisation as representative of stent-related efficacy, and definite stent thrombosis as representative of stent-related safety (table 4). Keeping in mind the limitations of underpowered secondary endpoints of low frequency and of comparisons between studies, rates of stent thrombosis seem to be lower for the Xience V everolimus-eluting and the Resolute zotarolimus-eluting stents than for the other drug-eluting stents (table 4).[14,16] Furthermore, our study was unique in reporting patient-related versus stent-related outcomes, and draws attention to the importance of comprehensive patient management in the treatment of patients with drug-eluting stents for symptomatic coronary artery disease, especially after stenting procedures.

| | Cypher sirolimus-eluting sent | Taxus paclitaxel-eluting stent | BioMatrix biolimus-eluting stent | Xience V everolimus-eluting stent | Resolute zotarolimus-eluting stent |
|---|---|---|---|---|---|
| TLR at 2 years | 7·1% | 5·9% | 6·3% | 5·1% | 5·7% |
| Definite stent thrombosis at 2 years | 2·5% | 2·7% | 2·2% | 0·5% | 1·3% |

TLR represents stent-related efficacy; and definite (early, late, and very late) stent thrombosis represents stent-related safety. Data are from LEADERS,[14] COMPARE,[16] and RESOLUTE All Comers trials. TLR=target lesion revascularisation.

*Table 4:* **Stent-related efficacy and safety of early and new generation drug-eluting stents from randomised trials in unrestricted populations at 2 years**

sites; yet in our study, a mean of 44% of patients treated at the 17 centres were enrolled. This finding is consistent with enrolment percentages from the LEADERS study of 46%. There are many reasons why studies including unrestricted patient populations do not include all consecutive patients: many patients seen in routine practice are often too ill to be able to provide consent, are unable to fully comprehend the protocol within the given time, or refuse to participate. Furthermore, our patient group was probably not highly complex, as represented by a mean SYNTAX score of 15 compared with a mean score of 26 in the SYNTAX trial;[28] however, our patients were similar to those studied in the LEADERS study with a mean score of 14.[29]

Randomised trials are powered for their primary endpoints. Rare events such as very late stent thrombosis or death are clinically important events, yet to power studies for such rare events the number of patients needed to show even non-inferiority is unrealistic. Although the p value might be regarded as significant, the reported differences might still be a chance finding because of insufficient power. The difference in the rates of definite and probable stent thrombosis between the two stents at 1 year (zotarolimus 1·6%; everolimus 0·7%) was unchanged at 2 years (table 2, figure 3). Similarly, any differences in the rate of any death in year 1 (zotarolimus 1·6%; everolimus 2·8%) were balanced in year 2 (table 2). The cumulative incidence of the combined two rare events of definite and probable stent thrombosis and any death was 4·8% for the zotarolimus-eluting stent and 4·6% for the everolimus-eluting stent (table 2, figure 3).

Another limitation of this study was that we did not collect data for cardiovascular drugs, such as statin use, apart from dual antiplatelet therapy after the first year of follow-up; therefore we are not able to draw any associations between this important aspect of cardiac medical management and patient-related outcome. Therefore, more intense secondary prevention and overall medical management are at least as important as the device; and only stent-oriented pharmacological therapy might be insufficient for these complex patients.

**Contributors**

S Silber, P W Serruys, and S Windecker (the RESOLUTE All Comers Steering Committee) contributed to the design and execution of the trial. S Silber drafted the report, which was critically revised by S Windecker and P W Serruys. P Vranckx served as the chair of the Clinical Events Committee and critically revised this report. All authors approved the final report.

**Conflicts of interest**

S Silber has received research grants and lecture fees from Abbott Vascular, Boston Scientific, and Medtronic. S Windecker has received research grants, consultancy fees, and payment for lectures from Abbott, Biosensors, Boston Scientific, Cordis, and Medtronic. P Vranckx and P W Serruys declare that they have no conflicts of interest.

**Acknowledgments**

This study was funded by Medtronic, Santa Rosa, CA, USA. Jane Moore, a Medtronic employee, drafted the introduction, methods, results, tables, and figures under the guidance of the authors, and facilitated author reviews.

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# CHAPTER 1.3

## Identifying stent thrombosis, a critical appraisal of the Academic Research Consortium definitions. Concensus definitions, lighthouse and a toe in the water

Vranckx P; Kint PP, Morel MA; Van ES GA, Serruys PW, Cutlip DE.

*EuroIntervention* suppl. 2008. [**technical report** ]

EuroIntervention

# Identifying stent thrombosis, a critical appraisal of the Academic Research Consortium (ARC) consensus definitions: a lighthouse and as a toe in the water

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*The authors have no conflict of interest to declare.*

## Introduction

Since the clinical introduction of the first drug-eluting stent (DES), in April 2002, this breakthrough technology, including the sirolimus-eluting coronary stent (SES), the paclitaxel-eluting stents (PES), and many other new investigational agents like everolimus-, zotarolimus-, and tacrolimus-eluting stents, has been tested extensively for its main purpose of preventing restenosis. Their effectiveness in reducing restenosis and the associated target vessel revascularisation (TVR) is not in dispute; however the long term safety of these devices is the subject of ongoing debate.[1-3] Especially the increased risk of potentially fatal late thrombotic events associated with the 'off-label' use of DES in complex lesions and specific patient subsets is of great concern.[4]

Accurately determining the incidence of adverse clinical events, especially in the case of rare but catastrophic occurrences such as stent thrombosis (ST), is a challenge for all constituencies, including regulatory authorities.[5] It is clear that detailed analysis of published trials in this field is critical for understanding the conclusions. The use of uniform, hierarchical definitions should help in evaluating risks across studies. In an effort to enable meaningful comparisons between clinical trials, the Academic Research Consortium (ARC), formed in 2006, proposed standardised definitions for clinical endpoints in coronary stent investigations and made them available to any and all interested parties via peer-reviewed publication.[6] ARC consisted of academic representatives in the field of invasive cardiology, academic research organisations active in the field, as well as members of industry and regulatory bodies. The ARC consensus definitions were developed completely separate from any considerations concerning potential applications of these definitions. They may serve as a lighthouse, a point of reference, for the medical community wishing to compare studies on DES technology and as a toe in the water when exploring the safety profile of new PCI devices or evaluation of more complex patients or lesion subsets.

In this manuscript we intend to introduce to the interested reader a comprehensive flow scheme for stent thrombosis (ST) adjudication following the ARC definitions. It may provide a visual guide to understand the numbers reported in tables of published manuscripts or abstracts. We implemented this tool while re-adjudicating potential stent thrombosis events from the ARTS II trial according to the ARC definitions. The results of this re-adjudication were published earlier in detail[5]. This exercise allowed for a critical appraisal of the ARC definitions. Specific elements of the definitions merit emphasis, clarification or possibly even a correction at some point. Finally, we will make a strong case for the importance of detailed clinical data, including a complete narrative summary to facilitate event adjudication.

## The spirit of the ARC consensus definitions

The ARC definitions provide a conceptual framework for the design, analysis and reporting of clinical trials evaluating the effectiveness and safety of DES in an elective percutaneous coronary intervention (PCI) population, as well as the pharmaceutical adjuncts related to this technology. They are based on considerations ranging from historical legacy to key pathophysiologic mechanisms and relevance to clinical interpretability.[5]

Ultimately, ARC stresses the importance of standard reporting of clinical outcomes according to both a device related composite, defined as cardiac death, myocardial infarction (MI) involving the target vessel territory or target lesion revascularisation (TLR), and

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a patient-related composite that assesses the net impact of device treatment on overall clinical outcome, defined as all cause death, any MI, or any repeat revascularisation procedure.

While either of these composites can be argued as appropriate primary clinical endpoints for a DES clinical trial, since they represent measurable outcomes that reflect overall safety and effectiveness and occur with sufficient frequency to provide adequate statistical power, the impact of the individual components of either composite or other safety outcomes such as stent thrombosis has been more difficult to measure and created substantial controversy.

In the case of stent thrombosis in particular, much of the controversy has been fuelled by inadequate and non-standardised clinical definitions, leading many to conclude that only the overall effect on death or MI should be considered. We believe this is problematic since small, but possibly significant differences in stent thrombosis may not have a quantifiable effect on death, myocardial infarction (MI), target lesion revascularisation (TLR) or the composite outcomes. Nevertheless, it is important to quantify differences in stent thrombosis in order to understand possible biologic differences between different DES or bare metal stents (BMS), even if balanced by other causes of death, MI, or repeat revascularisation.

The ARC acknowledges three temporal categories of ST to imply differences in the contribution of the various pathophysiologic processes during each of the intervals. A tri-level of certainty classification is introduced.[5] The highest level of evidence of ST requires signs of (acute) myocardial ischaemia with either angiographic[7] or autopsy confirmation at any time following the index procedure. The categories of probable and possible stent thrombosis add sensitivity to the ST-definition and should also be reported.

For practicality, we visualised the adjudication process for the different categories of certainty in a comprehensive algorithm (Figure 1). Aligned with the ARC definitions, this flow-diagram is dynamic by nature and may need specification according to specific populations or type of lesions studied. The quality of the clinical adjudication process and the utility of these categories strongly depend on the quality of the data available to the adjudication committee.

## Beyond any reasonable doubt

In quantitative clinical research, investigators use stories to investigate hypotheses that are conditioned by prior scientific knowledge and by their own experience and biases. Despite the potential biases in individual accounts, clinical trials rely on patient stories to provide otherwise unobtainable data about the natural history of diseases, the exposures that cause them, and the effectiveness of treatment. Each story is only provisionally informative until it is corroborated by consistency of findings and confirmed by the best available clinical evidence. These may consist of any patient source documents reporting investigator initiated or protocol driven diagnostic test results (laboratory exams, standard 12-lead electrocardiogram [ECG], angiograms, autopsy reports e.g.). Clinical autopsies are vital to establish the true cause of death and should be strongly encouraged. Quantitative pre-adjudication of coronary angiograms for lesion localisation, severity and visible intra-coronary thrombus by an independent quantitative coronary angiographic (QCA) core laboratory may significantly contribute to the quality of this process.

The clinical adjudication process is highly specific, being driven by the application of pre-specified criteria for event definitions, and does not always allow full elucidation of the pathogenesis of device related events based only on the individual case report form (CRF) responses. With the example of probable and possible stent-thrombosis adjudication, we make the methodological case for a (systematic) illness narrative inquiry as a unique means to get inside the history of a clinical event. To avoid any semantic confusion and to allow optimal implementation of information feedback loops, the exact wording, the use of consistent definitions and the structure used in narrative writing are crucial.

As indicated in the flow diagram a detailed narrative inquiry focusing on ST was performed using the three patient oriented composite safety endpoints (all cause mortality, myocardial infarction and any repeat revascularisation) as well as angiographic vessel occlusion in the absence of one of these events. The latter is not *de facto* evidence of ST, but should stimulate detailed re-evaluation of the full patient files for any evidence to implicate the presence of ST.

## Death

*"All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established."*

Cardiac deaths should include all events related to cardiac diagnosis, a complication of the procedure, treatment for a complication of the procedure (restenosis, e.g.) or unexplained causes. Considering the latter, any death during the follow-up period that can not be clearly attributed to a non-cardiac cause will be adjudicated as cardiac death based on a worse case scenario. According to the ARC definition, a patient who dies following a bleeding complication while on concomitant dual anti-platelet therapy following DES-implantation will be adjudicated as cardiac death. However, if dual antiplatelet therapy was not given per-protocol but indicated for other disease (cerebrovascular disease e.g.) this event would be adjudicated as a non-cardiac death.

According to the ARC ST definitions, any death during follow-up of truly unknown cause will be adjudicated as probable (if within 30 days) or possible (beyond 30 days) stent thrombosis using the same logic as above for cardiac death. For this process to have the highest level of specificity, it is crucial for the adjudication committee to have the best available clinical information to determine whether death is clearly not cardiac related or if cardiac is most likely not related to stent thrombosis. In the absence of these data, any unexpected death even in patients with coexisting potentially fatal non cardiac causes (e.g. cancer, infection) should be classified as cardiac. Figure 2 shows an example of a coronary thrombus aspirate following a subacute ST in a patient suffering a myelodysplastic syndrome with a rapid course of progression of neoplastic haematopoiesis terminating in a acute myeloid leukaemia.

This issue becomes more critical in the late follow-up period when there is a higher frequency of death and details are more likely to be inadequate for specifying a cause. Indeed, during application of the ARC definitions we have found that late deaths are often unexplained, resulting in assignment of a cardiac cause and attribution to possible ST. This results in what is likely a falsely

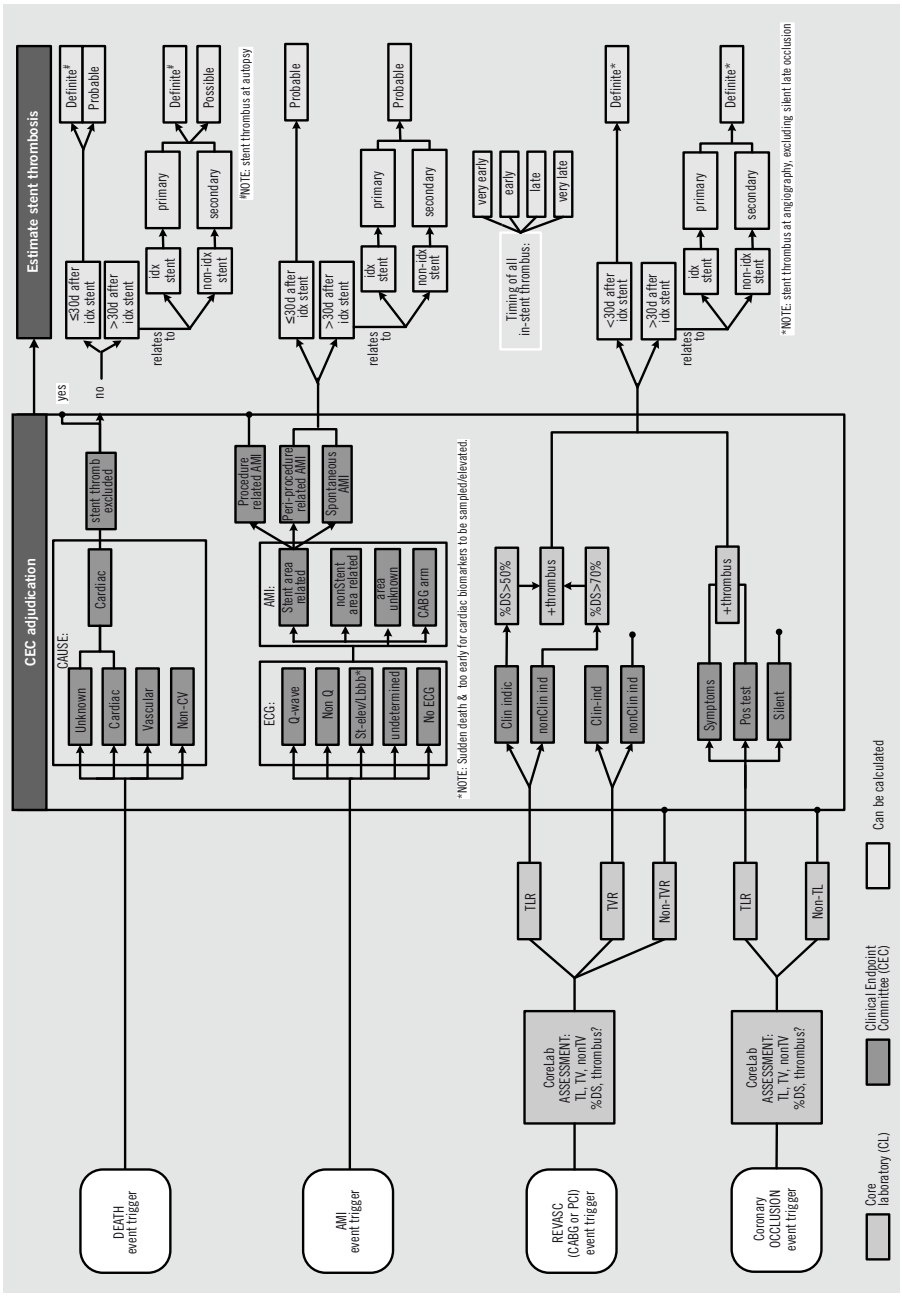


*Figure 1. ARC-flow.*

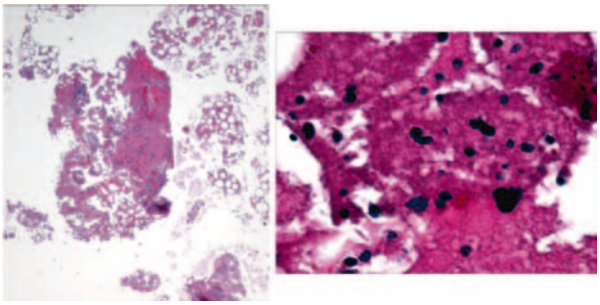

*Figure 2. Thrombectomy aspirate containing a fibrin and platelet-rich thrombus with moderate inflammatory cell infiltrate composed of neutrophils and chronic inflammation including lymphocytes with few immature granulocytes. The scattered immature granulocytes in the aspirate consistent with the patient's diagnosis of refractory anemia with excess blasts (Higher magnification at right).(courtesy of E.R. Ladich, R. Virmani, CVPath Institute, Gaithersburg, MD, USA)*

elevated rate of possible ST and the potential to dilute real differences in definite or probable ST, and has led to the suggestion that only definite or probable ST be reported. We believe this is also a concern as it clearly under reports true late, and very late, ST rates. Indeed, it may be clear that an unwitnessed, overnight death nine months following a DES implantation in an octogenarian should be valued differently from a sudden cardiac death in a 56 years old patient who stopped his dual anti-platelet therapy six days earlier for a planned orthopaedic intervention while working in his garden three months after DES implantation.

## Acute myocardial infarction

Table 1 highlights some particular elements from the recently published universal definition of myocardial infarction important for (drug-eluting) stent evaluations. The diagnosis of reinfarction (/infarct extension) in the setting of a PCI is not possible in the presence of unstable or declining troponin levels. In this setting the importance of obtaining baseline biomarkers to exclude elevation prior to the index procedure should be emphasised. Moreover, we like to stress that the reinfarction definition consist of two key components. As indicated in Table 1 there should be a 20% rise in troponin level three to six hours post-procedure as compared to baseline. Less clear from the original manuscript[8], the CK-MB or troponin rise should bring its value to at least three times above the URL.

Although a silent MI is not explicitly defined by ARC, any new pathologic Q waves compared to the pre-procedural ECG at any stage during follow-up may define an interval myocardial infarction and suggests its anatomic location. Blinded core laboratory readings and the use of relevant ECGs in event adjudication are strongly recommended. Finally, the diagnosis of spontaneous MI is possible in case of sudden death with ischaemic symptoms and ECG signs of transmural ischaemia (ST segment elevation, new LBBB) or proven vessel thrombus (angiography, autopsy).

Procedural (thrombotic) complications (dissection, guide-catheter [wire] thrombosis, e.g.) may occur during the index study procedure (primary) or during target lesion revascularisation (secondary). A PCI procedure ends when the guiding catheter is removed and the patient leaves the catheterisation laboratory. Thrombotic complications evolving during this time frame will not trigger a (device related) stent thrombosis event according to the ARC definitions.

Importantly, also a (biochemical) periprocedural myocardial infarction (<48 hours of the index procedure), in the absence of any angiographic or pathological confirmation of ST or a recurrent acute ischaemic event, will not connote a probable ST event. The latter reflects our intention to avoid diluting a potential real difference in ST events with the use of an overly sensitive definition that include cases of myocardial infarction due to periprocedural complications (distal embolisation, side-branch occlusion, e.g.). In the periprocedural period (after removal of the guiding catheter up to 48 hours) the element of a new (acute) ischemic event is critical when considering a probable ST. Any new ST-segment elevation myocardial infarction in the region of the index procedure may be related to ST. So any spontaneous ST-segment elevation myocardial infarction in the region of the index study procedure may be related to stent thrombosis. For those patients treated with thrombolytics, the presence of residual thrombus in the stented region triggers the diagnosis of definite ST. In the absence of any residual vessel thrombus and in the absence of any other culprit lesion in the target vessel, ST becomes probable according to the ARC definitions if accompanied by elevated cardiac biomarkers. However, any new ST-segment elevation myocardial infraction post PCI infarction, in the absence of angiography or histology confirmation, is considered a probable stent thrombosis.

## Repeat revascularisation procedures

*"Clear and consistent definition of target lesion revascularisation (TLR) is crucial to understanding variations in DES effectiveness."*

Any re-intervention procedure that "touches" the stented area is defined as TLR. ARC criteria for TLR are intended to define procedures that are performed for clinically significant re-narrowing. The adjudication process as to the clinical need of a TLR is based on two fundamental components 1) symptoms or any functional evidence of ischaemia, and 2) lesion severity > 50% diameter stenosis determined

**Table 1. Difference between Dublin definition and ARC**

| **Myocardial infarction, peri-procedural** | |
|---|---|
| **Old Version** | **ARC-1-Definitions** |
| Periprocedural interval: within 48 hours in PCI vs PCI trial and within ***seven days*** in PCI vs CABG trial | Periprocedural interval: within 48 hours in PCI vs PCI trial and within ***72 hours*** in PCI vs CABG trial |
| Periprocedural PCI related: CK >2 times URL, confirmed by positive CK-MB or positive troponin.<br>If total CK unavailable: CK-MB >3 times URL | Periprocedural PCI related: baseline <URL, Troponin >3 times URL or CK-MB >3 times URL |
| Periprocedural CABG related AMI: undefined | Peri-procedural CABG related: baseline <URL, rise in Troponin >5 times URL or CK-MB >5 timesURL, **AND:** new Q wave/LBBB or new native or graft vessel occlusion or loss of viable myocardium (elevated cardiac biomarkers alone is insufficient) |
| **Myocardial infarction, spontaneous** | |
| **Old Version** | **ARC-1-definition** |
| Spontaneous AMI: typical rise, gradual fall (troponin) or more rapid rise and fall (CK-MB) of markers myocardial necrosis AND at least one of:<br>– ischaemic symptoms,<br>– new Q-waves,<br>– ischaemic ECG changes | Spontaneous AMI:<br>troponin >URL or<br>CK-MB >URL |
| Pathologic finding of AMI | Sudden death (before biomarkers obtained or before expected biomarker rise) with ischaemic symptoms **AND** one of:<br>new ST segment elevation or LBBB,<br>presence of thrombus by angio/autopsy |
| New Q-waves only (silent MI) | No specific definition of silent MI |
| **Myocardial infarction, re-infarction** | |
| **Old Version** | **ARC-1-definition** |
| Re-infarction (extension):<br>If peak CK (or CK-MB) from index MI not yet reached its maximum level: a rise of CK (or CK-MB or troponin in absence of CK) within 24 h after the event is >2x URL AND at least 50% above the previous level.<br>or | Re-infarction (extension):<br>Stable or decreasing biomarker values on 2 samples **AND** a ≥ 20% increase 3 h-6 h post intervention as compared to the baseline sample |
| If elevated CK (or CK-MB) from the index MI are falling or has normalised within 24 h post index PCI: EITHER new rise of CK >2x URL (or CK-MB >3x URL) within 24h post index PCI if the CK level has returned to <URL OR rise by >50% above the previous nadir level if CK level has not returned to <URL. | Note: if biomarkers are increasing or the peak level was not reached, then there are insufficient data to diagnose MI-extension. |

by an independent quantitative coronary angiographic core laboratory. Ideally the evaluation for clinical signs should be performed by the investigator "prospectively", at a point in time prior to repeat angiogram. However, a TLR or target vessel revascularisation (TVR) for a diameter stenosis ≥ 70% in the absence of the above mentioned ischaemic signs or symptoms is also considered clinically indicated. An important lesson learned from previous DES studies is the influence of study design on reintervention rates, in particular, through the use and the timing of protocol-mandated angiography that encourages "occulo-stenotic" interventions with their attendant complications.[9] This reflex may be even more pronounced when treating more complex lesions like bifurcation lesions.[10] The latter may be of concern in the light of the increased procedural complexity and of the trend towards a higher rate of myocardial infarction in the bifurcation group.[11] Although for existing studies the independence of such evaluations may not be possible, for future studies, the completion of clinical evaluations before protocol angiography or the separation of angiographic follow-up studies from clinical studies may be useful.

In these cases we can concur to a strategy introducing invasive functional diagnostic testing as a tool for adjudication as to clinical need.[12] Along with this reasoning, any investigator/institution driven, non-protocol mandated, scheduled repeat angiograms in clinically stable patients, as encountered during ARTS-II, are problematic, and should be avoided, in the sense they may induce a bias towards increased TLR ("oculo-stenotic reflex")[13].

## Occlusion

A vessel occlusion is the absence of any antegrade luminal passage of contrast dye distal of the lesion of interest (TIMI flow 0-I). The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed (definite) stent thrombosis, since in the absence of a clinical event an abrupt occlusion is less likely than gradual re-narrowing due to restenosis. However, any silent (stent) occlusion should stimulate a detailed investigation of the patient source documents for any indication of spontaneous myocardial infarction (new Q waves, wall motion abnormalities, e.g.) in the area of the implanted stent. As indicated the latter may indicate a probable stent thrombosis.

## Censoring analysis?

*"Making every event count by counting every event"*

Clinical event analysis in randomised clinical trials (RCTs) of DES requires careful scientific and statistical consideration. In case of ST comparisons between bare metal stents (BMS) and DES, early pivotal study designs censored or excluded patients from a subsequent ST event after an intervening reintervention for restenosis. More recent

re-evaluations have noted that this analysis plan may bias perception of BMS safety (because of higher restenosis rates and more censored patients) relative to DES. Indeed, we have observed that definite or probable ST is more frequent after treatment of restenosis.[14] A dilemma exists in this case as whether to attribute stent thrombosis to the initial treatment strategy ("intention to treat") or the intervening treatment of restenosis ("as treated"). Elimination of such censorship actually would produce a more theoretically rigorous "intent-to-treat" analysis plan. This observation also adds further evidence against prior assumptions of restenosis as a benign clinical entity.[15] Re-intervention for restenosis is often complex and carries an elevated risk for procedural complications, morbidity and mortality.

## Reporting stent thrombosis

In the process of adjudicating stent thrombosis events, individual patients may sustain more than one indicator from the algorithm in Figure 1 for the same ST event or they may sustain subsequent ST resulting in > 1 ST during the follow-up period. We propose reporting stent thrombosis according to actual number of unique ST events, assigning each unique event to the highest level of certainty and not counting multiple levels of certainty for the same event. For example, if a patient presents with MI and does not undergo angiography initially but several days later does have angiography demonstrating thrombotic occlusion in the absence of a new clinical event, we propose this be reported as a single definite ST rather than probable and definite. On the other hand, patients with discrete scenarios consistent with ST should be counted as multiple events according to the level of certainty for each event. In the analysis, we propose a hierarchical report, identifying the number of patients with any event, number with >1 unique ST, and the number identified according to definite, probable, and possible level of certainty. This principle is illustrated in Figure 3 of the ARTS-II three-year follow-up paper previously published in EuroIntervention.[14]

## Time of follow-up

The issue of duration of follow-up is important. Ideally, we desire long-term follow-up, but this needs to be balanced against the knowledge that as time advances the probability increases that events are related to disease progression rather than complications of treatment of the original lesion. It is important to assess these events in relation to the overall clinical outcome as with the proposed patient-oriented composite. But, an effort to attribute these very late events to ongoing risk for ST loses specificity after some point and may again dilute real differences assessed at earlier times.

## Conclusion

The ARC-1 met the goal of developing standardised endpoints focussed on safety and effectiveness of (investigational) DES platforms in stable coronary disease patients with the *de novo* lesions. The adoption of a single set of consensus definitions reflecting possible, probable, and definite stent thrombosis is useful, even with the realisation that limitations of these definitions include the variability of sensitivity/specificity, depending on how they are applied and on the quality of the clinical source data. "Clinical narrative competence" is crucial to the quality of the clinical event adjudication. The ARC-1-definitions do not cover every situation. In the near future, specifications will be necessary addressing individual complex patient and lesion groups.

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# CHAPTER 1.4

## 5-Year Clinical Outcomes of the ARTS II (Arterial Revascularization Therapies Study II). of the Sirolimus-Eluting Stent in the Treatment of Patients With Multivessel De Novo Coronary Artery Lesions.

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*J Am Coll Cardiol.* 2010;**55**:1093-101. [**original research paper**]

# 5-Year Clinical Outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the Sirolimus-Eluting Stent in the Treatment of Patients With Multivessel De Novo Coronary Artery Lesions

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**Objectives** The purpose of this study is to compare the 5-year clinical outcomes, safety, and efficacy of sirolimus-eluting stents (SES) in the ARTS II (Arterial Revascularization Therapies Study II) with the outcomes of coronary artery bypass graft (CABG) and bare-metal stenting (BMS) from the ARTS I.

**Background** The long-term outcomes after SES implantation in patients with multivessel disease remains to be established.

**Methods** The ARTS I was a randomized trial of 1,205 patients with multivessel disease comparing CABG and BMS. The ARTS II study was a nonrandomized trial with the Cypher sirolimus-eluting stent (Cordis, a Johnson & Johnson Company, Warren, New Jersey), applying the same inclusion and exclusion criteria, end points, and protocol definitions. The ARTS II trial enrolled 607 patients, with an attempt to enroll at least one-third of patients with 3-vessel disease.

**Results** At 5-year, the death/stroke/myocardial infarction event-free survival rate was 87.1% in ARTS II SES, versus 86.0% ($p = 0.1$) and 81.9% ($p = 0.007$) in ARTS I CABG and BMS cohorts, respectively. The 5-year major adverse cardiac and cerebrovascular event (MACCE) rate in ARTS II (27.5%) was significantly higher than ARTS I CABG (21.1%, $p = 0.02$), and lower than in ARTS I BMS (41.5%, $p < 0.001$). The cumulative incidence of definite stent thrombosis was 3.8%. Thirty-two percent (56 of 176) of major adverse cardiac events (MACE) at 5 years were related to possible, probable, or definite stent thrombosis.

**Conclusions** At 5 years, SES had a safety record comparable to CABG and superior to BMS, and a MACCE rate that was higher than in patients treated with CABG, and lower than in those treated with BMS. Approximately one-third of the events seen with SES could be prevented through the elimination of early, late, and very late stent thrombosis. (J Am Coll Cardiol 2010;55:1093–101) © 2010 by the American College of Cardiology Foundation

The randomized RAVEL (Randomized Comparison of a Sirolimus-Eluting Stent With a Standard Stent for Coronary Revascularization), SIRIUS (Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions), and TAXUS VI studies have all demonstrated the efficacy and safety of drug-eluting stents (DES) compared with bare-metal stent (BMS) at 5-year follow-up (1–3). These studies, however, enrolled patients with simple de novo lesions, and although important, their results are not applicable to the 60% to 70% of today's percutaneous coronary intervention (PCI) patients who receive DES for "off-label" indications (4). Compared with "on-label" use, the use of DES for off-label indications is

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Manuscript received September 2, 2009; revised manuscript received November 11, 2009, accepted November 30, 2009.

**Abbreviations and Acronyms**

ARC = Academic Research Consortium
BMS = bare-metal stent(s)
CABG = coronary artery bypass graft
CVA = cerebrovascular accident
DES = drug-eluting stent(s)
MACCE = major adverse cardiac and cerebrovascular event(s)
MACE = major adverse cardiac event(s)
MI = myocardial infarction
OR = odds ratio
PCI = percutaneous coronary intervention
SES = sirolimus-eluting stent(s)
ST = stent thrombosis

associated with poorer outcomes and a higher risk of stent thrombosis (ST); conversely, for off-label lesions, DES are associated with superior outcomes when compared with BMS (4–8). These data are limited to only short- and medium-term follow-up, and the outcomes at 5 years in this complex patient group remain to be fully established. The ARTS II (Arterial Revascularization Therapies Study II) population clearly represents off-label use of sirolimus-eluting stents (SES), with a mean of 3.7 stents implanted per patient, and a mean total stent length of 72.5 mm per patient. Therefore, although a nonrandomized trial, ARTS II can address important issues regarding the safety of DES implantation in patients with complex multivessel disease.

The present analysis is the final report on the 5-year safety and effectiveness of the SES in patients with multivessel disease: it compares the outcomes of ARTS II with the outcomes of the 2 historical arms of ARTS I, and assesses the impact on long-term outcome of ST, which has been readjudicated according to the new Academic Research Consortium (ARC) definitions (9).

## Methods

**Study design.** ARTS II was a multicenter, nonrandomized, open-label trial designed to compare the safety and efficacy of the SES in patients with de novo multivessel coronary artery disease, with the surgical group of ARTS I acting as a historical control (10–16). In order to obtain a population comparable to ARTS I, patients were stratified by clinical site in order to ensure the inclusion of at least one-third of patients with 3-vessel disease. The details of patient selection and end point definitions are described elsewhere (16–21). In the current analysis, the ARTS II population, the PCI arm, and CABG arm from the ARTS I trials are labeled as SES, BMS, and coronary artery bypass graft (CABG) groups, respectively.

**Study objectives.** The primary objective of ARTS II was to compare the safety and effectiveness of coronary stent implantation using the SES with the surgical arm of ARTS I. End points are measured in terms of major adverse cardiac and cerebrovascular events (MACCE) comprising all-cause death, any cerebrovascular accident (CVA), nonfatal myocardial infarction (MI), or any repeat revascularization, which is equivalent to the patient-oriented clinical end points of ARC definition (9).

The secondary objectives of this study were to compare the ARTS II patients with both arms of ARTS I with respect to: MACCE at 30 days and 1, 3, and 5 years; the composite end point of death, CVA, and MI; the itemized outcomes of death, CVA, MI, and repeat revascularization; resource utilization at 30 days and 1 year; cost effectiveness at 1 year; and quality of life at 6 months and 1, 3, and 5 years. Finally, the study aimed at describing the prognostic value of the SYNTAX score (22,23) on the MACCE rates in the ARTS II population.

The tertiary objectives of the current study were to report the rate of ST and major cardiac adverse events (MACE; defined as a composite of all-cause death, nonfatal MI, or repeat revascularization) with post hoc readjudication of events according to the ARC definition, which was first described during the follow-up of this trial (9).

**End point measurement.** In ARTS II, the interventional procedure was performed within 48 h of inclusion, whereas in ARTS I, patients were randomized after informed consent had been obtained, after which, patients were placed on a waiting list; there were 3 deaths in the ARTS I CABG arm while patients were awaiting revascularization. To compensate for the temporal difference in allocation between groups, events for the present report were counted from the time of the procedure for all 3 arms and not from the time of allocation as previously published.

In ARTS I and II, only data on subacute thrombotic occlusion (<30 days) were collected in the case record form. In ARTS II, ST was readjudicated according to the ARC definitions. In this process, all coronary angiograms, both procedure-related (n = 104) and nonprocedure-related (n = 165), were reviewed by an independent core laboratory and adjudicated by an independent critical event committee. Thus far, no attempt has been made to assess data on ST in ARTS I in a similar fashion.

In addition, a detailed coronary risk score that has been previously published and tested in a subgroup of ARTS II patients with 3-vessel disease (the SYNTAX score) was used to characterise the complexity of the coronary anatomy (19). In brief, each coronary lesion producing ≥50% luminal obstruction, in vessels ≥1.5 mm, was separately scored and added to provide the overall SYNTAX score. The SYNTAX score was calculated using dedicated software that integrates the number of lesions with their specific weighting factors based on the amount of myocardium distal to the lesion according to the score of Leaman et al. (24), and the morphologic features of each single lesion, as previously reported (23). This SYNTAX score is now available for the entire ARTS II population and its implications in terms of prognosis at 5 years are reported in the current paper.

**Statistical analysis.** Binary variables are reported as percentages, and the difference between groups was presented with 95% confidence intervals. Time-to-event variables are

presented as Kaplan-Meier curves, and incidences were compared using the log-rank test.

A separate multivariate regression analysis was performed to determine independent predictors of MACE and ST (according to ARC definition) within the ARTS II population only. The following variables were tested on a per patient basis by univariate analysis to determine suitability for inclusion in the multivariate model: sex, previous history of MI, current smoking habit, left ventricular ejection fraction, presence of diabetes, hypertension, 3-vessel disease, family history of MI or sudden death at age <55 years, presentation with unstable angina, use of glycoprotein IIb/IIIa inhibitors, logistic euroSCORE, and SYNTAX score. Finally, a logistic regression model was built using the significant univariate predictors ($p < 0.1$).

## Results

**Baseline and procedural characteristics.** Between April 1997 and June 1998, a total of 1,205 patients were randomly assigned to PCI with BMS (n = 600) or CABG (n = 605) in 67 participating centers in the ARTS I trial. Between February 2003 and November 2003, 607 patients at 45 participating centers were treated by PCI using SES and entered into the ARTS II study. Table 1 presents their baseline demographic and angiographic characteristics. Patients treated in ARTS II were significantly older than those in ARTS I. ARTS II had a significantly higher incidence of diabetes mellitus, hypertension, hypercholesterolemia, and silent ischemia, and a lower percentage of current smokers or patients with a history of prior MI as compared with the CABG groups. Seven patients did not receive any stents during the index procedure (4 underwent elective CABG, 1 required emergent CABG, 1 underwent PCI 35 days later, and 1 remained on medical therapy).

The percentage of percutaneous 3-vessel treatment was 46.6% in SES versus 18.0% in BMS ($p < 0.001$). The mean number of significant lesions per patient was $3.6 \pm 1.3$ in SES versus $2.8 \pm 1.0$ in CABG ($p < 0.001$) and $2.8 \pm 1.0$ in BMS. SES patients received $3.7 \pm 1.5$ stents with an average total stented length of $72 \pm 32$ mm compared with $2.8 \pm 1.3$ stents and $48 \pm 22$ mm in BMS patients ($p < 0.001$). In the SES population, SYNTAX score and logistic euroSCORE were $20.8 \pm 9.51$ and $2.16 \pm 15.2$, respectively.

**5-year follow-up.** MACCE. Clinical follow-up at 5 years was available in 97.6% of ARTS II population (Fig. 1). The 5-year event rates are depicted in Table 2 and Figure 2. The survival rate in ARTS II was comparable to the historical, surgical, and PCI groups from ARTS I (SES: 94.5%, CABG: 92.6%, BMS: 92.0%). The death/CVA/MI event-free survival was 87.1% in ARTS II, versus 86.0% (log-rank p = 0.42) and the 81.9% (log-rank p = 0.008) in the CABG and BMS cohorts, respectively. At 5-years follow-up, the MACCE-free survival rate in ARTS II (72.5%), which had been comparable to the surgical cohort of ARTS I at 3 years, was significantly lower than CABG (78.9%, p = 0.02), and significantly higher than BMS (58.5%, log-rank $p < 0.001$).

ST ACCORDING TO THE ARC DEFINITIONS. In ARTS II, a total of 57 patients (Table 3) experienced at least 1 stent thrombotic event (definite, probable, or possible) at 5 years. The rate of ST (definite or probable or possible) in ARTS II was 1.5% at 30 days, 3.1% at 1 year, 4.4% at 2 years, 6.4% at 3 years, and 9.4% at 5 years, respectively. The rate of definite ST was 1.0% at 30 days, 1.6% at 1 year, 2.1% at 2 years, 3.5% at 3 years, and 3.8% at 5 years. Among the 23 patients with definite ST, the numbers experiencing acute (<30 days), late (>30 days, <1 year), and very late (>1 year) ST were 6, 4, and 13, respectively. Four of the acute thrombotic events occurred within the first 4 days post-procedure.

Although clopidogrel was only recommended for 3 months, a total of 266 patients were still using thienopyridines at 1 year. The impact of ST on the ARC-defined patient-oriented composite end point is presented in Figure 3A. If none of these ST events (definite, probable, and possible) had occurred, the event-free rate from mortality, the composite of mortality or any MI, and the patient-oriented composite end point would have increased from 94.5%, 84.3%, 70.7% to 96.8%, 92.7%, 78.0%, respectively (absolute difference: 2.3%, 8.4%, and 7.3%).

IMPACT OF SYNTAX SCORE ON CLINICAL OUTCOME. A significant separation of MACCE-free survival was observed when patients were stratified according to SYNTAX score tertiles, with low, intermediate, and high groups defined by SYNTAX scores of <16 (n = 209), 16 to 24 (n = 199) (Fig. 4). When compared with the lowest tertile group (SYNTAX score: <16, 5-year MACE-free rate: 80.1%), both the intermediate (SYNTAX score: 16 to 24) and high (SYNTAX score: >24) tertile groups demonstrated a lower MACE-free survival rate (intermediate: 70.1%, log-rank p = 0.02; high: 67.1%, p = 0.001).

**Multivariate analysis.** Univariable and multivariable independent predictors for 5-year MACE and ST were presented in Table 4. In univariate analysis, diabetes, logistic euroSCORE, and SYNTAX score were significant predictors of MACE. In multivariate analysis, diabetes (odds ratio [OR]: 1.68 [95% CI: 1.24 to 2.28]), logistic euroSCORE (OR 1.09 [95% CI: 1.003 to 1.14]), and SYNTAX score (OR: 1.68 [95% CI: 1.24 to 2.28]) remained significant, although history of carotid surgery was not. With respect to ST (definite, probable, or possible), SYNTAX score, use of glycoprotein IIb/IIIa inhibitors, and logistic euroSCORE were significant predictors in the univariate analysis, whereas multivariate analysis demonstrated that only SYNTAX score (OR: 1.03 [95% CI: 1.00 to 1.05]) and the use of glycoprotein IIb/IIIa inhibitors (OR: 1.71 [95% CI: 0.99 to 1.32]) were independent predictors of ST at 5 years.

**Table 1** Baseline and Procedural Characteristics of ARTS II and I Population

| | SES (n = 607) | CABG (n = 605) | BMS (n = 600) | SES/CABG Difference (95% CI) | SES/BMS Difference (95% CI) |
|---|---|---|---|---|---|
| **Baseline characteristics** | | | | | |
| Male sex | 77 | 76 | 77 | 0.6% (−4.2% to 5.4%) | −0.4% (−5.2% to 4.4%) |
| Age (yrs) | 63 ± 10 | 61 ± 9 | 61 ± 10 | 1.5 (0.4 to 2.6) | 2.1 (1.0 to 3.2) |
| Body mass index (kg/m$^2$) | 27.5 ± 4.1 | 27.4 ± 3.7 | 27.2 ± 3.7 | 0.2 (−0.3 to 0.6) | 0.3 (−0.1 to 0.8) |
| **Risk factors** | | | | | |
| Myocardial infarction | 34 | 42 | 44 | −7.6% (−13.0% to −2.1%) | −9.9% (−15.4% to −4.4%) |
| Diabetes | 26 | 16 | 19 | 10.3% (5.8% to 14.9%) | 7.5% (2.8% to 12.2%) |
| Hypertension | 67 | 45 | 45 | 22.3% (16.8% to 27.7%) | 22.5% (17.1% to 28.0%) |
| Hypercholesterolemia | 74 | 58 | 58 | 16.4% (11.2% to 21.7%) | 16.1% (10.8% to 21.4%) |
| Family history of MI or sudden death at age <55 yrs | 36 | 42 | 39 | −6.0% (−11.5% to −0.5%) | −3.2% (−8.7% to 2.2%) |
| Current smoker | 19 | 26 | 28 | −6.5% (−11.2% to −1.8%) | −8.7% (−13.4% to −3.9%) |
| Peripheral vascular disease | 7 | 5 | 6 | 1.8% (−0.9% to 4.5%) | 1.4% (−1.3% to 4.2%) |
| **Indication for treatment** | | | | | |
| Stable angina | 53 | 58 | 56 | −4.8% (−10.4% to −0.8%) | −3.1% (−8.7% to 2.5%) |
| Unstable angina | 36 | 37 | 38 | −0.8% (−6.2% to 4.6%) | −1.3% (−6.7% to 4.2%) |
| Silent ischemia | 10 | 5 | 6 | 5.6% (2.6% to 8.5%) | 4.4% (1.3% to 7.5%) |
| **Angiographic characteristics** | | | | | |
| Ejection fraction | 60 ± 12 | 60 ± 13 | 61 ± 12 | −0.2 (−1.6 to 1.3) | −0.8 (−2.2 to 0.7) |
| No. of lesions with stenosis >50% | 3.6 ± 1.3 | 2.8 ± 1.0 | 2.8 ± 1.0 | 0.8 (0.6 to 0.9) | 0.8 (0.6 to 0.9) |
| **No. of diseased vessels** | | | | | |
| 1 | 0 | 4 | 4 | −3.4% (−5.0% to −1.8%) | −3.6% (−5.3% to −2.0%) |
| 2 | 46 | 66 | 69 | −20.1% (−25.6% to −14.6%) | −22.4% (−27.9% to −17.0%) |
| 3 | 54 | 30 | 27 | 23.5% (18.1% to 28.9%) | 26.1% (20.7% to 31.4%) |
| **Vessel territory with stenosis (% of lesions)** | | | | | |
| Right coronary artery | 29 | 29 | 31 | −0.4% (−3.3% to 2.5%) | −2.1% (−5.0% to 0.9%) |
| Left main | 0 | 0 | 0 | −0.1% (−0.2% to 0.1%) | −0.1% (−0.2% to 0.1%) |
| Left anterior descending | 42 | 41 | 39 | 0.4% (−2.7% to 3.6%) | 2.1% (−1.1% to 5.3%) |
| Left circumflex artery | 29 | 29 | 29 | 0.0% (−2.9% to 3.0%) | 0.0% (−2.9% to 3.0%) |
| **Lesion length (visual) (% of lesions)** | | | | | |
| Discreet (<10 mm) | 61 | 68 | 66 | −7.3% (−10.4% to −4.2%) | −4.7% (−7.9% to −1.5%) |
| Tubular (10–20 mm) | 27 | 25 | 27 | 2.0% (−0.9% to 4.9%) | −0.1% (−3.0% to 2.8%) |
| Diffuse (>20 mm) | 12 | 7 | 7 | 5.3% (3.4% to 7.2%) | 4.8% (2.9% to 6.7%) |
| **Lesion classification (% of lesions)** | | | | | |
| Type A | 7 | 7 | 6 | 0.0% (−1.6% to 1.6%) | 0.9% (−0.7% to 2.5%) |
| Type B1 | 23 | 31 | 26 | −7.9% (−10.8% to −5.1%) | −3.0% (−5.8% to −0.2%) |
| Type B2 | 56 | 54 | 60 | 1.9% (−1.3% to 5.1%) | −3.7% (−6.9% to −0.5%) |
| Type C | 14 | 8 | 8 | 6.0% (4.0% to 8.0%) | 5.9% (3.9% to 7.8%) |
| **Procedural characteristics** | | | | | |
| Bifurcation requiring double wiring | 34 | 32 | 35 | 2.2% (−0.9% to 5.3%) | −0.6% (−3.7% to 2.6%) |
| Number of stents implanted | 3.7 ± 1.5 | — | 2.8 ± 1.3 | — | 0.9 (0.7 to 1.0) |
| Total stent length (mm) | 72.5 ± 32.1 | — | 47.6 ± 21.7 | — | 24.9 (21.8 to 28.1) |
| Maximum dilatation pressure (atm) | 16.4 ± 2.9 | — | 14.6 ± 2.8 | — | 1.7 (1.4 to 2.1) |
| Direct stenting (% of lesions) | 34.6 | — | 3.3 | — | 31.3% (29.1% to 33.6%) |
| Duration of procedure (min) | 85 ± 43 | 193 ± 67 | 99 ± 50 | −108.2 (−114.6 to −101.8) | −13.6 (−18.9 to −8.3) |
| Post-procedural hospital stay (days) | 3.4 ± 2.7 | 9.6 ± 4.9 | 3.9 ± 3.7 | −6.2 (−6.6 to −5.8) | −0.5 (−0.9 to −0.2) |

Values are % or mean ± SD. Data are expressed per patient unless stated otherwise.

BMS = bare-metal stent(s); CABG = coronary artery bypass graft; CI = confidence interval; MI = myocardial infarction; PCI = percutaneous coronary intervention; SES = sirolimus-eluting stent(s).

## Discussion

The current analysis reports the 5-year outcomes of patients with multivessel disease treated with SES, and historical cohorts treated with CABG and BMS. The main findings of the study are the following: 1) 5-year mortality was similar between SES, CABG, and BMS groups; 2) the 5-year composite safety end point of death, stroke, and MI in the SES group was comparable to the CABG group, and lower than the BMS group; 3) at 5 years, the MACCE rate in the SES group was higher than the CABG group, which was mainly driven by a higher rate of repeat revascularization in the SES group; however, the MACCE rate of the SES group remained lower than that of the BMS group; 4) at 5-year follow-up, ST events (early, late, and very late) were potentially involved in approximately one-third of

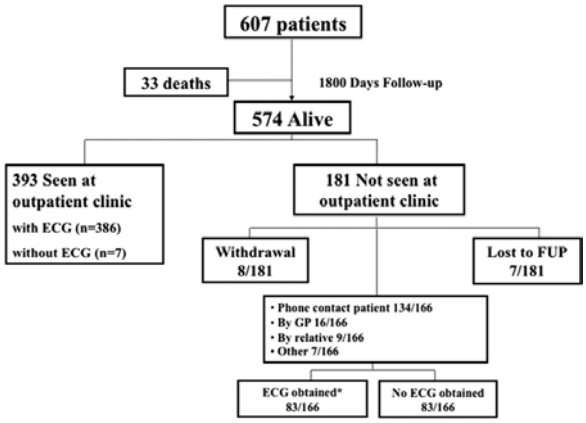


**Figure 1** Flow Chart of 5-Year Follow-Up

*Electrocardiogram (ECG) obtained by center. FUP = follow-up; GP = general practitioner.

MACE events; and 5) baseline SYNTAX score has a role in the prediction of 5-year MACCE events.

**Long-term safety.** Despite the more complex angiographic profile and clinical risk factors in the SES cohort, there was no difference in 5-year mortality between the ARTS II and I cohorts. Although the present study might have been underpowered to demonstrate any significant difference in mortality, the findings concur with the meta-analyses of randomized trials of CABG versus BMS and more specifically, CABG versus multivessel stenting with BMS (25,26). In the current study, the composite end point of mortality, stroke, and MI was lowest in the SES group and was significantly better than in the BMS cohort.

**Long-term efficacy.** The significantly higher MACCE rate in the SES group compared with the CABG cohort (21.1% vs. 17.5%, p = 0.02) at 5-years was not observed consistently through the study. At 1 year, the MACCE rate was slightly lower in the SES cohort compared with the CABG group, whereas at 2 and 3 years, following a

**Table 2** Clinical End Points at 5 Years (Hierarchical and Nonhierarchical MACCE Up to 1,800 Days, Per Patient) Counted Since Date of Procedure

| | SES (n = 607) | CABG (n = 602)* | BMS (n = 600) | SES/CABG Difference (95% CI) | SES/BMS Difference (95% CI) |
|---|---|---|---|---|---|
| Hierarchical | | | | | |
| Death | 33 (5.4) | 43 (7.1) | 47 (7.8) | −1.7 (−4.4 to 1.0) | −2.4 (−5.2 to 0.4) |
| CVA | 17 (2.8) | 16 (2.7) | 19 (3.2) | | |
| MI | 27 (4.4) | 24 (4.0) | 41 (6.8) | | |
| Death/CVA/MI | 77 (12.7) | 83 (13.8) | 107 (17.8) | −1.1 (−4.9 to 2.7) | −5.1 (−9.2 to −1.1) |
| Revascularization | 88 (14.5) | 42 (7.0) | 140 (23.3) | | |
| (re) CABG | 15 (2.5) | 5 (0.8) | 47 (7.8) | | |
| (re) PTCA | 73 (12) | 37 (6.1) | 93 (15.5) | | |
| Any MACCE | 165 (27.2) | 125 (20.8) | 247 (41.2) | 6.4 (1.6 to 11.2) | −14 (−19.3 to −8.7) |
| Nonhierarchical | | | | | |
| CVA | 22 (3.6) | 20 (3.3) | 23 (3.8) | 0.3 (−1.8 to 2.4) | −0.2 (−2.3 to 1.9) |
| MI | 35 (5.8) | 34 (5.6) | 49 (8.2) | 0.1 (−2.5 to 2.7) | −2.4 (−5.3 to 0.5) |
| Revascularization | 123 (20.3) | 52 (8.6) | 181 (30.2) | 11.6 (7.7 to 15.5) | −9.9 (−14.8 to −5.0) |
| (re) CABG | 17 (2.8) | 7 (1.2) | 63 (10.5) | 1.6 (0.1 to 3.2) | −7.7 (−10.5 to −4.9) |
| (re) PTCA | 108 (17.8) | 49 (8.1) | 138 (23.0) | 9.7 (5.9 to 13.4) | −5.2 (−9.7 to −0.7) |

Values are n (%). *3 patients on the waiting list died.

CVA = cardiovascular accident; MACCE = major adverse cardiac and cerebrovascular event; PTCA = percutaneous transluminal coronary angioplasty; other abbreviations as in Table 1.

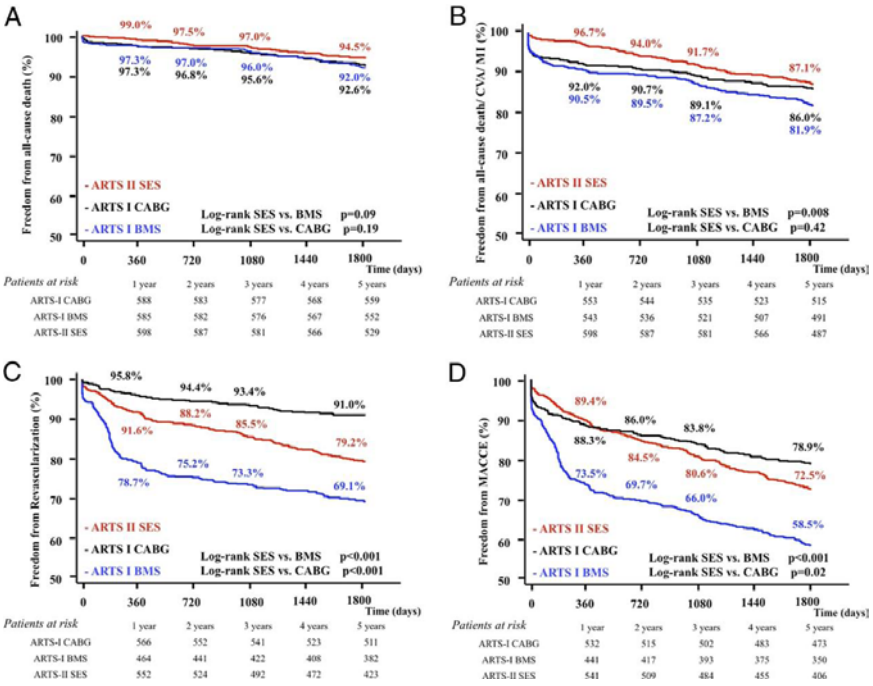


**Figure 2** Kaplan-Meier Curves of Freedom From Clinical Events

Kaplan-Meier estimates up to 1,800 days of: **(A)** freedom from all-cause mortality; **(B)** freedom from a composite of death, cerebrovascular accident (CVA), or myocardial infarction (MI); **(C)** freedom from revascularization; and **(D)** freedom from major adverse cardiac and cardiovascular events (MACCE) (all-cause mortality, any MI, CVA, or any reintervention). ARTS = Arterial Revascularization Therapy Study; BMS = bare-metal stent(s); CABG = coronary artery bypass graft; SES = sirolimus-eluting stent(s).

comparatively greater number of additional MACCE events in the SES group, the overall MACCE rate was insignificantly higher in the SES group compared with CABG (17,27). This reversal was mainly driven by the relatively higher rates of reintervention in patients in SES compared with CABG, such that the absolute difference in repeat revascularization between the 2 groups increased progressively from 4.2 % at 1 year to 6.2%, 7.9%, and 11.6% at 2, 3, and 5 years, respectively. Therefore, the current trial confirms that surgical revascularization is more durable than percutaneous revascularization. It is noteworthy, however, that the freedom from surgical or percutaneous reintervention at 5 years increased from 69.1% in the BMS to 79.2% in SES. Furthermore, at 5 years, only 2.8% of patients from the SES cohort required CABG compared with 10.5% from the BMS cohort.

**Table 3** ST According to the ARC Definitions

| | ARTS II | Death Up to 1,800 Days | MI Up to 1,800 Days* |
|---|---|---|---|
| Acute/subacute (<30 days) | 9 (1.4%) | 1/9 (11%) | 9/9 (100%) |
| Late (<1 yr) | 9 (1.4%) | 3/9 (30.0%) | 4/9 (40.0%) |
| Very late (>1 yr) | 39 (6%) | 10/39 (26%) | 29/39 (74%) |
| Definite | 23 (4%) | 2/23 (9%) | 19/23 (83%) |
| Definite or probable | 46 (8%) | 3/46 (7%) | 42/46 (91%) |
| Definite, probable or possible | 57 (9%) | 14/57 (25%) | 42/57 (74%) |

*MI according to ARC definition.
ARC = Academic research consortium; MI=myocardial infarction; ST = stent thrombosis.

**ST.** Occurrence of late and very late ST has been recognized as a long-term safety concern with drug-eluting stents (28,29). Recent studies have suggested that in patients with 2- and 3-vessel disease, ST negatively impacts long-term outcomes (30). There was a gradual rise in the rate of ST during follow-up, but overall rates of definite ST were similar to those reported in all-comer

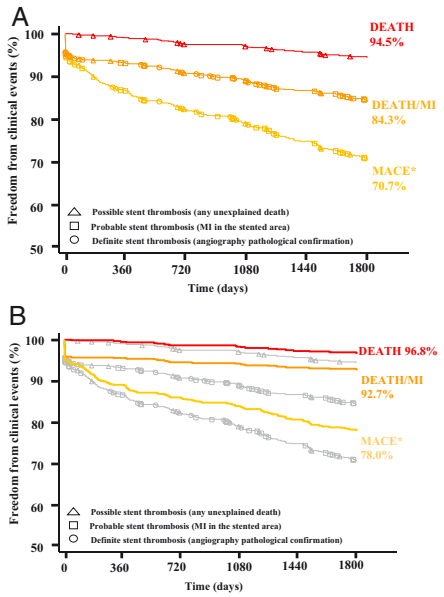


**Figure 3** **Kaplan-Meier Curves of Freedom From ARC-Defined MACE, With or Without ST**

Kaplan-Meier estimates of freedom from death **(red lines)**, death or myocardial infarction (MI) **(orange lines)**, and major adverse cardiac events (MACE) (all-cause mortality, MI, or revascularization) **(yellow lines)** according to Academic Research Consortium (ARC) definition **(A)**. Possible stent thrombosis (ST) is superimposed on the Kaplan-Meier curves as a **triangle**, probable stent thrombosis as a **square**, and definite stent thrombosis as a **circle**. If all these ST-related events had been eliminated **(B)**, freedom from death at 5 years would have increased from 94.5% to 96.8%, freedom from death or death/MI from 84.3% to 92.7%, and freedom from MACE from 70.5% to 78.0%. Please note MI and MACE were readjudicated according to ARC definition. *All-cause death, MI, or any revascularization according to ARC definition. Troponin was not collected in the ARTS II.

populations treated with DES (28,29). When analyzing the impact of ST on safety outcomes, reassurance can be obtained by considering the rate of all-cause mortality (5-year mortality, SES: 5.4% vs. BMS: 7.8%) and MI (5-year MI, SES: 5.8% vs. BMS: 8.2%), because despite the fact that two-thirds of the patients with definite ST sustained an MI or underwent a repeat revascularization, only 2 of these 23 patients died at 5-year follow-up. The ST events from ARTS I PCI have not been reported because of the absence of any adjudication of late and very late stent thrombotic events.

Figure 3 illustrates the fact that early, late, and very late, as well as definite, probable, or possible ST all contributed to a deterioration in the treatment effect expressed as freedom from death, death/MI, and death/MI/repeat revascularization. Of the 176 patients who had a major adverse cardiac event (ARC definitions), 22 had definite ST, 45 definite or probable ST, and 56 definite, probable, or possible ST (32% of adverse events). Thus, one-third of adverse events occurring during 5-year follow-up could be explained, and potentially prevented, by eliminating ST. These results emphasize the importance of optimal stent implantation, development of less thrombogenic devices such as DES with biocompatible or bioabsorbable coatings, or fully bioabsorbable DES, and in addition, more effective antithrombotic therapies (31–35).

**Impact of SYNTAX score on long-term clinical outcome.** The recently reported SYNTAX trial compared surgery with percutaneous treatment in patients with left main or 3-vessel disease (36). Of interest, when patients with 3-vessel disease from the SYNTAX trial were subdivided into tertiles of SYNTAX score (cutoff of 23 and 33), the lowest tertile group showed similar 1-year MACCE rates

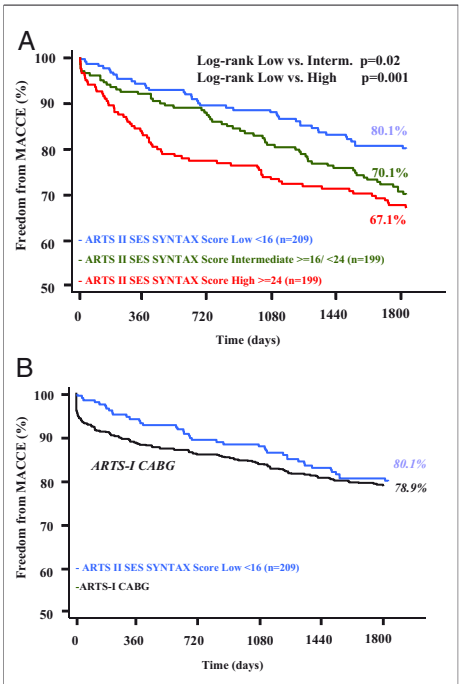


**Figure 4** **Kaplan-Meier Curves of Freedom From MACCE According to Tertiles of SYNTAX Score**

Freedom from protocol-defined major adverse cardiac and cerebrovascular event (MACCE) rate according to SYNTAX score tertiles **(A)**. When the coronary artery bypass graft (CABG) MACCE rate is superimposed, the lowest SYNTAX score tertile shows a similar event rate at 5 years **(B)**.

**Table 4** Independent Predictors of MACE and ST in the ARTS II Group

| | Univariable Predictors at 5 Yrs | | | Multivariable Predictors at 5 Yrs | | |
|---|---|---|---|---|---|---|
| Variables | Odds Ratio | 95% CI | p Value | Odds Ratio | 95% CI | p Value |
| MACE | | | | | | |
| Diabetes | 1.82 | 1.35–2.47 | <0.001 | 1.68 | 1.24–2.28 | <0.001 |
| Logistic euroSCORE | 1.11 | 1.03–1.21 | 0.01 | 1.09 | 1.003–1.14 | 0.04 |
| SYNTAX score | 1.04 | 1.02–1.05 | <0.001 | 1.68 | 1.24–2.28 | 0.001 |
| Any ST | | | | | | |
| SYNTAX score | 1.03 | 1.00–1.06 | 0.02 | 1.03 | 1.00–1.05 | 0.04 |
| Use of glycoprotein IIb/IIIa inhibitor | 1.68 | 0.99–2.83 | 0.05 | 1.71 | 1.01–2.89 | 0.045 |
| Logistic euroSCORE | 1.14 | 0.99–1.31 | 0.05 | 1.15 | 0.99–1.32 | 0.06 |

Major adverse cardiac events (MACE) are according to ARC definition (all-cause death, myocardial infarction, or revascularization).
Abbreviations as in Tables 1 through 3.

between PCI and CABG. On the other hand, for the highest tertile groups, the 1-year MACCE rate was significantly higher in the PCI group (36).

After applying the tertile division of the SYNTAX score to the ARTS II study (cutoffs 16 and 24), patients with a score of <16 had a MACCE-free survival rate that was greater than patients in the middle or highest tertiles. In addition, the SYNTAX score was identified as an independent predictor of 5-year ST and MACE, indicating that it has a role in the risk stratification of patients with multivessel disease. Furthermore, the MACE rate was similar between the lowest tertiles of the ARTS II group and the entire surgical cohort from ARTS I (Fig. 4). These results further support the notion that patients with multivessel disease and a low SYNTAX score may be adequately treated with PCI, whereas those patients with high SYNTAX scores benefit more from CABG.

Of note, the cutoff values for the tertile division of the SYNTAX score in the SYNTAX trial (23 and 33) are for obvious reasons different from those in the ARTS II trial (16 and 24). Further assessment of the distribution and clinical impact of the SYNTAX score in various populations is warranted; however, only a propensity-matched analysis based on SYNTAX score will allow a definitive comparison of outcomes between the SYNTAX randomized controlled trial and the ARTS II registry.

**Study limitations.** First, it was nonrandomized, and thus the groups are not directly comparable, precluding a formal noninferiority comparison. In view of the higher risks anticipated as a result of the greater severity of disease in the ARTS II population compared with the ARTS I population, the clinical outcomes may be biased against ARTS II; however, this may be partially offset by other advances in interventional technology. Statistical adjustment therefore might be required to correct for the differences. This is currently being conducted and will be presented in a separate report. Second, there was a 5-year time lag between the enrollment periods of the ARTS I and II cohorts. With recent improvements in surgical techniques and concomitant medication (statins), it is more than likely that the clinical results of a true randomized trial would have come out more in favor of surgical treatment. Third, the incidence and impact of ST was not readjudicated according to the ARC definitions in the ARTS I study, which was primarily because pieces of clinical information required for readjudication were missing and not obtainable retrospectively. Finally, the baseline SYNTAX scores in the historical cohorts have not been calculated because the baseline cineangiograms are no longer available.

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**Key Words:** multivessel disease ■ sirolimus-eluting stent ■ long-term outcomes.

# CHAPTER 1.5

## Autopsy validation study of the academic research consortium stent thrombosis definition

Cutlip DE, Nakazawa G, Krucoff MW, Vorpahl M, Mehran R, Finn AV, Vranckx P, Kimmelstiel C, Berger C, Petersen JL, Palabrica T, Virmani R.

*JACC Cardiovasc Interv*. 2011;**4**:554-9. [**original research paper**]

# Autopsy Validation Study of the Academic Research Consortium Stent Thrombosis Definition

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**Objectives** This study sought to validate the sensitivity and specificity of the Academic Research Consortium's (ARC) classification of stent thrombosis.

**Background** Classification of stent thrombosis according to ARC criteria has become widely accepted. The criteria have not been validated against an autopsy standard.

**Methods** An autopsy registry of 139 subjects with prior coronary stenting underwent detailed histopathological analysis to assess for stent thrombosis. Based on clinical data only, cases were adjudicated according to ARC stent thrombosis criteria, including a proposed modification of the possible classification to include death beyond 30 days due only to sudden death or acute ischemia.

**Results** Autopsy results confirmed 51 cases as positive and 88 as negative for stent thrombosis. Clinical adjudication classified 105 cases as definite (10), probable (31), or possible (64) ARC stent thrombosis. Specificity was high for definite (99%) and definite plus probable (83%) criteria, but sensitivity was poor at 18% and 51%, respectively. Including the possible cases improved sensitivity to 92% but reduced specificity to 34% (58 false positives). The modified possible criteria eliminated 13 false positive cases (specificity = 49%) and was the best approximation of a hypothetical gold standard in a sensitivity analysis if late death represented at least 20% of all stent thrombosis cases.

**Conclusions** In a selected autopsy sample, restricting ARC stent thrombosis to definite or definite plus probable criteria results in substantial under-reporting of confirmed cases. Inclusion of a modified possible classification may provide the best estimate of late and very late stent thrombosis rates. (J Am Coll Cardiol Intv 2011;4:554–9) © 2011 by the American College of Cardiology Foundation

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Manuscript received October 14, 2010; revised manuscript received December 23, 2010, accepted January 20, 2011.

Stent thrombosis is a catastrophic complication of coronary stenting, presenting as sudden death or nonfatal myocardial infarction (MI) in almost all cases (1,2). After a controversy surrounding possible inconsistent and incomplete reporting of stent thrombosis in drug-eluting stent (DES) trials, especially those events occurring more than 1 year after stenting (3), the Academic Research Consortium (ARC) proposed a standardized classification (4). This classification standardized the inconsistencies of previous trial protocol definitions, by including uniform criteria for angiographic confirmation, allowing for inclusion of probable events presenting as new acute myocardial infarction without angiographic confirmation, and maintaining the principle of intention-to-treat by not excluding patients with interval target lesion revascularization. Concern remained, however, surrounding those events occurring beyond 1 year that may present as unexplained death. Although these events were considered as possible stent thrombosis by ARC, it became recognized that an increasing proportion of deaths remain unexplained over time, leading to a potential exaggeration of the rates of very late stent thrombosis as well as possible dilution of a signal for differences between groups if events other than stent thrombosis were included in a substantial number (5,6). For these reasons, most studies have restricted the definition of cases to those meeting definite or probable criteria, and thereby have not accounted for the vast majority of cases presenting as late death (7,8).

Although the ARC classification has been accepted and recommended as a standard for determining stent thrombosis, it has not been validated for the adjudication of death events. We sought to apply the ARC classification for adjudication of stent thrombosis based on symptomatology immediately before death and other clinical data among subjects who had died after prior stent implantation and had been selected for detailed autopsy analysis of the stented coronary segments.

## Methods

**Patients and lesions.** From the CVPath registry of autopsies with coronary stents, 139 consecutive patients referred between June 2002 and March 2008 and who received at least 1 DES were examined. The study cohort included only sirolimus-eluting or paclitaxel-eluting DES. Cases were routinely referred to CVPath Institute, Inc. (Gaithersburg, Maryland) from the local medical examiners when the patients had received coronary stents. Cases from other institutions were referred to CVPath Institute, Inc. when the pathologist was unable to section the coronary artery with the stent intact. Causes of death were reported as stent-related cardiac deaths, nonstent-related cardiac deaths, and non-cardiac deaths as previously defined (9). Briefly, cardiac death was determined after a complete autopsy, including examination of the myocardium. The presence of an occlusive luminal thrombus or nonocclusive thrombus with distal embolization was considered a stent-related cardiac death. The presence of acute thrombus was defined as a platelet-rich thrombus that occupied >30% of the cross-sectional area of the lumen. Nonstent-related cardiac deaths were defined if the stent was patent without evidence of thrombus or restenosis (luminal stenosis <75% cross-sectional area) but other cardiac causes were likely, including other coronary artery disease with severe narrowing (>75% cross-sectional area stenosis) of 1 or more major coronary arteries, presence of prior myocardial infarction and history consistent with arrhythmia, or other myocardial or valvular heart disease that was deemed responsible for the death.

**Event adjudication.** Available clinical data including any details related to the previous stent procedure and relevant cardiac and other medical history leading up to the time of death were compiled for review by a clinical events committee (CEC). These data included pre-morbid electrocardiography, hospital discharge summary, and report of coronary angiography if performed, but the CEC did not have access to actual angiograms. The CEC was not aware of any information from the autopsy study.

**Abbreviations and Acronyms**

ARC = Academic Research Consortium

CEC = clinical events committee

DES = drug-eluting stent(s)

MI = myocardial infarction

The clinical data summary and a standard adjudication case report form were sent to each of 2 reviewers. The reviewers were asked to determine cause of death as cardiac versus noncardiac, and in cases of cardiac death, they were asked if the clinical data were consistent with ARC definite, probable, or possible stent thrombosis. If there was concordance for all aspects of the adjudication, this result was entered into the event database. If there was discordance, the event was reviewed by the full CEC panel for consensus and this decision was then entered into the database. All adjudications were patient-based. If >1 stent had been implanted, then stent thrombosis for any stent was considered as a confirmed case. If >1 stent thrombosis was confirmed for a patient, then the case with the highest ARC level of certainty was adjudicated.

**Adjudicated endpoint definitions.** The CEC determined cardiac death as any death related to cardiac diagnosis or occurring because of a complication from a cardiac procedure. Any other death for which a clear noncardiac cause was not identified was also considered as cardiac. MI was defined as any event with acute ischemic signs or symptoms and associated with any elevation of creatine kinase-myocardial band or troponin. MI was attributed to the target vessel unless a non-target vessel could be clearly implicated by electrocardiography or angiography. Stent thrombosis was defined according to the ARC classification

**Table 1. ARC Classification of Stent Thrombosis Plus Proposed Modified Possible Criteria**

| Classification | Criteria |
|---|---|
| Definite | Acute coronary syndrome with angiographic or pathological confirmation of thrombus |
| Probable | Unexplained death within 30 days *or* MI involving target vessel territory without angiographic confirmation |
| Possible | Any unexplained death beyond 30 days |
| Possible (modified) | Any unexplained death beyond 30 days where sudden cardiac death or acute ischemic event is likely |

ARC = Academic Research Consortium; MI = myocardial infarction.

except that cases adjudicated as possible were also further subclassified as either: 1) sudden cardiac death or acute ischemia likely; or 2) unexplained death, acute ischemia unlikely (Table 1). A new category termed "ARC modified possible" included only those cases classified as sudden death or acute ischemia likely. ARC definite stent thrombosis required angiographic report of thrombus or occlusion and clinical report consistent with acute coronary syndrome.

**Statistical analysis.** Stent thrombosis was classified according to CEC adjudication as definite, definite or probable, any ARC (definite, probable, or possible), or any ARC modified (definite, probable, or modified possible). The autopsy confirmation of stent thrombosis was considered as a true positive diagnosis and the absence of stent thrombosis by autopsy was considered as a true negative. Sensitivity was calculated for each category of stent thrombosis as the number of autopsy-confirmed cases that were adjudicated as confirmed cases divided by total number of autopsy-confirmed cases. Specificity was calculated for each category of stent thrombosis as the number of cases that were not confirmed as stent thrombosis by autopsy and were adjudicated as not being stent thrombosis divided by the total number of cases not confirmed as stent thrombosis by autopsy.

The time-to-death was calculated based on time from most recent stent procedure. The time-to-stent-thrombosis was calculated as time from most recent stent procedure unless prior specific stent other than most recent was identified as thrombotic. Time-to-stent-thrombosis could not be determined specifically for 3 cases that were presumed to be beyond 30 days and within 1 year, that is, late stent thrombosis. Results for time-to-event are presented as median and interquartile range.

We performed a simulated sensitivity analysis based on a hypothetical sample of 10,000 patients with variable proportion of stent thrombosis events presenting as late death, using the calculated sensitivity and specificity for possible and modified possible criteria from this study when stent thrombosis presented as late death and assuming 90% sensitivity and 99% specificity for definite and probable criteria when stent thrombosis events did not present as late death.

## Results

**Autopsy findings.** There were 139 cases referred for autopsy. Of these, cardiac death was confirmed in 111 (80%) cases. The median time-to-cardiac-death was 115 days (interquartile range 6 to 366). Among the cardiac deaths, stent thrombosis was confirmed in 51 (45%) cases, including 37 occlusive and 13 nonocclusive thrombi. Other causes of death are shown in Table 2. Of 12 subjects with analyzable stents in >1 vessel, thrombosis was present in >1 location in 8 subjects. There were 3 stent thrombosis cases that had DES and bare-metal stents in different locations with thrombosis of DES only in 1 subject, of bare-metal stent only in 1 subject, and of both DES and bare-metal stent in the other. The median time-to-stent-thrombosis was 51 days (interquartile range: 12 to 260 days). The timing of confirmed stent thrombosis was early in 21 cases, late in 22 cases, and very late in 8 cases. Stent thrombosis involved the left main in 3 cases, left anterior descending artery in 28 cases, circumflex artery in 13 cases, right coronary artery in 12 cases, left internal mammary artery bypass graft in 1 case, and a saphenous vein bypass graft in 1 case.

**Clinical event committee adjudication.** The CEC adjudicated any ARC stent thrombosis in 105 (76%) patients from this autopsy population. Sensitivity and specificity for each ARC level of classification according to timing of suspected stent thrombosis are shown in Table 3. ARC definite or probable stent thrombosis identified stent thrombosis asso-

**Table 2. Causes of Death Reported by Autopsy (n = 139)**

| | |
|---|---|
| Cardiac causes | 111 |
| Stent thrombosis | 51 (46) |
| Diffuse CAD | 20 (18) |
| Healed MI | 15 (14) |
| Acute MI or plaque rupture (not stent-related) | 7 (6) |
| Cardiac procedure complication | 6 (5) |
| Cardiogenic shock | 5 (4) |
| Congestive heart failure | 5 (4) |
| Cardiac rupture after MI | 2 (2) |
| Noncardiac causes | 28 |
| Trauma, accidents, suicide | 13 (46) |
| Drug overdose | 3 (11) |
| Bleeding complications | 3 (11) |
| Vascular complications | 2 (7) |
| Pulmonary embolism | 2 (7) |
| Chronic pulmonary disease | 2 (7) |
| Stroke | 1 (4) |
| Sepsis | 1 (4) |
| Diabetic ketoacidosis | 1 (4) |

Values are n and n (%).
CAD = coronary artery disease; MI = myocardial infarction.

**Table 3. Results of Sensitivity and Specificity for ARC Stent Thrombosis Criteria**

| Sensitivity/Specificity | Any ARC ST | Definite | Definite or Probable | Any ARC Modified* |
|---|---|---|---|---|
| Overall | Adjudicated ST = 105 | Adjudicated ST = 10 | Adjudicated ST = 41 | Adjudicated ST = 90 |
| Sensitivity 95% CI | 47/51 = 92 (81–98) | 9/51 = 18 (8–31) | 26/51 = 51 (37–65) | 45/51 = 88 (76–96) |
| Specificity 95% CI | 30/88 = 34 (24–45) | 87/88 = 99 (94–100) | 73/88 = 83 (73–90) | 43/88 = 49 (38–60) |
| Early ST (≤30 days) | Adjudicated ST = 33† | Adjudicated ST = 7 | NA | NA |
| Sensitivity 95% CI | 20/21 = 95 (76–100) | 6/21 = 29 (11–52) | NA | NA |
| Specificity 95% CI | 13/26 = 50 (30–70) | 25/26 = 96 (80–100) | NA | NA |
| Late ST (>30 days) | Adjudicated ST = 72 | Adjudicated ST = 3 | Adjudicated ST = 8 | Adjudicated ST = 57 |
| Sensitivity 95% CI | 27/30 = 90 (73–98) | 3/30 = 10 (2–26) | 6/30 = 20 (7–39) | 25/30 = 83 (65–94) |
| Specificity 95% CI | 17/62 = 27 (17–40) | 62/62 = 100 (94–100) | 60/62 = 97 (88–100) | 30/62 = 48 (36–61) |

Sensitivity = adjudicated ST/autopsy confirmed ST; specificity = adjudicated no ST/autopsy confirmed no ST. Sensitivity and specificity data are presented as %. *For ARC modified, possible ST is limited to late death where sudden death or acute ischemic event is considered likely. †For early ARC ST, possible category (late death >30 days) is not applicable, and any ARC ST includes definite or probable only.
ARC = Academic Research Consortium; CI = exact confidence interval; NA = not applicable; ST = stent thrombosis.

ciated with death slightly over 50% of the time. This was substantially improved (92%) when the possible classification was also included, but at a cost of reducing specificity from nearly 100% for ARC definite or 83% for definite or probable stent thrombosis to 34% for any ARC stent thrombosis. The 4 cases that were not identified by any ARC classification are described in Table 4.

Application of the modified possible criteria resulted in improved specificity over the current ARC possible criteria, with 13 fewer false positive cases, but did fail to detect stent thrombosis in an additional 2 cases. This included 1 subject who died 353 days after stenting with reported cause of sepsis in the clinical record and 1 subject who died 979 days after stenting with clinical report of being found after an alcohol-related fall and apparent head trauma. Despite improved specificity, ARC modified possible criteria continued to overdiagnose stent thrombosis in 45 of 88 cases (Table 5).

**Sensitivity analysis based on prevalence of stent thrombosis presenting as late death.** The impact of the sensitivity and specificity of ARC-adjudicated late stent thrombosis depends on the prevalence of late death as a presentation for stent thrombosis. Table 6 depicts the results of ARC definite or probable stent thrombosis, any ARC stent thrombosis, and any ARC-modified stent thrombosis compared with a hypothetical gold standard as the proportion of stent thrombosis cases presenting as late death varies. When the frequency of stent thrombosis presenting as late death exceeds 20% of all stent thrombosis events, the ARC-modified possible criteria provide a better estimate of the gold standard rate.

## Discussion

This is the first report to test the validity of the ARC stent thrombosis definitions in a relatively large number of autopsy cases. The results demonstrate that the ARC definition can be applied by experienced investigators to accurately identify stent thrombosis in this setting, but that there is large variability in sensitivity and specificity depending on ARC criteria being applied. Furthermore, the accuracy of the adjudicated rates depends on the prevalence of late death as the presenting manifestation of stent thrombosis.

**Table 4. Case Summaries of Autopsy Confirmed ST Not Diagnosed by Any ARC Definition**

| Time | Case Summary | Autopsy Findings | Comments |
|---|---|---|---|
| 6 days | Stent for inferior STEMI complicated by no-reflow and final distal occlusion. Patient had early VF arrest and died 6 days later. | Thrombus nonocclusive | ARC definition requires successful procedure before ST can be adjudicated |
| 34 days | 1 month after LAD DES admitted with intracerebral bleed secondary to brain tumor. Aspirin and clopidogrel discontinued. Patient died 4 days later without regaining consciousness. | Thrombus occlusive | Inadequate clinical information at time of death. CEC adjudicated that death was related to intracerebral bleed |
| 38 days | 1 month after LAD DES admitted with large stroke requiring craniotomy for midline shift. Patient died 4 days later without other information. | Thrombus occlusive | Inadequate clinical information at time of death. CEC adjudicated that death was related to large stroke |
| 120 days | Repeat angiography for heart failure symptoms 4 months after DES of RCA and CX showed severe occlusive disease (99% ostial RCA and CX). Patient died of cardiopulmonary arrest while awaiting CABG. | Thrombus nonocclusive RCA stent only | Original clinical scenario and angiography not consistent with primary thrombosis; possible subsequent thrombosis not evident in available clinical data |

CABG = coronary artery bypass graft; CEC = clinical events committee; CX = circumflex artery; DES = drug-eluting stent(s); LAD = left anterior descending; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction; VF = ventricular fibrillation; other abbreviations as in Table 3.

**Table 5. ST by ARC Modified Definition Not Confirmed by Autopsy Findings**

| ARC Classification and Criteria for Adjudication | n | Autopsy Findings and Comments |
|---|---|---|
| Definite | 1 | |
| STEMI and angiographic thrombus reported | 1 | Patient with chest pain and ST-segment elevation hours after stent; unsuccessful repeat procedure; autopsy did not confirm thrombus and noted perforation as cause |
| Probable | 13 | |
| Unexplained death within 30 days | 10 | |
| Sudden death after elective stent | 2 | Diffuse CAD in 1 case; no reported cause in 1 case |
| Sudden death after acute MI | 4 | 2 cardiac ruptures; 1 cardiogenic shock (not reported in clinical data); 1 no cause (suspected cocaine use) |
| Unexplained cause of death | 4 | 2 unreported procedural complications (1 perforation; 1 dissection with distal stent occlusion); 1 heroin overdose; 1 progressive heart failure; inadequate clinical data available |
| Target vessel MI without angiographic confirmation | 3 | MIs involving nontarget vessel 3; inadequate clinical data to determine MI territory |
| Possible (modified) | 31 | |
| Unexplained sudden death beyond 30 days with other cause identified | 23 | 12 diffuse CAD only; 6 healed MIs; 2 thrombus nontarget vessels; 2 DES total occlusions; 1 BMS total occlusion |
| Unexplained sudden death after noncardiac surgery | 2 | 1 discontinued dual antiplatelet therapy; 1 diffuse CAD and healed MI |
| Other unexplained sudden death | 6 | |
| | 2 | No coronary cause identified |
| | 1 | Restenosis with thrombus; second DES 6 months earlier for angiographic stent thrombosis |
| | 1 | Autopsy reports heart failure as cause; patient had acute event 20 days post-DES without angiography and died of heart failure several weeks later |
| | 2 | 1 diabetic ketoacidosis; 1 cocaine overdose; inadequate clinical data to determine noncardiac cause |

BMS = bare-metal stent(s); other abbreviations as in Tables 1 and 4.

At the height of the DES stent thrombosis controversy, the ARC definitions were welcomed by regulatory agencies and clinical trialists as a standardized method for defining stent thrombosis across clinical trials and various stent types. Such standardization has value for assessment of potential safety differences between new devices and other therapies compared with current treatments or alternative strategies. Despite such standardization, however, defining an event can only add value if there is adequate sensitivity to detect true and likely very weak safety signals while avoiding the introduction of noise that might dilute the signal.

The evaluation of any clinical definition of stent thrombosis is hampered by the unavailability of a gold standard—pathological examination of the stent segment—in most cases. In our study, detailed pathological evaluation was performed by a single and experienced pathology group and provides a gold standard against which to test each of the ARC criteria. Notably, the highly specific criteria for ARC definite stent thrombosis detected only 1 case that was not confirmed by autopsy, but was only present in 18% of autopsy-confirmed cases. Likewise, the most widely used ARC classification of definite or probable was falsely positive in only 17% of unconfirmed cases but present in only 51% of confirmed cases. The lack of sensitivity for definite and definite or probable criteria was related to the failure to diagnose stent thrombosis presenting as or resulting in deaths beyond 30 days. These late deaths represented 30 of the 51 (59%) confirmed stent thrombosis cases. Concern for

**Table 6. Estimated Accuracy of ARC ST Criteria According to Proportion of ST Presenting as Late Death**

| % ST Presenting as Late Death | Gold Standard % | ARC ST Definite or Probable % (Range) | Any ARC ST* % (Range) | Any ARC ST (Modified)* % (Range) |
|---|---|---|---|---|
| 50 | 3.0 | 1.6 (1.5–1.8) | 3.7 (3.3–4.0) | 3.3 (3.0–3.7) |
| 40 | 3.0 | 1.8 (1.7–2.0) | 3.9 (3.5–4.2) | 3.5 (3.3–3.8) |
| 30 | 3.0 | 2.1 (2.0–2.2) | 4.2 (3.8–4.4) | 3.7 (3.5–4.0) |
| 20 | 3.0 | 2.3 (2.2–2.4) | 4.4 (4.0–4.6) | 3.8 (3.7–4.2) |

Assumptions for hypothetical 10,000 patient population undergoing coronary stenting and known ST rate of 3.0% over 5 years: 1) 2.8 percentage points of study population experience unexplained death beyond 30 days (estimates from [7,8]); 2) 8% of study population experienced death before 30 days or acute ischemia (estimate from [7,8]); 3) sensitivity for ARC definite or probable criteria for events other than late death is 90%, and specificity for ARC definite or probable criteria for events other than late death is 99%; 4) sensitivity, specificity, and relative frequency for ARC classification of late death events from Table 3. *Any ARC = definite, probable, or possible. For any ARC modified, possible is limited to late death where sudden death or acute ischemic event is considered likely. Range calculated based on 95% CI for sensitivity and specificity as in Table 3. Abbreviations as in Table 3.

failure to account for late and very late stent thrombosis presenting as death was the basis for including the possible category in the ARC definition.

Indeed, when the cases of late death that were adjudicated as ARC possible stent thrombosis were included, the sensitivity improved to >90% in our study, but unfortunately resulted in a false positive diagnosis in 58 of 88 (66%) subjects that were not confirmed by autopsy. Such a false positive rate more than doubles the estimate of stent thrombosis and may mask any signal that might be detectable by more specific measures.

We assessed whether the signal-to-noise ratio might be improved by inclusion of only those late deaths that suggested a sudden ischemic event. Limiting the ARC possible criteria to sudden cardiac death or death associated with probable acute ischemia substantially improved specificity with 13 fewer false positives and only reduced sensitivity by 2 cases. Nevertheless, there remained 45 of 88 (51%) false positive diagnoses among this sample.

**Study limitations.** There are several questions raised by this analysis and limitations to be considered. There is obvious selection bias inherent in the autopsy sample. Thus, our results only apply to those cases with fatal presentation or death early after suspected stent thrombosis. Despite high fatality rates, clinical studies suggest that most cases of stent thrombosis present with nonfatal acute ischemia (1,2). It is also possible that more complete access to clinical data, including angiography and electrocardiography, in these cases would improve positive and negative diagnostic accuracy. As noted in Tables 4 and 5, inadequate clinical data inherent in the referral nature of the autopsy cases may have also reduced both sensitivity and specificity of the ARC definitions. This points to the importance of careful clinical follow-up and complete ascertainment of clinical data for the duration of any clinical study to minimize the uncertainty in determining cause of death.

## Conclusions

Despite these limitations, the results demonstrate that late or very late stent thrombosis presenting as death is not uncommon and that ignoring these events by only reporting ARC definite or probable stent thrombosis will clearly underestimate the true frequency of stent thrombosis. Because most cases likely present with acute ischemia and have some level of clinical evaluation rather than unexplained late death, this underestimation is clearly less than suggested by the 51% sensitivity in our study. Nevertheless, as demonstrated by sensitivity analysis, as the proportion of stent thrombosis presenting as late deaths increases, as might be expected during longer-term follow-up, the accuracy of the definite or probable classification decreases. It appears that a modification of the ARC possible category as was used in our study offers improved diagnostic accuracy in this setting.

Other modifications to the application of the ARC criteria may also improve accuracy. As was suggested previously, removing the inclusion of unexplained death within 30 days after stenting for acute MI may improve diagnostic accuracy of the ARC probable category (4). In our study, 4 of 13 false positive probable ARC stent thromboses were related to deaths within 30 deaths after MI.

Finally, our results point to the critical importance of obtaining autopsy in clinical studies in which accurate definition of stent thrombosis is a major determinant of safety. Furthermore, protocol definitions must include the potential to classify those events presenting as death beyond 30 days. Until there are more accurate clinical criteria available, we believe the preferred reporting of the ARC classification should include the modified possible category.

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**Key Words:** myocardial infarction ■ stent ■ thrombosis.

# CHAPTER 1.6

## Myocardial Infarction adjudication in Contemporary All-Comer Stent trials: Balancing sensitivity and specificity. Addendum to the Historical MI definitions used in stent studies

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*Eurointervention* 2010; **5**:871-74. [**technical report** ]

EuroIntervention

# Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity

## Addendum to the historical MI definitions used in stent studies

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### Background

In 2006, in an effort to standardise event reporting between clinical trials, the Academic Research Consortium (ARC), proposed standardised consensus definitions for clinical endpoints in coronary stent investigations in stable patients with *de novo* lesions and made them available to any and all interested parties via peer reviewed publication.[1,2] After careful deliberation, the ARC adopted the joint ESC/ACCF/AHA/WHF (European Society of Cardiology, American College of Cardiology, American Heart Association and World Heart Foundation) task force 2007 universal definition of myocardial infarction for consistent application across investigational studies.[3]

The term myocardial infarction (MI) refers to myocardial necrosis in a clinical scenario consistent with acute myocardial ischaemia.[4] The advent of more sensitive and specific cardiac, troponin I and T, assays to detect myocardial necrosis impacted the 2007 redefinition of MI and may have critical consequences for the analysis and reporting of safety and efficacy data in stent trials. The global task force recommends the implementation of a set of criteria to define myocardial necrosis based on troponin and/or creatinine kinase MB CKMB-mass, but notes the preference of troponin in all cases, provided normal or decreasing troponin levels before the index procedure[4]. Opposed to this recommendation, the ARC maintained CKMB-mass as the biomarker of choice for the diagnosis of periprocedural MI.[1]

Concerns were voiced over whether troponin may prove over-sensitive as biomarker of myocardial necrosis in coronary stent trials, especially in all-comers "real world" patient populations. In addition, legacy data may exist that did not use troponin values, making it difficult to reconcile previous trials with current/ongoing investigations, new standards need to be set to allow comparisons between stent trials. Moreover, with the apparent "demise"[5] of Creatine Kinase-MB (CKMB) some centres removed CK-MB from its cardiac biomarker panel, yet others did not make the transition to troponin only. As coronary stent trials evolve to include "real world" populations in both pre- and post-regulatory approval settings, an abrupt transition to troponin as the sole biomarker of myocardial necrosis poses two critical challenges: 1) The majority of historical coronary stent trial data does not utilise troponin values to define myocardial infarction, thus, making it difficult to compare previous trials with current/ongoing investigations; and 2) troponin as a biomarker of myocardial necrosis may prove overly sensitive and non-linear, thereby, elevating the overall rates of myocardial infarctions and diluting potential clinical differences based on size of injury.

The representatives of three international academic research organisations (AROs) considered these challenges in their efforts to

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harmonise clinical event adjudications for the Medtronic (Medtronic, Minneapolis, MN, USA) RESOLUTE clinical program.

The Medtronic RESOLUTE clinical program is a global program that will evaluate the performance of the Endeavor® Resolute Zotarolimus-Eluting Coronary Stent System versus an active control and against historical controls from the ENDEAVOR clinical program (Figure 1). The RESOLUTE clinical program will report endpoints according to the 2007 ARC universal definition of MI and the historical definitions of MI utilised in pivotal DES studies. The dual reporting framework will facilitate a transition to the 2007 ARC universal definitions while also allowing a "bridge" back to the historical data from previous coronary stent trials. This technical report aims to create transparency and to provide insights to the MI adjudication process based on the CK(MB) based historical definitions.

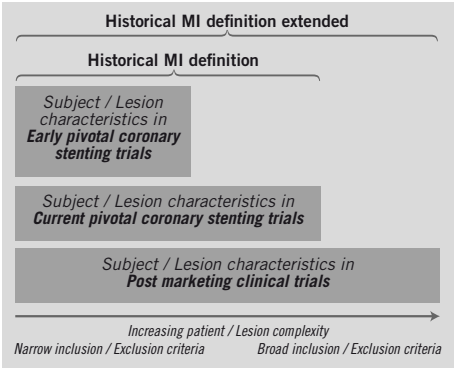


*Figure 1. Implementation of the (extended) MI definitions across the Endeavor Stent Trial programme to allow for between trials meaningful comparison.*

## The historical MI definitions used in early DES stent trials extended to accommodate real world populations

In an effort to adequately define efficacy, early DES stent trials evaluated highly selected subject cohorts undergoing planned percutaneous coronary interventions (PCI); the historical MI definitions facilitated clinical event adjudication in this setting. The number of clinical trials in a post marketing, "real world" context has increased; at the same time, pre-marketing clinical trials have extended inclusion/exclusion criteria to include broad, unselected patient populations. While the historical MI definitions are appropriate for adjudicating a significant portion of events in both highly selected subject cohorts and broad, unselected subject cohorts, we aimed to extend the definitions to account for both cohorts in order to completely link historical and current data sets.

Table 1 lists the different components of the definition considering the initial clinical setting. In a clinical setting consistent with acute myocardial ischaemia presentation, criteria are presented for defining MI that include a rise and/or fall in biomarkers of myocardial damage (BMD) together with symptoms of ischaemia, and/or appropriate ECG changes. MI during a trial of intracoronary devices may occur during the immediate periprocedural period related to the index procedure or long after the procedure as result of spontaneous MI or late complications of the study device or subsequent revascularisation procedures. Due to differences in expected rise and fall of cardiac biomarkers, we have defined the periprocedural period as the first 48 hours after PCI and first 72 hours after coronary bypass grafting (CABG).

The minimal clinical data requirements for MI event adjudication include a 12-lead electrocardiogram recorded before the procedure and at least one repeat recording within 24 hours or at discharge, whichever comes first. A 12-lead ECG should be repeated in case of suspected acute ischaemia. Biomarkers of myocardial damage (BMD) should be assessed at baseline, 6-8 hours later with follow-up every 6-8 hours if elevated until peak noted. A systematic analysis of CPK, CK-MB band and/or troponin curves is required to detect reliably unreported MI's, but it is unlikely that these data would be consistently available. A hierarchical approach is proposed to the clinical event committees (CEC) for adjudication when one or more biomarkers is missing. In this process measurement of mass concentration of CKMB is preferred over CKMB activity.

Periprocedural MI following PCI may occur in stable patients, with baseline biomarker levels below the upper limit of normal, or in the setting of an evolving (infarction extension) or recent (re-infarction) MI. Since historical clinical trials generally excluded these patients, it is necessary to modify the historical definitions to allow for adjudication of these events in the case of evolving MI a new event is triggered by clinical symptoms or ECG changes indicative of new myocardial ischaemia according to the Minnesota Code Classification.[6] Different scenarios may be considered taking into account the pre-PCI biomarker status (Figure 1). In case biomarkers have not yet peaked (Scenario A, Figure 2); myocardial (re-)infarction extension in the setting of PCI requires new signs or clinical symptoms of myocardial ischaemia accompanied by an additional 50% elevation of BMD (preferably CK using the historical definitions) within 24 hours after the index procedure and above a pre-specified threshold. The 24 hours time frame links the biomarker data to the new clinical signs or symptoms. After the biomarker has peaked (Scenario B-C, Figure 2) any significant rise starting within the 48 hours following PCI will define a (re-)MI (extension). For patients referred to CABG different thresholds for biomarkers and time-frames are proposed. The committee noted

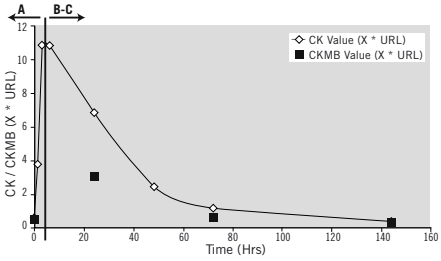


*Figure 2. Expected pattern of (CK)MB release in the context of an ST-segment elevation MI. URL: upper reference limit.*

**Table 1. Proposed extended historical MI definitions used in early DES stent trials.**

**I. PCI (percutaneous coronary intervention)**
**Ia. Baseline biomarkers of myocardial damage (CK and CKMB and troponin < 1*URL) and not acute MI in progress.**

**Periprocedural <48 hours post PCI**

**A.** New pathologic Q waves in ≥ 2 contiguous ECG leads AND
– any CKMB > 1*URL ***or***
– in the absence of CKMB: troponin > 1*URL ***or***
– in the absence of CKMB and troponin: CK > 1*URL ***or***
– in the absence of CKMB and troponin and CK: CEC decision upon clinical scenario

**B.** Appropriate cardiac enzyme data:

**b1.** CK ≥ 2* URL confirmed by:
– CKMB > 1*URL ***or***
– in the absence of CKMB, troponin > 1*URL ***or***
– in the absence of CKMB and troponin: CEC decision upon clinical scenario

***OR***

**b2.** In the absence of CK: CKMB > 3*URL

***OR***

**b3.** In the absence of CK and CKMB: troponin > 3*URL

URL: upper reference limit, defined as 99th percentile of normal reference range

**Ib. If baseline biomarkers of myocardial damage: CK and/or CKMB > 1*URL *or* acute MI in progress**

**Myocardial infarction, re-infarction (extension) <48 hours post PCI**

**A.** If CK (or CKMB) from index MI has not yet reached its maximum level:
– Recurrent thoracic chest pain or ischaemia equivalent >20 minutes (or new ECG changes consistent with MI)

***AND***

– Appropriate cardiac enzyme data:
- A rise in CK within 24 hours of the index event >2*URL (confirmed by either CKMB or troponin > 1*URL) and ≥50% above the previous level ***or***
- In absence of CK: a (post PCI) rise in CKMB within 24 hours of the index event >3*URL and ≥50% above the previous level ***or***
- In absence of CK and CKMB: a (post PCI) rise of troponin within 24 hours of the index event >3*URL and ≥50% above the previous level.

**B.** If elevated CK (or CKMB) following the index MI has peaked ***AND*** CK level has returned < URL then any new rise in:
– CK >2*URL(confirmed by either CKMB > URL or troponin >URL) ***or***
– in the absence of CK: CKMB > 3*URL ***or***
– in the absence of CK and CKMB, troponin > 3*URL

**C.** If CK (or CKMB) following the index MI has peaked AND CK level has NOT returned < URL:
– A rise in CK ≥50% above the previous level and > 2 URL confirmed by either CKMB > URL or troponin > URL ***or***
– In absence of CK, when CKMB has NOT returned < URL, a rise in CKMB ≥50% above the previous level and >3 URL ***or***
– In absence of CK, when CKMB and troponin has not returned <URL a rise in troponin ≥50% above the previous level and >3*URL

**Spontaneous MI >48 hours(PCI)**

**A.** Recurrent thoracic chest pain or ischaemic equivalent ***AND*** new pathologic Q waves in ≥2 contiguous ECG leads ***AND***
– any CKMB > 1*URL ***or***
– in the absence of CKMB: troponin > 1*URL ***or***
– in the absence of CKMB and troponin: CK > 1*URL ***or***
– in the absence of CKMB and troponin and CK: CEC decision upon clinical scenario

**B.** Appropriate cardiac enzyme data (respecting top-down hierarchy):

**b1.** CK ≥2* URL Confirmed by:
– CKMB > 1*URL or
– in the absence of CKMB: troponin > 1*URL ***or***
– in the absence of CKMB and troponin: CEC decision upon clinical scenario

***OR***

**b2.** In the absence of CK: CKMB > 3*URL

***OR***

b3. In the absence of CK and CKMB: troponin > 3*URL

***OR***

**b4.** In the absence of CK, CK-MB and troponin, clinical decision based upon clinical scenario.

**II. CABG (coronary artery bypass grafting)**
**IIa. Baseline biomarkers of myocardial damage (CK and CKMB and trop < 1*URL) and not acute MI in progress.**

**Periprocedural <72 hours post CABG**

**A.** New pathologic Q waves in ≥2 contiguous ECG leads or recurrent signs or symptoms consistent with myocardial ischaemia AND
– CK-MB >5x URL ***or***
– in the absence of CKMB: troponin > 5*URL ***or***
– in the absence of CKMB and troponin: CK > 5 URL ***or***
– in the absence of CKMB and troponin and CK: CEC decision upon clinical scenario

**B.** Appropriate cardiac enzyme data
– CKMB ≥10* URL ***or***
– In the absence of CKMB: trop > 10*URL. ***or***
– In the absence of CKMB and troponin: CK > 10*URL

**IIb. If baseline biomarkers of myocardial damage: CK and/or CKMB > 1*URL or acute MI in progress**

**Myocardial infarction, re-infarction (extension) <72 hours post CABG**

**A.** If peak CK (or CKMB) from index MI has not yet reached its maximum level:
– Clinical signs or symptoms consistent with recurrent myocardial ischaemia

***AND***

– Appropriate cardiac enzyme data:
- A rise in CKMB within 24 hours of the index event >10*URL and ≥50% above the previous level.
- In absence of CKMB: a rise in troponin within 24 hours of the index event >10*URL and ≥50% above the previous level.
- In absence of CKMB and troponin: a rise in CK within 24 hours of the index event >10*URL and ≥50% above the previous level.

**B.** If elevated CK (or CKMB) following the index MI has peaked AND CKMB level has returned < URL, any new rise in
– CKMB >10*URL or
– in the absence of CKMB: troponin > 10*URL or
– in the absence of CKMB and troponin: CK > 10*URL

**C.** If elevated CK (or CKMB) following the index MI has peaked AND CKMB level has NOT returned < URL:
– A rise in CKMB ≥50% above the previous level and > 10 URL or
– In absence of CKMB: a rise in troponin ≥50% above the previous level and > 10* URL. or
– In absence of CKMB and troponin: a rise in CK ≥50% above the previous level and >10*URL

that clinical symptoms should not be required in patients that are intubated, sedated or under the intra-operative or postoperative effects of anaesthesia. Early staged procedures (Table 2: definition) in the presence of elevated biomarkers at the time of the second intervention will be evaluated in this latter category.

Aligned with the historical definition, spontaneous MI required either clinical symptoms of MI and the development of pathological Q waves in at least two contiguous leads with a confirming biomarker (preferably CKMB) or, in the absence of pathological Q waves, an elevation in CK to greater than twice the upper limit of

**Table 2. Definition of staging in a contemporary all-comer trial.**

- Staging should be pre-specified by the investigator after index procedure.
- Staging should not involve the target vessel as assessed by an independent angiographic core laboratory.
- Every urgent coronary reintervention before the planned staged procedure is considered an event.
- Staging should occur within a fixed time period. Every delay of the planned procedure beyond this time frame is considered a protocol violation however not necessarily an event.

normal in the presence of a confirming biomarker (preferably CKMB). With sudden, unexpected cardiac death, involving cardiac arrest, especially when accompanied by clinical signs or symptoms of myocardial ischaemia, the CEC may adjudicate MI considering the clinical scenario including pathological findings, new wall motion abnormalities on non-invasive imaging. However, of note, silent MI was not considered per the historical definition.

## The 2007 ARC universal definition of myocardial infarction specification

The 2007 ARC universal definition of myocardial infarction has been detailed in a previous publication.[1] When considering the 2007 ARC universal definition of myocardial re-infarction following PCI (type 4a) multiple elements need to be highlighted. Re-infarction in the setting of primary PCI can only be assessed if troponin (or CKMB in the absence of troponin) is falling on serial measurements with 3-6 hours difference after the index event (Figure 2, scenario B-C) and requires new clinical signs or symptoms of MI. Program checks of biomarker data will only consider troponin values that are falling or have a rise <10%, correcting for the coefficient of variation of troponin at the level involved with reinfarction A 20% rise is considered significant, i.e., over that expected from analytical variability itself, however, we this value must exceed the appropriate threshold according to the timing of the event (post-PCI, post-CABG, or spontaneous).

## Conclusion

The expanded ability to detect myocardial injury using very sensitive and specific biomarker assays has been a major factor in the 2007 ARC universal definition of MI. The implementation of "better-performance" assays should be welcomed; moreover, the interventional cardiology community should seek to acquire additional experience in clinical investigations evaluating the safety and efficacy of new coronary stent technology. One should bear in mind that the sole implementation of troponin to define MI post-PCI has high (possibly too high) sensitivity and will inflate the number of periprocedural MI and by consequence major cardiac events. We have provided a framework to allow for inter trial standardisation and linkage to historical control data based mostly on total CK measurements. Importantly, criteria have been added to the historical definitions to allow their implementation in contemporary all-comers stent trials including emergency PCI patients.

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# CHAPTER 1.7

## Different cardiac biomarkers to detect peri-procedural myocardial infarction in contemporary coronary stent trials: impact on outcome reporting

Vranckx P, Farooq V, Garg S, Van Es GA, Silber S, Windecker S,
Stone GW, Serruys PW.

*Heart*. 2012;**98**:1424-30. [**original research paper**]

ORIGINAL ARTICLE

# Different cardiac biomarkers to detect peri-procedural myocardial infarction in contemporary coronary stent trials: impact on outcome reporting

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► Additional materials are published online only. To view these files please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2012-302267/content/early/recent).

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Accepted 19 June 2012

## ABSTRACT

**Objective** To assess the differential implications of cardiac biomarker type on peri-procedural myocardial infarction (PMI) reporting.

**Setting** The Resolute 'All-Comers' stent trial.

**Interventions** Blood samples for creatine kinase (CK), CK-myoband (CK-MB) mass or cardiac troponin (cTn) (optional) were collected before and at 6, 12 and 18 h after the assigned percutaneous coronary intervention or at discharge. PMIs were adjudicated using either the 2007 universal definition of MI (type-4a) or the extended historical definition of MI.

**Patients** 2121/2292 patients (92.5%) had an analysable dataset for either biomarker. 890/2121 patients (42%) presented with an acute coronary syndrome (ACS). 267/890 patients (30%) were within 24 h of an ST-segment elevation MI.

**Main outcome measures** Type-4a MI was diagnosed in 208/2121 patients (9.8%) when cTn was used (CK-MB mass if cTn not available), and in 93/2121 of patients (4.4%) when CK-MB mass was used (cTn if CK-MB mass not available). With the extended historical CK-based definition of MI, PMI was diagnosed in 65/2121 patients (3.1%). Adjudication of type-4a MI in patients with an ACS was problematic with <10% of the potential type-4a MI being confirmed as an event, as compared with approximately 95% in stable patients undergoing elective PCI. Type-4a MI was not associated with the subsequent hazard for cardiac mortality (p=0.6).

**Conclusions** The percentage of adjudicated PMI events is driven by the MI-definition criteria and biomarker type. Type-4a MI may not be a reliable component of the primary composite end point in coronary stent investigations which recruit patients with ACS.

**Trial registration number** http://www.ClinicalTrials.gov; Unique identifier: NCT00617084.

## INTRODUCTION

In coronary stent investigations the reported incidence of peri-procedural myocardial infarction (PMI) may vary according to the metrics (ie, the definition of MI used for adjudication and the preferred cardiac biomarker) and the clinical presentation of the patient at the time of the index percutaneous coronary intervention (PCI).[1–4] The clinical and therapeutic implications of PMI remain the subject of continuing debate.[1–3]

Contemporary all-comers coronary stent trials reflect routine PCI practice.[5–9] These studies provide a unique opportunity to compare clinical outcomes among patients presenting with and without acute coronary syndromes (ACS). In the Resolute 'All-Comers' (Resolute-AC) trial we implemented two different sets of criteria to define PMI, and sampled three different cardiac biomarkers to detect myocardial injury—namely, creatine kinase (CK), CK-MB isoenzyme (mass) and cardiac-specific troponin (cTn).[5 6]

The purpose of this prespecified subanalysis of the Resolute-AC trial is to improve the understanding of the differential implications of cardiac biomarker type on PMI reporting and the associated death of patients.

## METHODS

### Study design

The design, detailed methods and end point definitions of the Resolute-AC trial (ClinicalTrials.gov number: NCT00617084) have been detailed in a previous publication.[5] In brief the Resolute-AC is a prospective, multicentre, drug-eluting stent (DES)-versus-DES trial. Between 30 April 2008 and 28 October 2008 17 institutions enrolled a total of 2292 patients with symptomatic coronary artery disease on an all-comers basis, including patients with stable angina, silent angina and ACS. The main outcome measure for this analysis was cardiac death at 2 years.

All outcome measures in Resolute-AC, including MI, were adjudicated by three members of an independent clinical end points committee (CEC) blinded to treatment assignment before locking the database. The institutional review boards of all participating institutions reviewed and approved the protocol of the Resolute-AC trial. All enrolled patients gave written informed consent.

### Definitions of MI

MI was defined according to the 2007 universal definition, using as the preferred biomarker either cTn (CK-MB mass when cTn was not available) or CK-MB (cTn when CK-MB mass was not available; Academic Research Consortium (ARC) recommendation), and the extended, historical (WHO) CK-based definition.[10–12]

For the 2007 universal definition of MI, the joint European Society of Cardiology, American College

of Cardiology, American Heart Association and World Heart Foundation task force recently classified cardiac biomarker levels above ×3 the 99th centile of the upper reference limit (URL), as indicative of PMI following PCI. Furthermore, the replacement of CK-MB mass with cTn was recommended for the diagnosis of a PMI in all cases. Although the 2007 universal definition of MI was endorsed by the ARC, after long and intense discussions the ARC recommended that CK-MB mass should remain the preferred biomarker for the diagnosis of PMI.[10 11]

The historical (WHO) definition of MI was used to adjudicate PMI in previous (Medtronic) stent trials in elective patients with simple lesions. The historical definition was adapted ('extended') to better accommodate 'all-comers' populations by considering patients presenting with ACS.[12 13] A hierarchical approach was used for the adjudication of PMI based upon cardiac biomarker availability when an analysable cardiac biomarker dataset was missing (CK-MB mass when CK was not available, cTn when CK and CK-MB mass were not available) (online supplementary table 1). In order to be adjudicated as a trial end point, PMI had to be new, and therefore distinguishable (ie, new clinical signs or symptoms, angiographic flow-limiting complications) from the index clinical event. Dependent on the clinical situation at the time of the index procedure, PMI could be adjudicated considering either (new) symptoms suggestive of ischaemia/infarction (>20 min), ECG changes, appropriate cardiac biomarker data or pathological evidence of MI, or a mixture of these factors.

### Ascertainment of peri-procedural myocardial infarction

Blood samples for cardiac biomarkers—CK and CK-MB mass—were issued according to protocol (cTn was optional) within 6 h before the index-PCI procedure, and at 6, 12 and 18 h after the assigned study procedure or at hospital discharge, whichever came first. Additional samples up to 48 h after the index-PCI procedure were also considered in this analysis. An analysable cardiac biomarker set consisted of a baseline value, and at least one other measurement of the same biomarker in the 48 h period after the index-PCI procedure.

Cardiac biomarkers were analysed at local site laboratories, yielding a mixture of biomarker tests and upper limits of normal (supplementary table 2, supplementary appendix). The limitations of the analytical performance of commercial assays for biomarkers were considered. A coefficient of variation at the MI decision limit (99th centile of a healthy reference population) was expected at <10% for CK-MB mass and cTn assays used during this trial.[14–17]

### Current analysis

For the purpose of this analysis the Resolute-AC study population was assessed as a cohort. All patients with a reference biomarker available before the index-PCI (baseline), and one or more corresponding samples in the same biomarker family (CPK, CK-MB, cTn) within 48 h after the index-PCI, were suitable for analysis. Seven (7.1) per cent of patients (163/2290) were excluded from the analysis, because either no baseline (n=81, 3.5%) or no samples within 48 h after the index-PCI (n=82, 3.5%) were taken. Six patients had no baseline and no post-PCI biomarker of the same family. Two patients in the study underwent coronary bypass graft surgery within 48 h of the index-PCI procedure and were excluded from this analysis.

A comparison of the rates of PMI using the 2007 universal definition, measuring either cTn (joint task force recommendation) or CK-MB mass (ARC recommendation) as the preferred biomarker, with the extended historical definition, in the adjudication of PMI was undertaken. Subgroup analyses were performed for patients with (n=890, 42.0%) or without ACS (n=1231, 58.0%). Patients in this analysis were categorised as having ACS at the time of the index-PCI procedure if they had either a biomarker above the URL before the index-PCI procedure and/or clinical signs and/or symptoms (>20 min) consistent with continuing myocardial ischaemia as declared by the investigator. The analysis was repeated in the cohort of patients who had both an analysable cTn and CK-MB dataset (935, n=44.1%).

We assessed the 2-year cardiac mortality in patients with or without PMI according to either the 2007 universal definition of MI using either cTn or CK-MB as preferred biomarker (as outlined earlier) or the extended historical definition of MI.

### Statistics

All statistical analyses were exploratory. The counts of PMI are summarised and tabulated according to frequency. Differences in outcomes between patients with and without PMI are compared by Fisher's exact test or $\chi^2$ testing. For univariate analyses, cumulative event rates of cardiac mortality for the different types of PMI at up to 2 years were estimated with Kaplan–Meier analyses and Cox proportional HRs with 95% CIs. Multivariable analyses evaluating the association between PMI and mortality were performed by Cox proportional hazards regression. Multivariable models considered the following baseline covariates: age, sex and diabetes mellitus. Statistical analyses were performed with the use of SAS software, version 9.2 by a dedicated independent statistician. A two-sided p value $<0.05$ was considered to indicate statistical significance.

## RESULTS

Two thousand one hundred and twenty-one of 2290 (92.5%) patients from the Resolute-AC were suitable for analysis. Baseline demographics and clinical characteristics are listed in supplementary table 3. Over one-fifth of patients (n=452, 21.3%) presented with an acute MI within 24 h of symptom onset, including 267 patients (59.1%) with an ST elevation MI. The mean SYNTAX Score was 14.7±9.2.

### Availability of biomarkers of myocardial necrosis before and within 48 h after the index-PCI

Figure 1A depicts the number of patients with available cardiac biomarker of myocardial injury (BMI) sample values at baseline and one or more sample values within 48 h ('analysable cardiac biomarker dataset', n=2121). The Venn diagrams illustrate the availability of one BMI (CK or CK-MB mass or cTn), two BMI (CK and CK-MB mass or CK and cTn or CK-MB mass and cTn) or all three BMI (CK and CK-MB mass and cTn). Although cTn sampling was an optional investigation in the Resolute-AC trial, an analysable dataset for cTn was available in 55.3% (1173/2121) patients. In addition 44.1% (935/2121) patients had an analysable dataset for both cTn and CK-MB.

Figure 1B depicts all analysable cardiac biomarker sample values datasets (n=2121) in all patients in the analysis, stable patients and patients presenting with ACS with at least one cardiac biomarker sample value above the designated threshold for defining a PMI. Notably, 19.0% (178/935) (figure 1A) of patients with an analysable biomarker dataset available for both cTn and CK-MB mass had a peak cTn >3 times 99th centile URL, but a peak CK-MB ≤3 times 99th centile URL. Figure 1C is limited to patients with an ACS at the time of the index-PCI (n=890). Figure 1D is limited to stable patients having an elective PCI (n=1231).

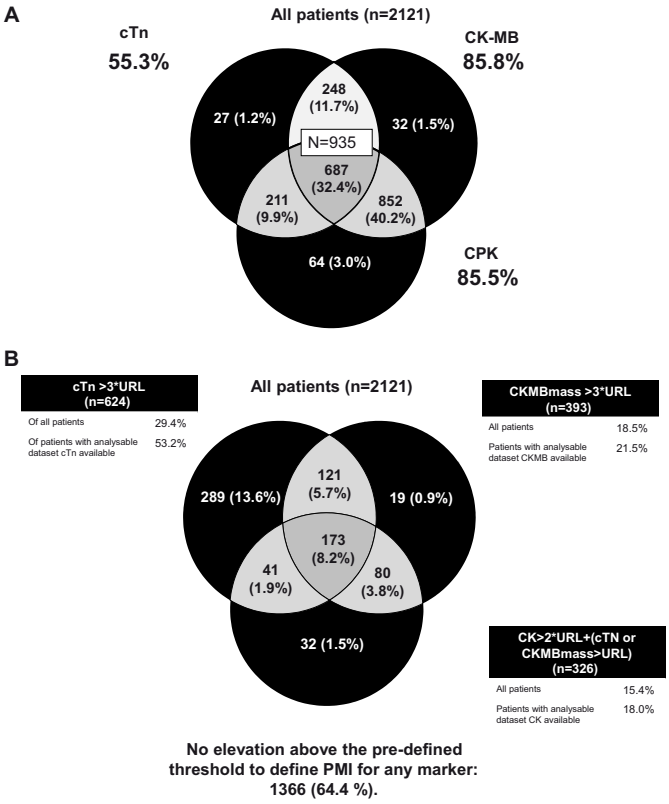



**Figure 1** (A) Patients with an analysable cardiac biomarker sets with both a pre- (baseline) and one or more post-PCI biomarker sample value(s) of the same family. (B—D) Patients, either with or without ongoing MI, with a baseline cardiac biomarker sample value (either for cTn, CK-MB mass, CK) and an increase in the corresponding 6—48 h post-PCI biomarker sample value above the predefined threshold to qualify as a suspect PMI, before final PMI-event adjudication by the clinical end points committee (figure 2B). For patients presenting with an acute coronary syndrome a 20% increase in cardiac biomarker sample value was taken into account (see also figure 1, flowchart). Patients with suspected ongoing MI (figure 2C) at the time of the index-PCI and stable patients undergoing elective PCI (figure 2D) are represented separately. CK-MB, creatine kinase-myoband; CPK, creatine kinase; cTn, cardiac troponin; PMI, peri-procedural myocardial infarction; URL, upper reference limit upper reference limit.

### Diagnosis of PMI based on selection of cardiac biomarkers

#### Elevated biomarkers of myocardial necrosis before and within 48 h after the index-PCI

The number of stable patients undergoing elective PCI with cardiac biomarker elevations above the designated threshold required to define PMI was four times higher when measuring cTn than when measuring CK (161 vs 46 patients), and double when measuring CK-MB mass rather than CK (68 vs 46 patients). Conversely, the number of patients with an ACS at the time of the index-PCI with cardiac biomarker elevations above the designated threshold required to define PMI was only 1.5 times higher when measuring cTn compared with CK (47 vs 19 patients) (table 1).

#### PMI adjudicated by the CEC

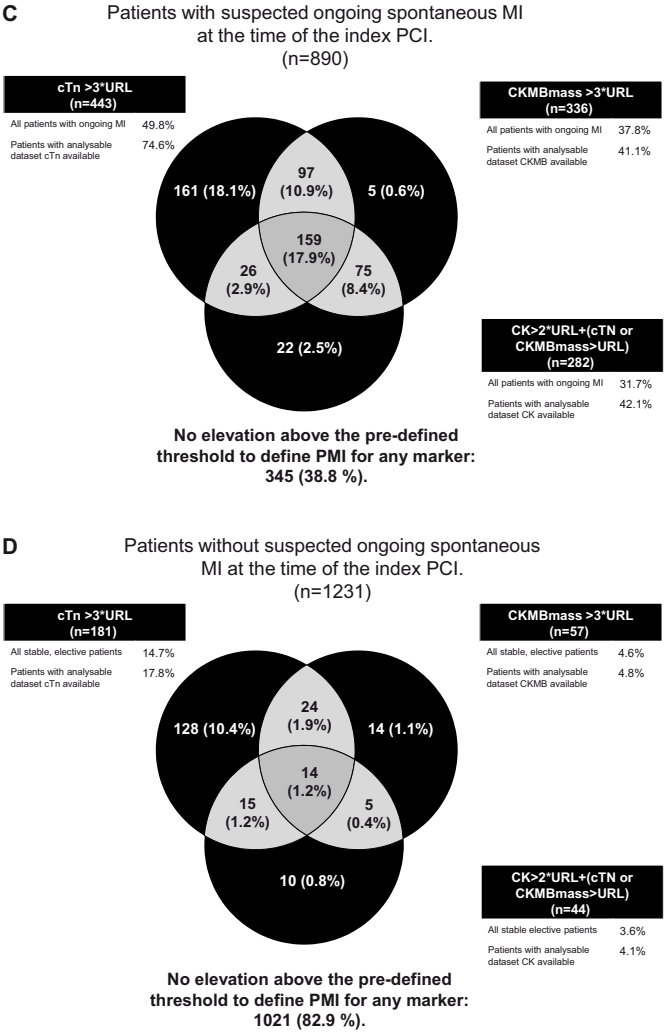
For the 2007 universal definition of MI, type-4a MI was adjudicated by the CEC in 208/2121 patients (9.8%) when cTn was used (CK-MB mass if cTn not available), and in 93/2121 of patients (4.4%) when CK-MB mass was used (cTn if CK-MB mass not available, ARC recommendation). With the extended historical CK-based definition of MI, PMI was adjudicated in 65/2121 patients (3.1%).

The percentage of the adjudicated PMI over the suspected events based on cardiac biomarker elevations ('event-to-trigger percentages') was predominantly driven by the clinical presentation at the time of the index-PCI, with this percentage being nearly 10-fold higher for stable patients undergoing elective PCI than for patients presenting with an ACS. Adjudication of type-4a MI in patients with a suspected ongoing MI was problematic with <10% of the potential type-4a MI being confirmed as an event by the CEC, as opposed to approximately 95% in stable patients undergoing elective PCI.

### PMI in patients with an analysable dataset for both CK-MB mass and cTn

The trends outlined above are similar for the patient subpopulation with analysable cardiac biomarker datasets for both CK-MB and cTn (supplementary table 4). In the subset of patients, in whom an analysable dataset for both cTn and CK-MB mass was available (n=935), myocardial injury—as defined by a cardiac biomarker sample value >99th centile URL—was

**Figure 1** Continued




detected in 54.0% (505/935) measuring cTn and in 49.7% (465/935) measuring CK-MB mass. Type-4a MI was diagnosed in 11.0% (103/935) patients and 5.2% (49/935) patients, respectively.

### Associated 2-year cardiac mortality

During the 2-year follow-up 54 patients in Resolute-AC died owing to cardiac causes, 51 of them are in the 2121 cohort. PMI versus no PMI adjudicated by the extended historical definition of MI was associated with 2-year crude cardiac mortality (HR=3.5; 95% CI 1.4 to 8.9; p=0.007), but not type-4a when cTn was used (HR=1.2; 95% CI 0.5 to 2.9; p=0.65) or when CK-MB (HR=1.4; 95% CI 0.4 to 4.4; p=0.61) was used to adjudicate MI (table 2, figure 2). After adjustment for baseline covariates, PMI by the extended historical definition of MI, analysed as dichotomous variable, remained a significant correlate of 2-year mortality (HR=3.7, 95% CI 1.4 to 9.2, p=0.0065).

## DISCUSSION

The Resolute-AC study design provided a unique opportunity to study the implications of the use of different biomarkers for the detection of myocardial injury in patients undergoing PCI, and

**Table 1** Peri-procedural myocardial infarction (PMI) adjudication upon cardiac biomarkers guided either by the 2007 universal (troponin based)-myocardial infarction (MI) definition or the WHO (creatine kinase (CK)-based)-MI definition in counts and percentages (all patients; N=2121)

| | 2007 Universal-MI definition | | WHO-MI definition extended for AC trials |
|---|---|---|---|
| | Primary marker cTn, (CK-MB mass if cTn unavailable)* | (ARC recommendation) Primary marker CK-MB mass, (cTn if CK-MB mass unavailable)* | Primary CK (with confirming cTn or CK-MB), (CK-MB mass if CK unavailable, cTn if CK and CK-MB mass unavailable)* |
| Stable angina (N=1231) | | | |
| Adjudicated PMI/trigger† to PMI | 161/190 (84.7) | 68/75 (90.7) | 46/52 (88.5) |
| *Investigator reported* | 73/84 (86.9) | 35/35 (100.0) | 30/31 (96.8) |
| ACS (N=890) | | | |
| Adjudicated PMI/trigger† to PMI | 47/519 (9.1) | 25/366 (6.8) | 19/354 (5.4) |
| *Investigator reported* | 12/20 (60.0) | 7/12 (58.3) | 6/10 (60.0) |

*In 1533/2121 (72%), 1975/2121 (93%) and 1983/2121 (93.4%) cases the preferred biomarker, respectively cardiac specific troponin (cTn), creatine kinase (CK) and CK-myoband (MB), was available for analysis.
†Trigger is defined as a suspected PMI based upon cardiac biomarker sample value elevation and/or clinical signs or symptoms consistent with myocardial ischaemia.
ACS, acute coronary syndrome; ARC, Academic Research Consortium.

the adjudication of unreported PMI among patients presenting with or without an ACS at the time of the index procedure. The main conclusions of this analysis are:

1. PMI constituted the majority of all MIs in the Resolute-AC PCI trial. However, the PMI event count varied considerably according to the choice of cardiac biomarker and/or the criteria used for adjudication. Comparing the 2007 universal definition of MI and the extended historical (WHO) CK-based definition of MI, using cTn resulted in a tripling of the rate of PMI. Applying the 2007 universal definition of MI with cTn resulted in a doubling of the rate of PMI compared with CK-MB mass.
2. The PMI 'event-to-trigger' percentage was dependent on the clinical presentation at the time of the index-PCI procedure, rising from <9% in patients presenting with ACS at the time of the index-PCI procedure, to >80% in patients undergoing elective PCI for stable symptomatic coronary artery disease regardless of which biomarker one uses.
3. The frequency of undetected MI with the 2007 universal definition of MI was approximately five times higher than the extended historical (WHO) CK-based definition of MI, mainly reflecting the greater sensitivity of cTn to detect myocardial injury (with subsequent investigator under-reporting).
4. More than 50% of adjudicated PMI events in patients undergoing elective PCI for stable symptomatic coronary artery disease were unreported and only detected through analysis of serial cardiac biomarker sample values.
5. In Resolute-AC, type-4a MI with the actual proposed biomarker thresholds and regardless of the biomarker used, was not associated with subsequent cardiac mortality at 2 years.

This analysis represents the largest prospective comparison of the three most commonly used serum biomarkers for detection of PMI. These findings are likely to be representative of contemporary PCI practice, as patient-, lesion- and procedure-related risk factors are all previously established predictors of PMI,[3] and the baseline and angiographic characteristics of Resolute-AC have been reported to be consistent with other recently reported 'real-world' coronary stent investigations.[5–8 18] The stable patient subset undergoing elective PCI to treat stable coronary lesions matched those recruited in historical stent trials.

The diagnosis of acute, evolving or recent MI requires, in the absence of pathological confirmation, a typical rise and/or fall of biomarkers of myocardial necrosis in conjunction with clinical evidence of myocardial ischaemia.[10] A PMI is defined by a typical new cardiac biomarker elevation above a predefined threshold occurring during the immediate peri-procedural period (<48 h), and an established causality to the index study procedure. This causality may or may not be declared by the investigator (eg, coronary artery dissections, distal plaque embolisation). With ACS the PMI must be identified as a new event, clearly distinct from the index clinical event in the same predefined peri-procedural period of 48 h. In the Resolute-AC trial, most suspected PMIs were reported by the investigators at clinical sites. Yet not all cardiac biomarker elevations above the predefined threshold ('triggers') will identify new events.

The adjudication of PMI in an 'All-Comers' trial resembling everyday PCI practice may be characterised by a signal-to-noise problem. For this analysis we disentangled two specific clinical situations—patients with or without an ACS at the time of the index-PCI. The adjudication of type-4a MI, implementing the 2007 universal definition of MI, in patients with acute presentations (ie, ACS) at the time of the index-PCI is problematic, and exacerbated when measuring a sensitive biomarker such as cTn.[19] Unless there is a clear indication that the cardiac biomarker sample values were falling after the index event and then rising again (above the predefined thresholds) after the index-PCI procedure, there would be insufficient biomarker data

**Table 2** Two-year cardiac mortality according to the occurrence of procedure-related MI (different definitions) or not

| Primary biomarker | KM estimate, PMI* (%) | KM estimate, no PMI* (%) | Log rank, p value | HR and 95% CI† |
|---|---|---|---|---|
| cTn | 2.90 | 2.43 | 0.649 | 1.2 (0.5 to 2.9) |
| CK-MB | 3.25 | 2.44 | 0.606 | 1.4 (0.4 to 4.4) |
| CK | 7.74 | 2.31 | 0.007 | 3.5 (1.4 to 8.9) |

*Percentage failure based on Kaplan–Meier (KM) estimates.
†Cox Model, assuming proportional Hazards.
CK-MB, creatine kinase-myoband; cTn, cardiac troponin; KM, Kaplan–Meier; PMI peri-procedural myocardial infarction.

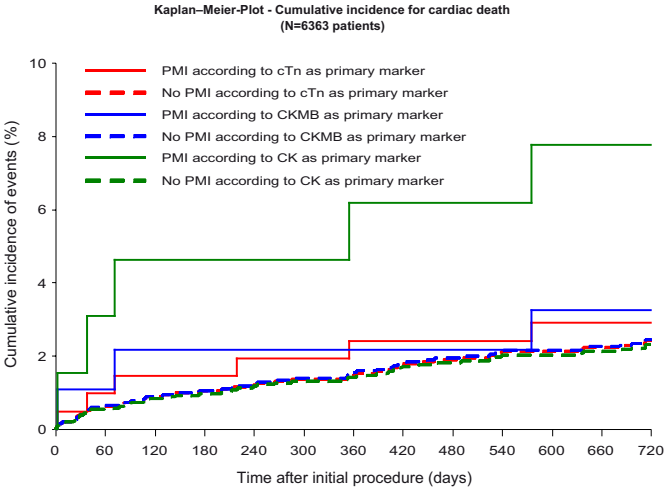



**Figure 2** Cumulative cardiac mortality according to PMI up to 2-years. Shown are the Kaplan—Meier curves for cardiac mortality after the occurrence of PMI according to either the extended historical definition of MI (green) and the 2007 universal definition of MI measuring cTn (CK-MB if cTn is not available) (red) or CK-MB (cTn if CK-MB is not available, Academic Research Consortium recommendation) (blue). CK-MB, creatine kinase-myoband; cTn, cardiac troponin; PMI, peri-procedural myocardial infarction.

to adjudicate a PMI.[19 20] The critical challenge for the members of the CEC is to distinguish whether a new MI was induced by the index-PCI procedure (ie, additional component of an already injured myocardial region, new procedural flow-limiting complications), or if the cardiac biomarker release was still the tail end of the continuing initial myocardial insult.[1 19]

In Resolute-AC, while the event-to-(biomarker) trigger ratio was as low as 5% for the 2007 universal definition of MI, these events proved to be numerically important and contributed to half of the unreported PMIs (based on serial cardiac biomarker sample value analyses only) (table 1). It should be emphasised that including clinical information from the investigator, such as evidence of new myocardial ischaemia and coronary artery flow-limiting complications, resulted in a 10 times higher event-to-trigger percentage, and may improve the signal-to-noise ratio (table 1). Conversely, in stable patients undergoing uncomplicated contemporary elective PCI, >50% of PMIs were detected upon review of serial cardiac biomarker sample values alone, with >80% of all suspected type-4a MI adjudicated as an event. On the basis of the traditional concept of PMI described here, considering a high 'trigger' and 'trigger-to-event ratio' in stable patients undergoing elective PCI, the missing biomarker data may affect outcome reporting and should be considered while interpreting trial results.

The extent of myocardial injury following PCI, as detected by release of CK and/or CK-MB mass, has been correlated with late clinical outcomes in several studies.[21–27] Despite these findings, the threshold level of cTn associated with a prognostic significance remains elusive.[1 10] This analysis adds to the evidence that type-4a MIs, as a class in real-world patients with the current set biomarker thresholds, are not of significant prognostic importance after PCI using contemporary management strategies. Cardiac biomarker elevation following PCI should therefore always be interpreted in relation to the clinical presentation at the time of the index procedure.

The lack of association between a CK-MB mass elevation more than three times the diagnostic level based on the 2007 universal definition of MI, and 1-year mortality among patients with moderate to high risk ACS undergoing PCI, was also reported in the ACUITY trial.[23] Conversely, in the EVENT (Evaluation of drug eluting stents and ischaemic events) registry, consisting of almost 5000 patients undergoing elective PCI, the same degree of cardiac enzyme elevation independently predicted 1-year mortality. In addition, the EVENT investigators reported similar hazards for negative clinical outcomes related to cTn, but only when 20 times the upper limit of normal was used as decision limit.[24] Patients in the subanalysis in the EVENT registry were, however, not separated on the detection of a baseline cTn level ≥99th centile of the URL.

In patients with ACS it is undisputed that an increased cTn (baseline) is a marker of patients at increased risk.[27] Furthermore, it appears that almost all the prognostic information is contained in the baseline cardiac enzyme value, and that this may be a reflection of the underlying coronary atherosclerotic burden and/or plaque instability. At what level, if any, additional cTn elevation following PCI contributes to the hazard for 1-year negative outcomes remains unanswered.

This issue(s) and the stark variations in reported rates of PMI call into question the inclusion of PMI as a component of the primary composite end points of contemporary coronary device trials, particularly when recruiting patients presenting with ACS.

### Limitations

This study has several limitations. First, in 2008 cTn was not yet widely implemented as cardiac biomarker to detect myocardial injury, thereby according to protocol cTn sampling was optional in Resolute-AC. Despite this limitation, up to 54% of patients had an analysable cTn dataset and the major conclusions of the study were unchanged when a subset of patients with both cTn and CK-MB were sampled (supplementary table 3). While recent advances in assay technology have led to more sensitive and precise cTn assays, the issues raised in this manuscript towards trial conduct and data interpretation remain, and may even be accentuated.[28]

Our results did not include the direct metrics (eg, MRI) of the extent of myocardial injury. The findings of the study do, however, suggest that most MIs were small or moderate. We cannot exclude the possibility of a slight variation in the results if a central core laboratory had undertaken the analyses of the cardiac biomarkers.[29] The 99th centile of the reference medical decision cut-off point for the cTn assays was determined in each local laboratory by internal studies with the specific assay that is used in clinical practice. The previous limitations do, however, cause no concern in interpreting the major conclusions of this analysis.

## CONCLUSIONS

As currently defined, type-4a MI following PCI is not a valid outcome measure in contemporary outcome trials. Meaningful thresholds for individual cardiac biomarkers should be identified based on large outcome trials. Adjudication of PMI in patients with an ACS at the time of the index-PCI remains problematic.

**Acknowledgements** We thank Yvonne Teunissen and Peter Paul Kint for their support towards the completion of this analysis. Tessa A M Rademaker-Havinga was responsible for the preparation of the dataset and statistical programming and analysis. We thank all staff of the participating hospitals for their care of the study patients.

**Contributors** PV, PWS: Study concept and design, data analysis and interpretation, manuscript writing. VF, SG, G-AvE, GWS: Critical revision of the intellectual content of the manuscript and final approval of the version to be published. SS: Data collection. Critical revision of the intellectual content of the manuscript and final approval of the version to be published. SW: Study concept and design, data collection. Critical revision of the intellectual content of the manuscript and final approval of the version to be published.

**Funding** Funding for Resolute-AC and its analysis was provided by grants from Medtronic Cardiovascular, Santa Rosa, California, USA.

**Competing interests** GWS reports consulting fees from Abbott Vascular, Boston Scientific and Medtronic; SW reports grants support through his institution from Abbott Vascular, Boston Scientific, Biosensors, Cordis and Medtronic. No other potential conflict of interest relevant to this article was reported.

**Patient consent** Obtained.

**Ethics approval** Ethics approval was provided by the institutional review board of participating sites.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** I am unable to share data beyond the ones used in this analysis owing to data sharing agreements in place with the sponsor and Cardialysis. Data are stored in a central database (Med Net Solutions INC, Minnetonka, USA) and maintained by a contract research organisation (Cardialysis BV, Rotterdam, The Netherlands).

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# CHAPTER 1.8

## Clinical endpoint adjudication in an all-comers coronary Stent study: methodology and external validation

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*Contemporary Clinical Trials* 2012. [**original research paper**]

Contents lists available at SciVerse ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

# Clinical endpoint adjudication in a contemporary all-comers coronary stent investigation: Methodology and external validation ☆

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ARTICLE INFO

*Article history:*
Received 3 March 2012
Received in revised form 30 August 2012
Accepted 31 August 2012
Available online 10 September 2012

*Keywords:*
Adjudication
Clinical event committee
Endpoints
Validation
PTCA
Stenting

ABSTRACT

*Background:* Globalisation in coronary stent research calls for harmonization of clinical endpoint definitions and event adjudication. Little has been published about the various processes used for event adjudication or their impact on outcome reporting.
*Methods and results:* We performed a validation of the clinical event committee (CEC) adjudication process on 100 suspected events in the RESOLUTE All-comers trial (Resolute-AC). Two experienced Clinical Research Organisations (CRO) that had already extensive internal validation processes in place, participated in the study. After initial adjudication by the primary-CEC, events were cross-adjudicated by an external-CEC using the same definitions. Major discrepancies affecting the primary end point of target-lesion failure (TLF), a composite of cardiac death, target vessel myocardial infarction (TV-MI), or clinically-indicated target-lesion revascularization (Cl-TLR), were analysed by an independent oversight committee who provided recommendations for harmonization. Discordant adjudications were reconsidered by the primary CEC. Subsequently, the RAC database was interrogated for cases that based on these recommendations merited re-adjudication and these cases were also re-adjudicated by the primary CEC.
Final discrepancies in adjudication of individual components of TLF occurred in 7 out of 100 events in 5 patients. Discrepancies for the (hierarchical) primary endpoint occurred in 5 events (2 cardiac deaths and 3 TV-MI). After application of harmonization recommendations to the overall RAC population (n = 2292), the primary CEC adjudicated 3 additional clinical-TLRs and considered 1 TV-MI as no event.
*Conclusions:* A harmonization process provided a high level of concordance for event adjudication and improved accuracy for final event reporting. These findings suggest it is feasible to pool clinical event outcome data across clinical trials even when different CECs are responsible for event adjudication.



## 1. Introduction

The process by which clinical trials in cardiovascular medicine, and coronary stent devices in particular, are designed, conducted, analysed, presented, and published has

☆ Conflict of interest: No conflict of interest to be reported.

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evolved dramatically over the last decade. Large, truly global studies with relatively long-term clinical endpoints are conducted to evaluate the effects of a particular treatment strategy on mortality and major morbidity within a disease entity. Unrestricted study populations, including more complex patients, have become the norm [1–4]. Uniform endpoint definitions, terminology and clinical trial design paradigms are an essential prerequisite [5,6]. Yet, an important challenge is to maintain accuracy and consistency in the interpretation of clinical endpoints across geographic areas and over the course of the study. Clinical Event Committees (CEC) are used routinely to adjudicate efficacy and/or safety endpoints in clinical investigations. These expert groups comprise physicians with particular expertise in the relevant therapeutic area but without any active involvement in the study. It is the responsibility of the CEC to review all relevant source data and provide an independent, blinded determination of trial endpoints or events. Little data have been published regarding the processes of CEC event adjudication or their validation; or the potential impact of variability of the overall process on reported event rates. Variability is a particular concern in global programs involving multiple clinical trials possibly with different CECs.

We studied the level of consistency in event adjudication for the resolute-all comers trial [1], between two independent CECs, hosted by two different academic research organisations (AROs). We determined the cause for discordant adjudications and analysed the potential impact of this external validation on the final reported patient outcomes.

## 2. Methods

### *2.1. The resolute all-comers trial study design*

The Resolute-AC trial (ClinicalTrials.gov number: NCT00617084) is a prospective, multi-center, randomized, two-arm international, open-label, non-inferiority trial designed to compare on a 1:1 basis the efficacy and the safety of the Medtronic Resolute zotarolimus-eluting stent (R-ZES; Medtronic Inc, Santa Rosa, CA, USA) and the Abbott Xience everolimus-eluting stent (EES; Abbott Vascular, CA, USA). The rationale, design and methodology of the RAC trial have been detailed elsewhere [1].

In brief, 17 institutions enrolled a total of 2292 patients, undergoing percutaneous coronary intervention (PCI), on an all-comers basis, including patients with chronic stable angina, silent ischemia, and acute coronary syndromes between 30th April 2008 and 28th October 2008. DES effectiveness is measured by enduring relief of symptoms or objective evidence of ischemia related to treated flow-limiting coronary obstructions. The primary endpoint in the Resolute-AC trial was defined as target lesion failure (TLF), a composite of cardiac death, target-vessel myocardial infarction (TV-MI), or clinical indicated target-lesion revascularisation (CI-TLR) with the use of either PCI or coronary bypass graft surgery (CABG) within 12 months. Target lesion failure is a commonly used endpoint in coronary stent trials as it captures all potential adverse outcomes related to the stent itself or to the procedures needed to deliver the stent into the diseased vessel. Moreover, this device oriented composite allows to adjusts for the potential bias introduced when patients who die or sustain MI before the end of the target lesion revascularization (TLR) end point time are considered to be free from TLR. Comprehensive definitions of all the trial end-points used in this analysis have been previously published, a short description is provided in the supplementary appendix [1,6–8].

### *2.2. Process for event adjudication in Resolute-AC. role of 'the global oversight committee,' external validation*

The workflow and working procedures, including all administrative as well as methodological aspects of the CEC work were pre-specified in detail.

#### *2.2.1. suspected event ('triggers')*

Suspected events in the Resolute-AC trial could either be reported by the investigators at the clinical sites, identified through programmed queries from the clinical data base (e.g., laboratory values, ECG or coronary angiogram review) or detected by the CEC during their review process. Independent study monitors (Premier Research Group, Montagny-près-Yverdon, Switzerland) verified all suspected events from data on-site. Complete (100%) source data verification was performed for all items collected in the clinical report forms. Data were stored in a central database (MedNet Solutions Inc, Minnetonka, MN, USA), which was maintained by Cardialysis (Rotterdam, The Netherlands). Clinical follow-up visits for Resolute-AC were done at 1 month ($\pm$5 days), 12 months ($\pm$30 days), with a telephone follow-up at 6 months ($\pm$14 days). Detailed clinical narrative summaries, created using automated information tracking from the eCRF, were provided to the CEC.

#### *2.2.2. The CEC review process*

The primary Resolute-AC CEC was a multidisciplinary expert group dedicated to review of adverse events and event adjudication hosted by an independent academic contract research organisation, Cardialysis (Rotterdam, The Netherlands); Harvard Clinical Research Institute (HCRI, Boston, MA, USA) served as the external counterpart CEC. The CEC adjudicated all events using the independent, web-based (FDA 21 CFR part 11 compliant), review method and/or the consensus meeting method. The CEC panels were asked to deliberate until every effort was made to reach a unanimous decision, whenever possible. In case of disagreement the decision was by majority vote (>50% of voting members present) of the members present. A summary of the rationale for the decision was recorded. Specific complex scenarios that warranted extended discussion and decisions that were not unanimous were recorded in the CEC meeting minutes. These minutes were provided to the GOC.

#### *2.2.3. The external CEC validation process*

An (external) check for variability in event adjudication was pre-specified on a random sample of events. A minimum of 10% of the events per study, with a maximum of 100 events for the study in total was re-adjudicated by the external CEC. The external CEC adjudicated the events without knowledge of the adjudication outcome by the primary CEC.

In an effort to ensure consistency in clinical data review and to harmonize the event adjudication process within the RESOLUTE coronary stent clinical trial program, a CEC-Global

Oversight Committee (GOC) was introduced (Fig. 1). The GOC consisted of the CEC Chairperson of each CRO, one clinical reviewer from each CRO (observer), one active CEC members from each CRO (ad hoc members) and a representative of the study sponsor. Only the Chairpersons and active CEC members had voting rights.

This GOC provided a forum for discussion of complex clinical cases and scenarios and served as an instrument for CEC adjudication quality control. The GOC reviewed the decisions of both CECs and determined the cause for discordance, if present. Based on its deliberations, the GOC issued explicit recommendations for adjudication of specific scenarios. Any event that was adjudicated differently by the external CEC was returned to the primary CEC for reconsideration. On their advice, we also interrogated the database to identify any "event triggers" (e.g. cases where the primary CEC had adjudicated a periprocedural MI where the troponin level was exactly 3 ULN), where the adjudication might potentially have been modified by the GOC recommendations. All such "triggers", identified from the database, were returned for re-consideration to the primary CEC. Criteria were determined to classify discordances in adjudication of primary endpoint events ('major discordances'). Where any major discordance was identified, all other potential events meeting these criteria were identified by programmed queries from the Resolute-AC trial database and returned to the primary CEC for reconsideration. The GOC process described in this manuscript took place and was finalized before the 12 months Resolute-AC trial database lock, data analysis and reporting.

*2.3. Events included in this analysis*

For the purpose of this pre-specified analysis, we randomly identified a subset of 100 potential trial events including 5 deaths, 40 MI's, 21 repeat revascularisation and 34 cases of stent thrombosis. This breakdown was set based on the specific type of event (related to the primary endpoint of TLF) and the prevalence of the event. After the external validation process and review by the GOC, we performed a dedicated central study base screening process to detect any events whose adjudication might be affected by the GOC recommendations

*2.4. Statistical analysis*

Variables were summarized as percentages for dichotomous variables or medians (25th-75th percentiles) for continuous variables. The Resolute-AC trial was powered for non-inferiority testing of the primary endpoint at 12 months on an intention-to-treat basis. (1) Based on the published statistical analysis plan we challenged the primary conclusion of the main paper implementing a worst case scenario for the R-ZES: any discrepancies in adjudication of individual components of TLF were set in favour of the EES and non-inferiority testing repeated. Analyses were performed with SAS version 8.02 by a dedicated statistician.

## 3. Results

A total of 2245 of 2292 patients (97.9%) completed 12-months follow up in RAC. We identified 1336 suspected events for the primary endpoint of TLF (49 deaths, 1019 non-fatal MI, 268 percutaneous coronary revascularisations), and 206 for stent thrombosis Table 1 shows the data source break down for the event triggers in the Resolute-AC trial and their relative contribution to the reported outcome.

Table 2 details the results of the cross-adjudication process on a pre-specified random sample of 100 event triggers. For the individual components of the primary endpoint of TLF (non-hierarchical), there was a final discordance between CECs for 7 out of 100 suspected events in 5 patients: 2 deaths, 3 MIs and 2 TLRs. In the context of the GOC-process, the primary CEC unilaterally reviewed all discrepancies on adjudications implicating TLF, yet maintained their initial judgement.

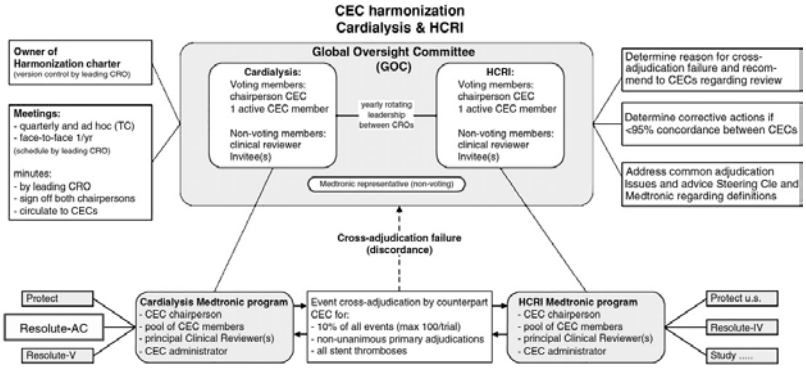


**Fig. 1.** The global oversight committee (GOC). This GOC provides a forum for discussion of complex clinical cases and scenario's and an instrument for CEC adjudication quality control. The GOC maintains a CEC master document according to the result of its deliberations. Their members will review trial specific elements related to event adjudication and data management. Appropriate channels of communication, lines of responsibility and authority are important prerequisites in its contribution to the smooth and effective clinical trial conduct. The Committee consists of the CEC chairperson of each aCRO (co-directors), one clinical reviewer from each aCRO (observer), one active CEC members from each aCRO (ad hoc members) and a representative of the study sponsor.

**Table 1**
Breakdown of the suspected primary endpoint events and primary endpoint events during the consecutive steps in data review and reporting in the resolute all-comers trial within 12 months (results on event level).

| | Initial adjudication | After GOC database review | Confirmed pre-validation process | Confirmed post-validation process |
|---|---|---|---|---|
| Target lesion failure[a] | 1318 | 1336 | 275 | 272 |
| Cardiac death | 49 | 49 | 34 | 34 |
| Target vessel MI | 1019 | 1019 | 99 | 95 |
| Clinical TLR | 250 | 268 | 92 | 95 |
| Stent thrombosis | 205 | 206 | 48 | 48 |

[a] Non hierarchical.

### 3.1. Death

Of 5 deaths, the primary CEC adjudicated 5 as cardiac death, implementing a conservative ('worst case') view unless a clear non-cardiac cause, with independent confirmation by source documentation, was evident. The option "unexplained" was generally used to indicate that additional source documentation would potentially alter the initial decision but that, in its absence, cardiac death would be the default. In accordance with the ARC recommendations unexplained death defaulted to cardiac death. Whilst the external CEC adjudicated 2 cases of cardiac death by the primary CEC as non-cardiac death, the GOC endorsed the position taken by the primary CEC, based on the worst case scenario.

**Table 2**
Results for cross adjudication (expressed as counts and percentages).

| Suspected event | Primary CEC | Cross CEC | |
|---|---|---|---|
| | | Concordant | Discordant |
| Death | 5/5 (100.0) | 5/5 (100.0) | 0 (0.0) |
| Cardiac death | 5/5 (100.0) | 3/5 (60.0) | 2/5 (40.0) |
| Non-cardiac death | 0/5 (0.0) | 2/5 (40.0) | 3/5 (60.0) |
| Myocardial Infarction[a] | 12/40 (30.0) | 9/40 (22.5) | 3/40 (7.5) |
| Target vessel MI | 7/40 (17.5) | 6/40 (15.0) | 1/40 (2.5) |
| Non target vessel MI | 3/40 (7.5) | 1/40 (2.5) | 2/40 (5.0) |
| Unknown[b] | 2/40 (5.0) | 0.40 (0.0) | 2/40 (5.0) |
| Q-wave-MI | 1/40 (2.5) | 0/40 (0.0) | 1/40 (2.5) |
| Non-Q wave MI | 7/40 (17.5) | 7/40 (17.5) | 0/40 (0.0) |
| Undetermined[c] | 4/40 (10.0) | 0/40 (0.0) | 4/40 (10.0) |
| Revascularisation | 21/21 (100.0) | 21/21 (100.0) | 0/21 (0.0) |
| Clinical signs and/or symptoms of myocardial ischemia | 18/21 (85.7) | 17/21 (81.0) | 1/21 (2.0) |
| CI-TLR | 6/21 (28.6) | 6/21 (28.6)) | 0/21 (0.0) |
| CI-TVR | 12/21 (57.1) | 11/21 (52.3) | 1/21 (4.8) |

CEC denotes clinical events committee, CI-TLR denotes clinical indicated target lesion revascularization, CI-TVR denotes clinical indicated target vessel revascularization.
[a] Extended historical (World Health Organization)-MI-definition.
[b] Target vessel cannot be attributed.
[c] The presence of a Q-wave could not be determined.

### 3.2. Myocardial Infarction

Of 40 suspect MI events, the primary CEC confirmed 12 MI events. One was a Q wave and 7 were non-Q wave MIs according to the extended historical definition. In 4 patients the MI could not be unequivocally classified as Q or non-Q with the source documentation provided. Cross-adjudication resulted in 4 discrepancies. The external CEC did not confirm 3 MI events (1 was not clearly attributable to a non-target vessel and thereby potentially contributed to the primary endpoint of TLF). One (1/3) discordance between CECs was based on interpretation of the ECG-readings; 2 were based on interpretation of the biomarker data (both patients had primary PCI at index).

#### 3.2.1. MI (extended historical) not clearly attributable to a non-target vessel

Discrepancies in this category were 2. Both were related to differences in the attribution of the MI to the target vessel ('in the territory of the implanted stent'). However, as 'Target vessel location unknown' defaults to target vessel, one discrepancy was resolved.

#### 3.2.2. Qversus non-Q-MI

In 7 cases both CECs agreed on a non-q-wave MI. Q-wave versus non-Q-wave discrepancies were all driven by missing or poor quality follow-up ECG recordings and new (or pre-existing) bundle branch block. In the absence of ECG data (i.e., missing baseline or follow up ECG), or when Q-wave could not be determined (e.g. left bundle branch block, poor ECG quality) the primary CEC took a conservative approach resulting in all such MIs being classified as Q. After review by the GOC, the option "cannot be determined" and "no ECG available" defaults to "non-Q-wave MI," unless the CEC felt (on review of all other available data) that it should be classified, on clinical grounds, as a Q-wave MI. After readjudication by the Primary CEC, two discrepancies were resolved.

### 3.3. Clinical indicated TLR-TVR

For clinically indicated-TLR, no discrepancies were identified. There was one discrepancy in clinical indicated TVR, based on difference in appreciation of the clinical justification for re-intervention between CECs.

### 3.4. Stent thrombosis

There was no discordance for stent thrombosis events: the primary CEC changed their initial decision on 3 events in the interim based on additional source documents, not available at the time of the initial adjudication but provided to the external CEC for the cross-adjudication. These readjudications, by the primary CEC, were automatically triggered by the availability of the new source documents independent of the current study.

### 3.5. Implementation of oversight committee recommendations: effect on event rates

As shown in Table 3, after the initial adjudication by the primary CEC, the primary endpoint of TLF (hierarchical) at 12-months was positively adjudicated in 184 patients. Stent

**Table 3**
Resolute all-comers trial outcomes at 12 months (entire patient cohort).

| Outcome | Final adjudication | Changes during GOC review [a] | | Index CEC adjudication |
|---|---|---|---|---|
| | | Added | Removed | |
| Target lesion failure[b] | 186 | 2 | 0 | 184 |
| Death | | | | |
| All cause | 49 | – | – | 49 |
| Cardiac | 34 | – | – | 34 |
| Noncardiac | 15 | – | – | 15 |
| Myocardial infarction[c] | | | | |
| All | 100 | 0 | 2 | 102 |
| Target-vessel | 93 | 0 | 3 | 96 |
| Non-target-vessel | 8 | 1 | 0 | 7 |
| Q-wave | 16 | 1 | 12 | 27 |
| Non-Q-wave | 85 | 12 | 3 | 76 |
| TLR[d] | 82 | 3 | 0 | 79 |
| TVR[d] | 109 | 6 | 0 | 103 |
| Stent thrombosis | | | | |
| ARC definite or probable | 26 | – | – | 26 |
| ARC definite | 16 | – | - | 16 |
| ARC probable | 11 | – | – | 11 |
| ARC possible | 18 | – | – | 18 |

ARC denotes Academic Research Consortium.
[a] Changes on per patient base.
[b] Target Lesion Failure is defined as a composite of death from cardiac causes, any myocardial infarction (not clearly attributable to a nontarget vessel), or clinically indicated target-lesion revascularization. Results for TLF are hierarchical.
[c] Extended historical (World Health Organization)-MI-definition.
[d] TLR denotes clinical indicated target lesion revascularization, TVR denotes clinical indicated target vessel revascularization, these events represents ischemia-driven events.

thrombosis, either definite or probable, was adjudicated in 26 patients. Following the GOC validation process, but before data base closure, TLF (hierarchical) was positively adjudicated in two more patients based on removal of 1 MI event (one out of 4 additional MI events in 3 patients was censored, 2 MI events occurred in patients that also died from a cardiac cause and were counted as cardiac death), and 3 added clinical TLRs (Table 1, 12 month outcome on a per event level). The total count for stent thrombosis cases did not change. Of notice, during the GOC-process specific queries on this item were performed on all 1019 (100%) of the MI-triggers. There were no unreported new ischemic events, and therefore no probable stent thrombosis cases (6), from the time the guiding catheter was removed and the patient left the catheterisation suite up to 48 h. By protocol, the CEC could adjudicate a Q-wave MI in the context of an appropriate clinical scenario and cardiac enzyme data (supplementary appendix). The RAC database was interrogated to identify all MIs, previously adjudicated as 'Q-wave cannot be determined' or 'no ECG available' to determine whether the default to non-Q-MI was appropriate considering the clinical scenario and/or cardiac biomarker elevations. As a result, two more MIs were adjudicated as Q-wave based on the cardiac enzyme data. One non-target vessel MI was no longer considered an event upon review (Data not shown).

Table 4 shows the primary endpoint analysis in Resolute-AC biased against the study stent (R-ZES) stent by adding 3 clinically indicated TLR to R-ZES and removing 4 target vessel MI from EES. In this worst case scenario, the one-sided 95% confidence interval for the difference between the two stents remained on the positive side of the pre-specified non-inferiority margin of 0.035 (3.5%).

## 4. Discussion

The principal findings and potential consequences of the Resolute Clinical Program GOC external CEC validation process described in this manuscript are the following:

- The cross-adjudication of a predefined subset of 100 potential primary endpoint events and/or stent thrombosis resulted in 6 discrepancies between 2 different and independent CECs. They were mainly related to the adjudication of target-vessel MI and revascularisation events and explained by a difference in clinical judgement and/or interpretation of angiographic source data.
- The primary CEC reconsidered all individual discordant events and maintained its initial judgement for all adjudications related to TLF.
- In total seven primary outcome events in 5 patients were reclassified based on the harmonization procedures. The (hierarchical) primary endpoint of TLF increased by two events.

This is the first report on an external CEC-process validation in a coronary stent program. It reflects the ongoing effort of 3 AROs, experienced in the field, to improve the quality of the CEC adjudication process. The aim is to identify and address factors related to human error or misjudgement, and to identify complex clinical scenarios where a harmonized approach will facilitate consistency across AROs. This should allow meaningful comparisons between trials and pooling of trial results. It is important to recognize that this validation was performed after robust, pre-specified, internal checks, by the primary ARO. Thus, while the discrepancies in the present study were limited, much greater differences would be expected in studies

**Table 4**
Modelling the primary endpoint analysis biased against the zotarolimus eluting study stent. A comparison with the parent resolute-AC trial results.

| | Primary endpoint | Resolute (ZES) N = 1140 patients | Xience-V (EES) N = 1152 patients | Difference (%) | One sided 95% upper confidence bound (%) | Delta (%) | P-Value |
|---|---|---|---|---|---|---|---|
| RAC-III | TLF 360 days | 8.2% (92/1119) | 8.3% (94/1126) | −0.1 | 1.8 | 3.5 | <0.001 |
| Worst case scenario considering the GOC-process | TLF 360 days | 8.5% (95/1119) | 8.0 (90/1126) | 0.5 | 2.4 | 3.5 | 0.005 |

TLF denotes target-lesion failure a composite of death from cardiac causes, any myocardial infarction (not clearly attributable to a non-target vessel), or clinically indicated target-lesion revascularization within 12 months.

where less stringent monitoring of source documents occurred and where less robust procedures were in place to ensure internal consistency in event adjudication. This external CEC-process validation involved reassessment of a substantial proportion of all suspected events in RAC. Based on the initial identification of potential discrepancies in a limited subset of one hundred events, up to 70% of all suspected primary endpoint events were reassessed. In the end, 7 out of 224 (3.0%) primary outcome events were reclassified, with only two additional patients identified as having a TLF. The current CEC-process validation contributed to a more correct outcome reporting without challenging the main Resolute-AC trial results or conclusions.

The RAC was open label for the stent component with a risk for systematic 'differential' misclassification of events (i.e. peri-procedural MI) by the investigators. With this in mind and provided the non-inferiority design of RAC, protection against non-differential misclassification of events, by the use of an independent CEC –blinded to treatment assignment-, may be most important [9]. Ideally the clinical adjudication process by itself should be highly specific, based on a uniform application of pre-specified criteria for event definitions. In the Resolute-AC, the primary-device oriented- endpoint was aligned with the ARC consensus definitions for stent investigations in stable coronary disease patients with de novo lesions. [6] A specific challenge was the implementation of the ARC definitions in an all-comer study design. The inclusion of patients with ACS and/or more complex lesion morphology (e.g. left main lesions, bifurcations or trifurcations) may jeopardize uniform clinical endpoint adjudication. We emphasize the importance of process guidance and rules with an effort to anticipate complex adjudication scenarios especially in contemporary large, near real world studies with relatively long-term clinical endpoints. We call for an on-going effort to codify, and document the rationale for, adjudication decisions for complex scenarios in order to maintain consistency throughout a trial.

The available ARC-definitions had evident limitations when addressing re-infarction/MI extension due to PCI in patients with an on-going spontaneous MI. As discussed in the recent literature, adjudication of an MI due to PCI in patients with an ongoing spontaneous MI using the 2007 Universal MI definitions may be problematic [10,11]. Unless there is a clear indication that the cardiac biomarker sample values were falling following the index event and rising again, there would otherwise be insufficient biomarker data to adjudicate a PMI based on the biomarker data. For Resolute-AC, the steering committee considered MI events adjudicated according to the modified historical definitions of MI [1–8]. While it was anticipated that MI adjudication might prove problematic as nearly one third of the all-comers patient population presented with an ACS, no major discordance between CECs was noted while implementing these pre-specified MI adjudication rules. However, attributing the MI event to the target vessel implicated clinical judgment and caused divergence in opinion between CECs.

With this external validation, all aspects of clinical endpoint adjudication, from data collection to final CEC judgement, were addressed. Relevant with respect to the interpretation of a specific clinical trial is the percentage of permanently missing minimal required data for event adjudication and the way these were handled. Permanently missing data can potentially impact the power of a trial and introduce bias in the outcome analysis [12].

The impact of an external validation process on the final Resolute-AC outcome reporting may be considered important. Currently much published trial data is not based on adjudication and data analysis by a truly independent CEC. In that context, the potential for error is a source of major concern and its potential impact on the reliability of published data is not something that is widely appreciated by the general medical community.

External validation of the CEC process to judge accuracy and consistency in event adjudication should be considered as a factor in the assessment of the quality of a trial and in the relative weight given to published data.

There are limitations to our analysis. Only a limited subset of suspected events was cross-adjudicated in this process so the potential impact on the trial outcome reporting may have been underestimated. However, as already indicated, up to 70% of all event triggers, including all MI event triggers were re-examined, and re-adjudicated where necessary, based on specific issues identified by the GOC.

## 5. Conclusions

CEC's must be rigorous and consistent in their analysis of data to maximize the clinical and research value of clinical trial data. The quality of the CEC-process should be assessed on an on-going basis throughout the clinical trial and/or trial program via internal and/or external validation. Pooling of data within a coronary stent trial program is possible if uniform endpoint definitions are used and the CEC- adjudication process harmonised.

## 6. Disclosures

The authors have no conflicts of interest to report related to the content of this manuscript.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.cct.2012.08.012.

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# CHAPTER 1.9

## Standardisation of coronary pressure-derived fractional Flow Reserve measurements in clinical research

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*Circ Cardiovasc Interv.* 2012; **5**: 312-7. [**technical report** ]

# Coronary Pressure–Derived Fractional Flow Reserve Measurements

## Recommendations for Standardization, Recording, and Reporting as a Core Laboratory Technique. Proposals for Integration in Clinical Trials

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Evaluation of new coronary devices and demonstration of their conformity to essential principles of safety and effectiveness requires clinical trials in human subjects. Today, many trials designed to address device-oriented safety and effectiveness rely on quantitative coronary angiographic lesion severity, as an objective reproducible end point to determine whether revascularization for progressive luminal renarrowing after device therapy is clinically indicated. Given the known limitations of angiography to reflect clinical ischemia, concern exists regarding the applicability of such angiographic end points. An invasive objective functional (physiological) assessment of moderate stenoses by coronary pressure–derived fractional flow reserve has evident potential as an adjunct to quantitative coronary angiography in clinical trials. To be implemented as a potential core laboratory technique, standardization in technique and archiving of permanent data storage are imperative. The intent of this report is to propose standards for fractional flow reserve data acquisition and interpretation in coronary device research.

Controlled trials with predefined safety and efficacy end points are a critical element in the assessment of new therapies or devices, for approval by regulatory bodies, and subsequent adoption for clinical use by the medical community. It is important that randomized trials adopt meaningful clinical end points that relate to the pathophysiological mechanism(s) most likely responsible for the clinical outcome.[1–3] In coronary device investigations, clinically driven repeat revascularization of the target lesion is a key (device-oriented) outcome measure of clinical effectiveness.[1] Adjudication of this end point has been based on the presence of clinical symptoms and angiographic lesion severity as determined by a central core laboratory using quantitative coronary angiography (QCA), such that even moderate stenosis (>50% diameter stenosis) by QCA may be considered clinically significant. Most clinical trial designs do not require functional assessment prior to repeat revascularization.

The coronary pressure–derived fractional flow reserve (FFR) index provides a valuable tool to assess the justification for coronary revascularization in patients that have a moderate to severe coronary lesion.[1] The coronary pressure–derived FFR index is a well-validated, accurate, and objective index for assessing lesion-specific physiological stenosis severity and a surrogate marker of long-term outcome in various clinical conditions and anatomic subsets.[4–26]

To be implemented as a potential core laboratory technique (eg, in coronary stent investigations), standard procedures for data acquisition and storage are essential prerequisites. Accuracy, elimination of technical or operator-related artifacts, and reproducibility of FFR measurements are critical. The aim of this report is to propose a standard methodology for FFR data acquisition and to highlight potential pitfalls in data interpretation. We will also propose guidelines for how FFR may be incorporated into clinical trial designs. Detailed reviews of coronary physiology and the fundamentals of FFR are available elsewhere.[27–29]

### Specific Requirements for Core Laboratory Analysis

Routine measurement of FFR in the cardiac catheterization laboratory involves standard catheters (diagnostic or guiding), a dedicated pressure wire, drugs used during coronary intervention (vasodilator and anticoagulant), and a pharmacological stimulus to produce maximal hyperemia. For research purposes, standardization is warranted. Technical or operator-related artifacts should be identified and avoided.

### Catheters

Although the use of diagnostic catheters is technically feasible, guiding catheters without distal side holes are a prerequisite for research measurements. Guiding catheters facilitate manipulation of the pressure wire. Furthermore, immediate intervention can be performed where indicated (including the rare event of vessel injury by the wire).

### Pressure Wire

There are 2 commercially available pressure wires. Both systems [the Pressure Wire (RadiMedical Systems Inc, Upp-

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(*Circ Cardiovasc Interv*. 2012;5:312-317.)



*Circ Cardiovasc Interv* is available at http://circinterventions.ahajournals.org

DOI: 10.1161/CIRCINTERVENTIONS.112.968511

sala, Sweden) and the Volcano Wave Wire (Volcano Inc, Rancho Cordova, CA)] measure intracoronary pressure using a dedicated solid-state (electronic) sensor mounted on a 0.014-inch (0.33-mm) floppy-tipped guide wire. The sensor is located at the junction between the 3-cm–long radiopaque tip of the wire and the nonradiopaque section of the wire. The cross-sectional area of a sensor guide wire is negligible relative to all but the most critical stenoses.[12]

## Pharmacologically Induced Maximal Hyperemia

Hyperemia is essential for stenosis assessment. Maximal vasodilatation of the 2 compartments of the coronary circulation (epicardial or "conductance arteries >400 $\mu$m" and the microvasculature or "resistance arteries") is required for accurate and reproducible measurements.

To abolish epicardial vasoconstrictor tone, an intracoronary bolus of 2 mg of isosorbide dinitrate or an equivalent dose of another nitrate such as nitroglycerin (200 $\mu$g) should be administered at least 2 minutes before FFR measurement. To obtain maximum microvascular vasodilation and eliminate coronary autoregulation, a continuous infusion of adenosine through a large-bore cannula, in a large vein, at a rate of 140 $\mu$g/kg per minute, is recommended. It provides steady-state maximum hyperemia within 2 minutes. Continuous adenosine infusion is advocated because it allows for FFR measurement in specific settings (ie, at aorta-coronary ostial lesions) and permits recording of a pressure pullback curve to differentiate focal from diffuse coronary artery disease. The injection of additional intracoronary boluses of adenosine, in an attempt to stimulate maximal hyperemia, is discouraged because it may provoke artifacts in the FFR tracing due to the injection that complicate off-line analysis. Similarly, other vasodilators such as papaverine and sodium nitroprusside, administered as boluses, are not advocated due to the transient steady state achieved.

## Pressure Measurement

For clinical research purposes, a uniform systematic and 5–step-by-step FFR procedure is proposed.

***Step 1: Zero the Pressure System to the Atmosphere***

A standard fluid-filled pressure transducer is used for aortic pressure recordings. Special attention should be paid to purging the system of air, zeroing of the catheter tubing system, and obtaining an optimal aortic pressure waveform. The guiding catheter should be frequently flushed with normal saline (at least every 10 minutes). Because contrast medium may subtly dampen the catheter pressure waveform, all contrast medium should be flushed from the catheter during the zeroing steps before pressure measurement. If any pressure damping or ventricularization of the catheter pressure waveform is observed, the guiding catheter should be gently disengaged from the ostium, taking care not to alter the position of the pressure wire in the distal vessel.

Zero the sensor of the pressure wire ex vivo, following the instructions of the manufacturer.

***Step 2: Insert the Pressure Sensor Guide Wire Into the Guide and Equalize the 2 Pressures In Vivo***

The sensor of the pressure wire should be advanced a few millimeters beyond the tip of the guiding catheter. For aorto-ostial lesions, this should be performed with the disengaged catheter in the ascending aorta. Then, equalize the pressures registered by the guiding catheter and the pressure wire. The introducer needle can remain in the Y connector during equalization and measurement of FFR when intravenous adenosine is used to induce maximal hyperemia.

***Step 3: Advance the Pressure Wire Sensor Distal to the Region of Interest***

The sensor should be advanced to the distal two-thirds part of the coronary artery and at least 2 to 3 cm distal to the index lesion and its final position documented angiographically. Ensure that the wire tip is rotating freely and no resistance is felt when torque is applied.

***Step 4: Induce Maximal Hyperemia***

When the sensor has been optimally positioned distal to the stenotic region, administer adenosine 140 $\mu$g/kg per minute intravenously for at least 2 minutes for calculation of the FFR. FFR is then calculated as the ratio of distal coronary pressure (Pd) to aortic pressure (Pa) at maximal hyperemia, the nadir of (Pd).

If needed, a pullback curve should be performed to determine the exact location of the lesion most likely responsible for ischemia. The pressure pullback curve may demonstrate either a single (or several) abrupt change(s) in FFR across focal narrowing(s) or a gradual change in the presence of diffuse disease without focal obstructions. Before pullback curves are performed, an angiogram should be obtained and the position of the image intensifier should not change subsequently. When appropriate, insert "bookmarks" to indicate areas where abrupt changes occur and use the "store fluoroscopy" function to document these sites to facilitate off-line, Core Laboratory, analysis.

***Step 5: Wire Pullback to Check for Signal Drift***

Verification of equal pressure signals from the pressure wire and the guiding catheter must be documented at the end of the procedure to check for potential drift.[13] Where the difference is minimal (<5 mm Hg), this difference should be taken into account in the calculation of the final FFR. Where the difference is >5 mm Hg, the last measurement must be repeated.

All measurements should be stored on an external medium (eg, hard disc) for core laboratory review.

## Pitfalls and Artifacts of FFR Measurement

***Instrumentation Issues***

Care must be taken to avoid potential impairment to coronary flow during maximum hyperemia. This is most commonly induced by the presence of the guiding catheter in the coronary artery and can be detected by observing a change in the morphology of the aortic pressure curve (ie, damping or ventricularization) (Figure). When this occurs, it is important to disengage the guiding catheter from the ostium during the measurement while continuing the adenosine infusion. On occasion, particularly in tortuous vessels, the presence of the wire may create multiple "pseudostenoses" and render FFR measurements uninterpretable.[28,30,31]

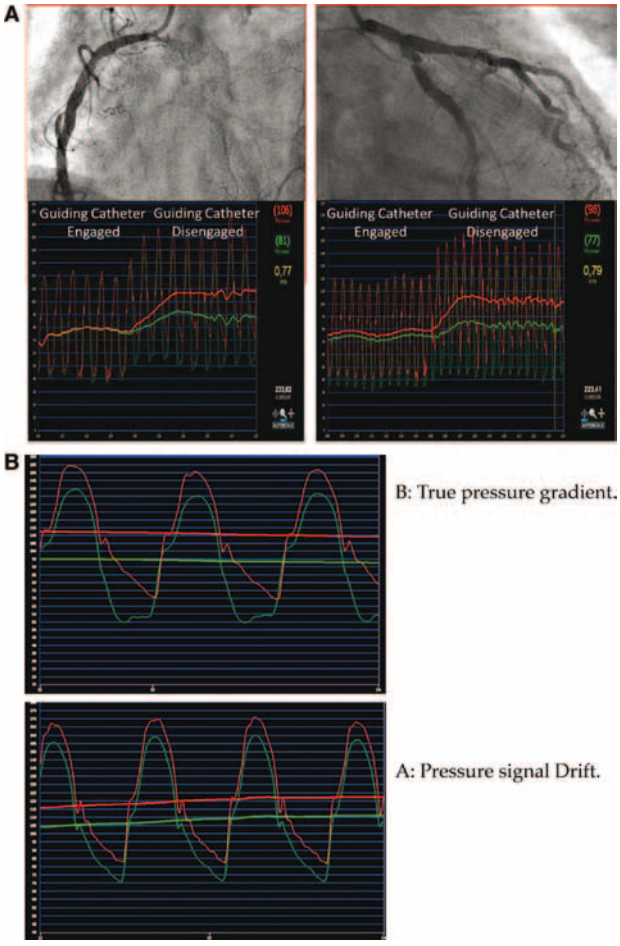


**Figure.** Pitfalls and artifacts of fractional flow reserve (FFR) measurement. All panels shows simultaneous aortic pressure (Pa) and distal coronary pressure (Pd) recordings during steady-state maximal hyperemia as induced by an intravenous infusion of adenosine. **A**, Example of the impact of catheter ventricularization/damping on the accuracy of FFR measurement. Disengaging the guiding catheter from the coronary artery ostium may prove critical in cases where the lesion under evaluation is "borderline." **B**, Example of pressure signal drift (as compared with a true pressure gradient). Pressure signal drift should be suspected in the case of parallel pressure signals (similar morphology for Pa and Pd signal) throughout diastole and systole. The aortic dicrotic notch is preserved (Pd pressure signal) despite a large pressure difference. **C**, Example of a pressure pullback tracing in a diffusely diseased left anterior descending coronary artery under steady-state maximal adenosine intravenously induced hyperemia. The distal pressure increases progressively in 4 or 5 "steps." This indicates that the abnormal FFR value is due to diffuse disease rather than to 1 focal lesion. **D**, Example FFR in a tortuous right coronary artery with the development of pseudostenosis (uninterpretable FFR').

***Pressure Signal Drift Versus True Pressure Gradient***

With currently available electronic sensor-tipped pressure guide wires, temporal drift is minimal. Drift (a resetting of the baseline pressure signal) can be detected by assessing the pressure curve (dicrotic notch, pressure curve morphology) and by comparing the pressure recorded by the wire to the pressure recorded at the guiding catheter at the end of the procedure (should be $<5$ mm Hg/h) (Figure). In the case of drift, the sensor should be pulled back to the tip of the guiding catheter to equalize pressures again. The measures should then be repeated.[30,31]

***Influence of the Guide Wire Across the Lesion on Stenosis Hemodynamics***

For lesions of intermediate angiographic severity, the cross-sectional area of the 0.014-inch guide wire is $<10\%$ of the minimal lumen area, and FFR should provide a true gradient that reliably reflects epicardial resistance.[3]

## Data Collection and Interpretation

In clinical research, the clinical event adjudication process should be highly specific, accurate, and consistent and mainly driven by the application of prespecified criteria for event definitions applied within a specific scenario.

FFR is reproducible and reaches per-segment accuracy with a spatial resolution of a few millimeters. FFR is specific and provides well-defined cutoff values that distinguish normal from abnormal levels for a given measurement with a narrow "gray zone" between 0.75 and 0.80 (up to 10% of all measurements), the use of which requires clinical judgment. Because the latter may introduce a factor of variability in

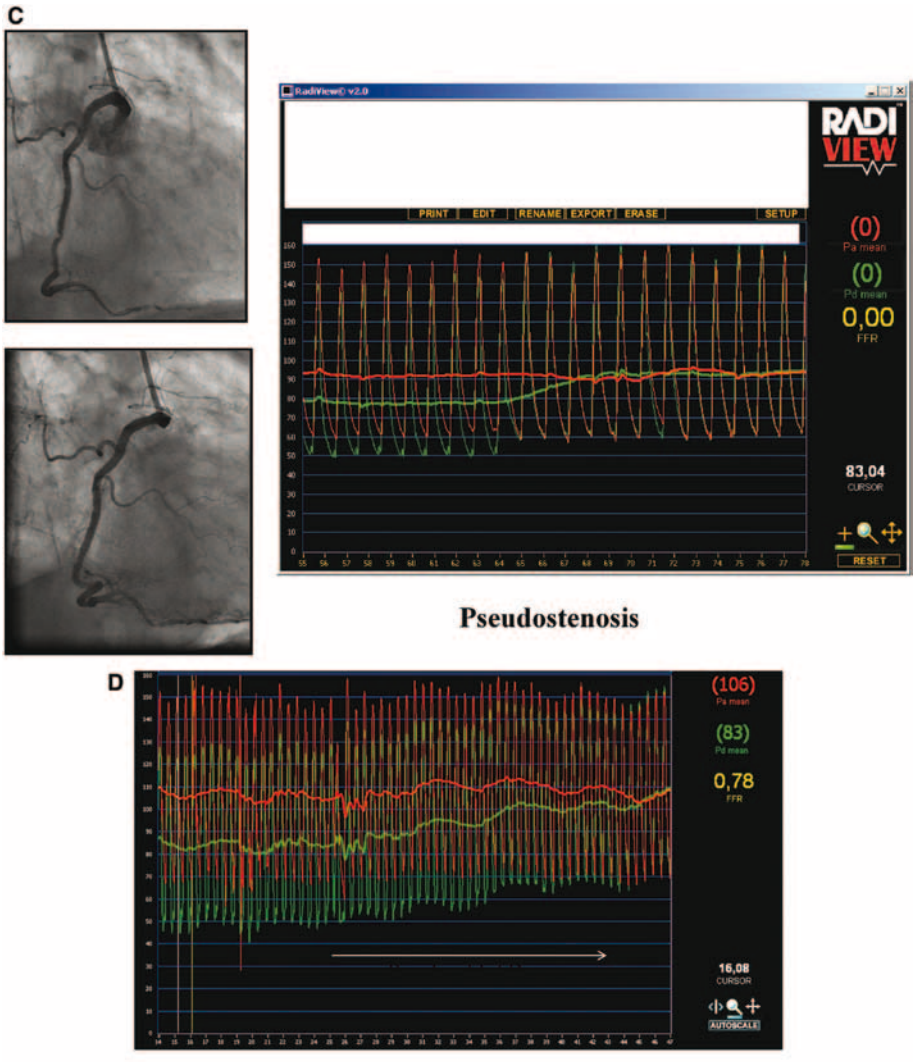


**Figure (Continued).**

judgment, for research purposes the single cutoff value of 0.80 is proposed. It should be recognized that the nonischemic threshold of FFR (<0.75) was derived from a selected, stable patient population with single-vessel coronary disease and normal left ventricular function.

We advocate the use of FFR as a marker of hemodynamically significant luminal renarrowing associated with moderate-to-severe stenosis within the stented segment or other discrete lesions elsewhere in the target vessel (Table). Its use to justify target lesion revascularization is discouraged

**Table. Fractional Flow Reserve in Coronary Device Trials**

| |
|---|
| FFR may be used to guide patient inclusion in coronary device trials, to select patients with moderate-to-severe coronary lesions who will benefit from coronary revascularization. |
| FFR may be considered as marker of coronary device performance failure and clinical justification for repeat revascularization in coronary device trials. |
| In patients with isolated coronary stenosis of moderate severity (>50% diameter stenosis determined by an independent quantitative coronary angiographic core laboratory or visual assessment), including isolated left main coronary artery renarrowing, and assessment of jailed side branch lesions. |
| FFR should not be considered as a marker of coronary device failure in: |
| Patients with diffuse coronary atherosclerosis with a <50% diameter luminal renarrowing at angiography and a graded, continuous fall along the arterial length. |
| Patients with serial stenoses within 1 coronary artery. |

FFR indicates fractional flow reserve.

in patients with diffuse coronary atherosclerosis and serial focal lesions or extensive coronary atherosclerosis on angiography and a graded, continuous pressure fall along the arterial length. The data are limited for patients with acute or recent myocardial infarction, and the proposed criteria should not currently be extended to this specific patient subgroup.[10,21]

### Incorporating FFR Into Clinical Trial Designs

We propose that FFR assessment be incorporated into clinical trial designs as a criterion for determination of clinical significance of moderate-to-severe angiographic lesions. Our focus is on the use of FFR for justification of repeat revascularization procedures as a part of clinical end point adjudication, but its value at the time of study entry should also be considered. There are several requirements for standardization and quality assurance of data measurement and interpretation.

### Establish a Central Core Laboratory

A central laboratory should be selected that is charged with training and review of sample data from prospective clinical centers. The core laboratory should review recorded data from study procedures to validate accuracy and make a central determination of FFR, based on the recorded data.

### Quality Assurance of FFR Measures

Each clinical center should be trained in the 5-step procedure as outlined herein. Study data capture methods should document the steps in the procedure. Sample cases should be reviewed by the core laboratory before study subject entry. Any concerns with data ascertainment or interpretation detected by the core laboratory should be provided by immediate feedback to the clinical center.

### Trial Design Issues

The most important trial design concern with incorporating FFR data into the end point adjudication process will be the assurance of uniform ascertainment. The protocol must specify clearly which suspected lesions should undergo FFR assessment. We propose that all moderate-to-severe lesions, determined to be 50% to 80% by visual estimate, should undergo FFR measurement unless there are both typical ischemic symptoms and another functional study showing evidence of ischemia in the target vessel territory. The study protocol and clinical events committee manual of operations must also clearly outline, in advance, how FFR data will be incorporated into the adjudication process in specific scenarios. Examples are cases in which the percent diameter stenosis is assessed as moderate (50% to 70%) by QCA and FFR is not performed before repeat revascularization or cases in which there is discordance between the FFR result and the results of prior noninvasive testing. We recommend that where protocol-mandated FFR is not performed, a worst-case scenario should be adopted, and that where FFR results differ from the results of noninvasive testing, FFR should take precedence in the decision-making hierarchy.

### Conclusion

Invasive coronary physiological studies have demonstrated favorable outcomes for decision-making in patients with intermediate single-vessel stenosis and have evident potential as an adjunct to QCA in the setting of clinical trials. Based on the value of FFR in terms of objective and clinically relevant information, we support its incorporation into clinical studies to establish standardized reporting of specific device-related angiographic and clinical events.

## Disclosures

Dr Kern has served as a speaker for Volcano Therapeutics and St Jude Medical, manufacturers of pressure guide wires.

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KEY WORDS: fractional flow reserve ■ stenosis ■ stent

# APPENDIX 1.1

## Clinical end points in coronary stent trials: a case for standardized definitions

Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW , and Academic Research Consortium.

*Circulation* 2007; **115**: 2344-51. [**technical report, only provided as a reference**]

# Clinical End Points in Coronary Stent Trials

## A Case for Standardized Definitions

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***Background***—Although most clinical trials of coronary stents have measured nominally identical safety and effectiveness end points, differences in definitions and timing of assessment have created confusion in interpretation.

***Methods and Results***—The Academic Research Consortium is an informal collaboration between academic research organizations in the United States and Europe. Two meetings, in Washington, DC, in January 2006 and in Dublin, Ireland, in June 2006, sponsored by the Academic Research Consortium and including representatives of the US Food and Drug Administration and all device manufacturers who were working with the Food and Drug Administration on drug-eluting stent clinical trial programs, were focused on consensus end point definitions for drug-eluting stent evaluations. The effort was pursued with the objective to establish consistency among end point definitions and provide consensus recommendations. On the basis of considerations from historical legacy to key pathophysiological mechanisms and relevance to clinical interpretability, criteria for assessment of death, myocardial infarction, repeat revascularization, and stent thrombosis were developed. The broadly based consensus end point definitions in this document may be usefully applied or recognized for regulatory and clinical trial purposes.

***Conclusion***—Although consensus criteria will inevitably include certain arbitrary features, consensus criteria for clinical end points provide consistency across studies that can facilitate the evaluation of safety and effectiveness of these devices. **(*Circulation*. 2007;115:2344-2351.)**

**Key Words:** restenosis ■ stents ■ thrombosis ■ clinical trials

Clinical trials designed to evaluate the safety and effectiveness of drug-eluting coronary stents (DES) play pivotal roles in both new device approval and in their adoption for clinical use. Although surrogate markers may have some role in the definition of device performance, direct measures of clinical outcomes are preferable in the understanding of the response of human subjects' exposure to these combination drug–device products.[1]

The selected end points must serve several purposes. They must have both short- and long-term pathophysiological relevance to device performance, they must represent clinically meaningful events, and they must be sufficiently defined, preferably through blinded processes, to be subjected to statistical analysis. Because of the intrinsic limitations in the ability to obtain histology, serial examinations, or other mechanistic detail from human subjects, clinical end points for DES studies are bound to include certain arbitrary assumptions and will frequently vary across clinical trials as the result of different approaches to such assumptions. Variability in end point definitions, however, creates a formidable barrier to the understanding of results across clinical trials or the pooling of results for the detection of rare safety signals.

With the recognition that consistency across well-considered end point definitions is critical to this process, 4 academic research organizations involved in the design and management of current DES clinical trials combined efforts in an informal collaboration termed the Academic Research Consortium (ARC) to orchestrate a set of consensus definitions for DES study end points. Two meetings that also

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No official support or endorsement of this article by the US Food and Drug Administration is intended or should be inferred.

**The online-only Data Supplement, consisting of a list of participants, is available online at http://circ.ahajournals/org/cgi.content/full/115/17/2344/DC1.**

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***Circulation* is available at http://www.circulationaha.org** **DOI: 10.1161/CIRCULATIONAHA.106.685313**

included representatives of the US Food and Drug Administration (FDA) and device manufacturers that worked at the time with the FDA on DES clinical trial programs were held in Washington, DC, in January 2006 and in Dublin, Ireland, in June 2006 (see the online-only Data Supplement). The charge for the consortium was to select appropriate individual clinical end points, define the criteria to determine the occurrence of the end point, and consider the potential to group individual end points into meaningful composites of both device-oriented and patient-oriented outcomes. Importantly, the mission of this first ARC effort was to achieve well-considered consensus definitions without detailing per se all aspects of how these definitions should be applied for trial designs or other related analyses.

## General Criteria for DES Clinical End Point Definitions

Three general criteria were considered for each end point definition. First, the end point definitions should support the characterization of device effectiveness or safety. In the following discussion, it is the ARC consensus that safety end points represent any adverse outcome whether specifically related to the use of the device or not, and effectiveness end points refer specifically to maintenance of coronary artery luminal patency. Second, the end point definitions should relate to the pathophysiological mechanism(s) most likely responsible for the clinical outcome. Finally, the proposed criteria should balance the need for consistency with the legacy of published literature against the need for adaptation of definitions based on newly emerging knowledge.

## Clinical End Point Measures of Device Safety: General Considerations

DES-related safety issues are governed to some degree by time. Adverse outcomes within 30 days of implantation are generally considered temporally related to the procedure. In the setting of a progressive entity such as coronary disease, the later that adverse events occur, the more likely they are to represent an interaction between the device and the disease or to represent new disease activity altogether.

Event definitions may also vary in relation to the treated population. For example, periprocedural myocardial infarction (MI) or sudden death within 30 days in elective patients may clearly be device- or procedure-related, whereas in patients with acute or evolving MI such relationship may not be clear.

## Clinical End Point Measures of Device Effectiveness: General Considerations

DES are implanted for the treatment of obstructive coronary artery disease. Their effectiveness is measured by the relief of such flow-limiting obstructions, initially through structural mechanisms and later with preservation of the luminal dimension through inhibition of neointimal hyperplasia or restenosis.

Effectiveness clinical end points are designed to assess clinically significant restenosis, assessed objectively as a requirement for ischemia-driven repeat revascularization, either of the stented segment itself (target lesion revascularization [TLR])[2] or of the stented vessel or its side branches (target vessel revascularization).[2] Target vessel failure, proposed as any target vessel revascularization, death, or MI attributed to the target vessel, is an even broader metric of failed effectiveness and adjusts for the potential bias introduced when patients who die or sustain MI before the end of the TLR end point time are considered to be free from TLR. Ostensibly, one might also consider persistence or recurrence of angina during follow-up as evidence of failed effectiveness (because not all episodes of clinical restenosis will lead to repeat revascularization), but we believe that this end point does not lend itself as readily to objective assessment as the other proposed end points and is better measured as a stand-alone end point with the use of formal, validated health status instruments.[3]

## Patient-Oriented (Global) Cardiovascular End Points: General Considerations

The optimal basis for DES evaluation should be overall cardiovascular outcomes from the patient's perspective, including all death, MI, and repeat revascularization procedures.[4] These outcomes reflect the complex interplay between device performance, revascularization strategy, secondary prevention, and key patient descriptors. Both the time course and the composite selected should characterize patient well-being related to the pathophysiology of the implanted DES device and its impact on underlying coronary artery disease outcome. For example, whether a device improves functional capacity and quality of life, but does not affect MI rates or mortality—as is the case for percutaneous intervention in elective cases—should be clear so that regulatory authorities, clinicians, and reimbursement agencies can carefully weigh the net benefit against possible safety concerns.

### Proposed Safety and Efficacy End Points

#### *Death*

Death that occurs after a coronary stent procedure may by clearly related to a device- or procedure-related complication, in which case the role of the device is clear. Death may also occur unexpectedly during the follow-up period, either as a result of an evident cardiac event, unexplained sudden death, or noncardiac cause. ARC considers all-cause mortality the most unbiased method to report deaths in a clinical trial or observational study, even though it may be less specific than deaths adjudicated as cardiac in origin (Table 1).

For times when attribution to cardiac versus noncardiac causes is desired, such as during long-term follow-up studies, ARC proposes a conservative approach (Table 1). Specifically, all deaths are considered cardiac unless an unequivocal noncardiac cause can be established. Cardiac deaths should include all events related to a cardiac diagnosis, a complication of the procedure, treatment for a complication of the procedure, or an unexplained cause. Unexpected death even in patients with coexisting and potentially fatal noncardiac disease (eg, cancer, infection) should be classified as cardiac unless history related to the noncardiac diagnosis suggests death was imminent. Mortality should then be reported as all-cause as well as cardiac mortality versus noncardiac. It

**TABLE 1. Classifications of Death**

| | |
|---|---|
| Cardiac death | Any death due to proximate cardiac cause (eg, MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment, will be classified as cardiac death. |
| Vascular death | Death caused by noncoronary vascular causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular diseases. |
| Noncardiovascular death | Any death not covered by the above definitions, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma. |

All deaths are considered cardiac unless an unequivocal noncardiac cause can be established. Specifically, any unexpected death even in patients with coexisting potentially fatal noncardiac disease (eg, cancer, infection) should be classified as cardiac.

may also be desirable to subcategorize noncardiac death by vascular versus nonvascular causes.

***Myocardial Infarction***

MI during a clinical trial of a percutaneous coronary intervention (PCI) device may occur during the immediate periprocedural period as a result of the index study procedure or long after the procedure, as a result of spontaneous MI or late complications of the study device or subsequent revascularization procedures. Even the most recent DES clinical trials have relied on older modified World Health Organization criteria to establish the diagnosis of MI, with threshold values of total creatine kinase ≥2 times the upper limit of normal rather than more sensitive and specific biomarkers.[5,6] Furthermore, these definitions have not included more variable thresholds to distinguish periprocedural from spontaneous MI. Representatives of the European Society of Cardiology and the American College of Cardiology have provided recommendations to redefine diagnostic criteria for MI[7,8] and together with the American Heart Association and World Heart Federation have recently updated these guidelines to call for a universal definition for clinical as well as investigational trial use.[9] In its most recent document, this global task force strongly encourages clinical trialists to adopt the proposed definitions for consistent application across investigational studies (Tables 2 and 3).

**TABLE 3. Presentation of MI Outcomes in Clinical Trial Reports**

| |
|---|
| Primary end point |
| Total of MIs defined by any of the classifications in Table 2. Troponin recommended as the preferred biomarker at all time points |
| Secondary analyses |
| All data for troponin and CKMB should be tabulated for each classification to include at least the following multiples of the URL by treatment groups: <1, 1 to 2, 2 to 3, 3 to 5, 5 to 10, and >10 |
| Cumulative frequency distribution of troponin and CKMB by treatment group |

After careful consideration, the ARC agrees with this added level of consensus and proposes a classification system that is consistent with the global task force recommendation and highlights areas that require additional consideration. The global task force recommends the establishment of criteria based on troponin or creatine kinase Mb (CKMB) but notes the preference for troponin in all cases. For either troponin or CKMB, the upper range limit is defined as the 99th percentile of the normal range. The periprocedural period includes the first 48 hours after PCI and first 72 hours after coronary artery bypass grafting (CABG).

***Periprocedural MI After PCI***

For periprocedural MI after PCI, it is important to distinguish events defined by a threshold level of enzyme or biomarker elevation where the degree of elevation has a proven relationship to other more meaningful clinical outcomes.[10,11] Although the global task force notes the absence of solid scientific evidence for the establishment of such a threshold, they have recommended a value >3 times the upper range limit. Several investigators have reported correlation of elevated CKMB of >3, >5, or >8 times normal with increased mortality,[10–13] but there has been reluctance to use troponin in this setting because of concerns over its extreme sensitivity as a measure. In 1 study, many more patients reached the threshold of >3 times the normal range for troponin than for CKMB (22% versus 4%).[14] Although even minimally elevated troponin has been associated with increased late mor-

**TABLE 2. Myocardial Infarction Classification and Criteria for Diagnosis***

| Classification | Biomarker Criteria† | Additional Criteria |
|---|---|---|
| Periprocedural PCI | Troponin >3 times URL or CKMB >3 times URL | Baseline value <URL |
| Periprocedural CABG | Troponin >5 times URL or CKMB >5 times URL | Baseline value <URL and any of the following: new pathologic Q waves‡ or LBBB, new native or graft vessel occlusion, imaging evidence of loss of viable myocardium |
| Spontaneous | Troponin >URL or CKMB >URL | |
| Sudden death | Death before biomarkers obtained or before expected to be elevated | Symptoms suggestive of ischemia and any of the following: new ST elevation or LBBB, documented thrombus by angiography or autopsy |
| Reinfarction | Stable or decreasing values on 2 samples and 20% increase 3 to 6 hours after second sample | If biomarkers increasing or peak not reached then insufficient data to diagnose recurrent MI. |

*Adapted from Global Task Force.[9] URL indicates upper reference limit, defined as 99th percentile of normal reference range; LBBB, left bundle-branch block; and ST, stent thrombosis.

†Baseline biomarker value required before study procedure and presumes a typical rise and fall.

‡Q waves may be defined according to the Global Task Force,[9] Minnesota code, or Novacode.

tality, the positive predictive value remains low (<10%).[11] Nevertheless, the use of a more sensitive marker to diagnose any MI of potential clinical significance may be useful, as there appears to be a strong correlation of troponin levels and measurements of infarct size.[15,16]

The ARC remains concerned whether 3 times the normal range for troponin will prove to be overly sensitive and fail to discriminate among devices with variable risk for clinically significant periprocedural MI. We agree with the global task force that clinical trials should report complete biomarker data with different multiples of the upper range limit as well as the total distribution. This practice may allow for improved discriminatory ability if higher levels are more frequent for a particular device and will provide investigators with ability to translate across studies if different thresholds are used. It may also be advisable to collect CKMB data whenever possible until more experience has been acquired with the evaluation of outcomes on the basis of troponin, especially in cases where comparisons with historical controls are needed. The ARC recognizes that the FDA and individual trial sponsors may prefer the use of total creatine kinase or CKMB definitions in cases where historical comparisons are critical, but in these cases we encourage CKMB rather than total creatine kinase.

***Periprocedural MI After CABG***

The diagnosis of MI after CABG may be an issue during follow-up in PCI trials or at the time of the index treatment in studies where CABG is compared with DES. Although studies have reported associations of adverse outcome and CKMB elevations >5, >10, or >20 times the upper rate limit, the interpretation of isolated biomarker elevation after CABG is difficult because several sources of such elevation can be anticipated, including cardiac manipulation, ventricular venting, and suture placement. The ARC concurs with the global task force that biomarker elevation alone is inadequate for the diagnosis of periprocedural MI after CABG and accepts the proposed definition of troponin or CKMB >5 times the upper rate limit when associated with new pathological Q waves or left bundle-branch block, angiographically documented new graft or native vessel occlusion, or imaging evidence of new loss of viable myocardium.

***Spontaneous MI***

MI after the periprocedural period may be secondary to late stent complications or progression of native disease. Performance of ECG and angiography supports adjudication to either a target or nontarget vessel in most cases.

With the unique issues and pathophysiological mechanisms associated with these later events as well as the documented adverse impact on short- and long-term prognosis, the ARC proposes a more sensitive definition than for periprocedural MI and supports the global task force criterion of any elevation of troponin above the upper range limit. For the purposes of evaluation of results of PCI clinical trials, we do not find it useful to distinguish spontaneous events caused by acute coronary ischemic events from those related to increased demand or other causes for decreased supply as proposed by the task force, and we will consider all late events that are not associated with a revascularization procedure simply as spontaneous.

***Special Situations***

The global task force addresses other specific situations that are applicable to the diagnosis of MI in PCI clinical trials. The importance of baseline biomarkers is highlighted to exclude elevation before the index procedure. Recurrent MI or reinfarction may be diagnosed when biomarker levels are stable on 2 samples that are >6 hours apart or are in decline if a subsequent value 3 to 6 hours after the procedure is increased by ≥20% from the baseline sample. If the baseline value is not stable, then insufficient data exist to recommend biomarker criteria for diagnosis, and the ARC recommends that these events be considered as preprocedure MI. The global task force also addresses the role of ECG for diagnosis of MI. Pathological Q waves are defined according to amplitude, location, and depth if present in at least 2 contiguous leads; other classifications, such as Minnesota code and Novacode, are also acceptable for diagnosis. The presence of Q waves as defined may be used to diagnose interval or prior MI and have also been used to subclassify periprocedural and spontaneous MI as Q wave or non–Q wave. ECG interpretation by a blinded core laboratory is recommended. Finally, the global task force addresses patients who suffer sudden death before biomarker data can be obtained or before the appearance of cardiac biomarkers in the blood. In the presence of supporting data, such as ischemic symptoms, new ST-segment elevation, new left bundle-branch block, or documented vessel thrombus MI should be diagnosed.

***Repeat Revascularization***

*Assessment of Clinical Effectiveness, Reduction of Restenosis*

Clear and consistent definition of TLR is crucial to the understanding of variations in DES effectiveness, whether across different patient populations, lesion categories, or the devices themselves. Criteria for TLR should define procedures that are performed for clinically significant renarrowing and thus include 2 fundamental components: the luminal measurement and the clinical context. Luminal renarrowing provides anatomic evidence of device performance failure. The clinical status of the patient provides a more direct reflection of the clinical outcome associated with an ineffective device-based intervention. The ARC definition requires symptoms or functional evidence of ischemia as well as lesion severity of >50% diameter stenosis determined by an independent quantitative coronary angiographic core laboratory (Table 4).

The ARC recommendation extends to encouraging DES study designs to require completion of clinical evaluations at a point in time before any protocol recatheterization, intravascular ultrasound, or other imaging. Implicit to this approach is that all interval catheterizations, and hence all TLRs that take place during the clinical evaluation window, will de facto be clinically driven.

Several studies have confirmed the bias of increased TLR events introduced by protocol catheterization.[17,18] With this

**TABLE 4. Repeat Revascularization**

| | |
|---|---|
| Target lesion revascularization | TLR is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. All TLRs should be classified prospectively as clinically indicated* or not clinically indicated by the investigator prior to repeat angiography. An independent angiographic core laboratory should verify that the severity of percent diameter stenosis meets requirements for clinical indication and will overrule in cases where investigator reports are not in agreement. The target lesion is defined as the treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent. |
| Target vessel Revascularization | TVR is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion, which includes upstream and downstream branches and the target lesion itself. |

TLR indicates target lesion revascularization; TVR, target vessel revascularization; and QCA, quantitative coronary angiographic.

*A revascularization is considered clinically indicated if angiography at follow-up shows a percent diameter stenosis ≥50% (core lab QCA assessment) and if one of the following occurs: (1) a positive history of recurrent angina pectoris, presumably related to the target vessel; (2) objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent), presumably related to the target vessel; (3) abnormal results of any invasive functional diagnostic test (eg, Doppler flow velocity reserve, fractional flow reserve); (4) A TLR or TVR with a diameter stenosis ≥70% even in the absence of the above-mentioned ischemic signs or symptoms.

comes the dilemma of whether patients would have remained stable for a long time without further revascularization or would soon have become symptomatic if revascularization had not been performed. Although attempts have been made to stratify TLR driven by protocol catheterization, even independent adjudication is very complex in this setting.[2] Thus, the ARC consensus for DES evaluation is to primarily assess clinically driven TLR within a time interval that precedes any protocol-mandated repeat catheterization and include subsequent TLR in secondary analyses, with best adjudication as to clinical need. We suggest determination of TLR at 12 months with protocol follow-up angiography at 13 months.

Early TLR events (before 30 days) also require special consideration. The pathophysiology is more likely to be caused by an angiographic complication, because this time course is too short for fibrointimal hyperplasia, which is the more likely mechanism after 30 days.[19,20] The ARC consensus is that TLR before 30 days is a safety end point and not a measure of restenosis, whereas TLR after 30 days is a measure of failed DES effectiveness.

### *Composite End Points*

Composites generated by the combination of individual end points provide additional statistical power to detect potentially meaningful differences between treatments. The individual components should each represent clinically meaningful events and should be linked by common elements of pathophysiology. Composite acronyms such as MACE (major adverse cardiac event) have been used so frequently with so many variations in definition that ARC recommends that the term be avoided altogether (Table 5).

**TABLE 5. Composite End Points**

| |
|---|
| Device-oriented composite (hierarchical order) |
| Cardiac death |
| MI (not clearly attributable to a nontarget vessel) |
| TLR |
| Patient-oriented composite (hierarchical order) |
| All-cause mortality |
| Any MI (includes nontarget vessel territory) |
| Any repeat revascularization (includes all target and nontarget vessel) |

The ARC consensus suggests 2 composite end points for DES trials, one that is device-oriented and one for overall patient-oriented clinical outcome. The device-oriented composite includes cardiac death, MI attributed to the target vessel, and TLR. The broader patient-oriented outcome composite includes all-cause mortality, any MI, and any revascularization (includes TLR), target vessel revascularization, or revascularization of nontarget vessels.

Other composites, such as a net clinical benefit that may include safety-related events such as bleeding or stroke, might have application for specific clinical trials. The ARC consensus for DES end points was to recognize such events as secondary safety end points.

### *Stent Thrombosis*

Stent thrombosis is a rare but usually catastrophic event, frequently associated with large MI or death.[21,22] In the bare metal stent clinical trials of mostly noncomplex lesions, stent thrombosis rates were <1% with the use of dual antiplatelet therapy and high-pressure postdilation,[21] although higher rates (2% to 3%) were reported when more complex patients and lesions were treated.[23] Almost all events occurred within the first few days and were not reported after 30 days by definition. In fact, it was not until late thrombosis events were recognized with increasing frequency during early brachytherapy clinical trials that reports of late thrombosis after bare metal stents appeared.[24–27] Initial reports of DES clinical trials showed no increased risk for stent thrombosis during 1- and 2-year follow-up compared with bare metal stents,[5,6,28] but concerns have been heightened recently by reports of increased risk beyond the recommended dual antiplatelet therapy period,[29] continued risk beyond 2 years in real-world patients,[30] and pooled or meta-analysis of published studies that showed increased mortality or MI for sirolimus DES compared with bare metal stents (Tables 6 and 7).[31,32]

The sensitivity and specificity of definitions of stent thrombosis will vary depending on whether the evidence required is more conservative or more expansive. In previous DES and bare metal studies, stent thrombosis definitions have ranged from requiring evidence of acute myocardial ischemia with angiographic confirmation of thrombus or unexplained sudden death within 30 days[5,6,21,33] to including MI that involves the target vessel territory[6,21,22,34,35] or unexplained

**TABLE 6. Stent Thrombosis: Timing**

| | |
|---|---|
| Acute stent thrombosis* | 0 to 24 hours after stent implantation |
| Subacute stent thrombosis* | >24 hours to 30 days after stent implantation |
| Late stent thrombosis† | >30 days to 1 year after stent implantation |
| Very late stent thrombosis† | >1 year after stent implantation |

Stent thrombosis should be reported as a cumulative value over time and at the various individual time points specified above. Time 0 is defined as the time point after the guiding catheter has been removed and the patient has left the catheter laboratory.

*Acute or subacute can also be replaced by the term early stent thrombosis. Early stent thrombosis (0 to 30 days) will be used in the remainder of this document.

†Includes primary as well as secondary late stent thrombosis; secondary late stent thrombosis is a stent thrombosis after a target lesion revascularization.

cardiac deaths regardless of timing as representative of at least possible or presumed stent thrombosis.[22,35]

The ARC consensus is that both levels of evidence and timing of events can be stratified to define varying degrees of certainty and to imply different pathophysiological mechanisms, respectively. The trilevel of certainty classification recommended is shown in Table 7.

Definite stent thrombosis classification requires angiographic[36] or autopsy confirmation, is highly specific, and is patterned on the definition developed when these events were first detected during early brachytherapy clinical trials.[37,38] Although it maximizes specificity, the definite classification may not be sufficiently sensitive for the capture of a relatively rare safety event. The categories of probable and possible stent thrombosis add such sensitivity, but the utility of these categories will vary depending on the quality of data available to the adjudication committee. This is particularly true for the least specific thrombosis category, possible, which could be assigned to all late deaths unless sufficient detail is provided for adjudication. It is important to avoid the dilution of a potential real difference in events with the use of an overly sensitive definition that may include cases unlikely to represent thrombosis. The ARC recommends the combination of adjudicated definite and probable stent thrombosis to best characterize this aspect of DES safety; however, the reporting of definite only and overall rates is also encouraged.

In addition to the level of certainty, stent thrombosis should be stratified relative to the timing of the event. The ARC consensus recommends temporal categories of early (0 to 30 days), late (31 days to 1 year), and very late (>1 year) to distinguish likely differences in the contribution of the various pathophysiological processes during each of these intervals. Most stent thrombosis events after bare metal stents or DES occur within the first 30 days, with procedural or technical characteristics and compliance with dual antiplatelet therapy as the major risk factors.[21,35,39,40] During the next 6 to 12 months, events are less frequent, and compliance with dual antiplatelet therapy remains the major risk factor in most studies,[35,40,41] although technical issues such as bifurcation stenting may also be important in this time period.[35] Perhaps most concerning are apparent stent thrombosis events that occur beyond 1 year. Although limited data exist on these events, available reports have noted that these events continue to occur despite dual antiplatelet therapy or after long periods

**TABLE 7. Definite,* Probable, and Possible Stent Thrombosis**

| |
|---|
| Definite stent thrombosis |
| Angiographic confirmation of stent thrombosis† |
| The presence of a thrombus‡ that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window: |
| Acute onset of ischemic symptoms at rest |
| New ischemic ECG changes that suggest acute ischemia |
| Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI) |
| Nonocclusive thrombus |
| Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream. |
| Occlusive thrombus |
| TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch). |
| Pathological confirmation of stent thrombosis |
| Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy. |
| Probable stent thrombosis |
| Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases: |
| Any unexplained death within the first 30 days§ |
| Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause |
| Possible stent thrombosis |
| Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up. |

*Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation.

†The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).

‡Intracoronary thrombus.[36]

§For studies with ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis.

of clopidogrel discontinuation and without clear relationship to the usual technical or lesion risk factors.[41,42] Furthermore, events continue to occur at similar rates up to 3 years.[30] Histopathological evaluations have suggested idiosyncratic hypersensitivity and persistent inflammatory changes with delayed or absent stent strut endothelialization as possible mechanisms for this ongoing risk.[43,44]

Reporting of late or very late stent thrombosis may be complex to interpret when events occur secondary to an intervening TLR, especially if an additional or different stent is implanted at that time. Censorship of all such events, however, may bias reporting in favor of devices with higher restenosis risk. The ARC consensus recommends reporting of

all stent thrombosis events, with secondary reporting of primary (no intervening TLR) stent thrombosis. It should be noted that the ARC definitions require evidence of a clinical event and do not include silent late occlusions as manifestations of stent thrombosis. It is our opinion that, although these clinically silent events may represent thrombosis, they more likely represent a gradual renarrowing caused by severe restenosis.

## Conclusion

The DES represents an exciting area of breakthrough technology, which has generated an enormous literature in parallel with widespread use in a short period of time. Interaction of innovative stent platforms, polymers, and molecular entities, as well as pharmaceutical adjuncts such as dual antiplatelet therapy, present a unique degree of complexity for systematic ongoing evaluation of these devices, their optimal use, and their real safety and performance results.

Toward this end, clinical trials and DES industry programs have developed a broad variety of end point definitions, which differ across a heterogeneous array of arbitrary cut-off values, timing of end point assessment, and outcome composites that are nominally the same but are inconsistent in terms of individual components and in the mixing of device- and patient-oriented outcomes.

The ARC was created as an informal orchestration of academics, clinical trialists, the FDA, and DES device manufacturers grounded in the recognition that consistency of end point definitions across the DES literature would contribute far more than would the application or abandonment of any particular arbitrary cut-off values. The process combined available mechanistic and outcomes data with clinical and logistical perspectives to consider what end point definitions would be most informative for DES performance evaluation (pivotal) studies. The primary deliverable was not intended to outline study requirements or practice standards, but rather to communicate the consensus definitions and a brief context of their rationale as a point of reference for manufacturers, trialists, clinicians, and regulatory authorities. Although consensus for DES trials was the impetus for our effort, the definitions are likely applicable to trials of any PCI device.

The final document is by nature dynamic, but modifications should follow a similar mechanism for consensus. In principle, the consensus calls for recognition of the importance of standard reporting of specific device-related clinical events of death, MI, TLR, and stent thrombosis and the net impact of device treatment on overall clinical outcome assessed by all-cause mortality, MI, and repeat revascularization procedures. Use of central core laboratories and independent, blinded, end point adjudication is central to standardization of the definitions. In this manner, the balance of device risk and benefit can best be assessed for clinical trial subjects and future individual patients.

### Limitations

This informal consensus document and the ARC end point definitions have a number of limitations. First, the clinical trial end point definitions proposed are not easily supported by scientific evidence as single gold standards, but represent reasonable options that are based on available data. Second, attempts to evaluate previous clinical trials through retrospective application of these definitions and readjudication of events should be undertaken with caution and for the generation of hypotheses only, given the potential for bias relative to prospectively defined end points. Finally, it must be recognized that, although broadly based consensus definitions are an important step in the right direction, how these definitions are actually applied in specific clinical trials for specific DES investigations is not fully addressed in this first ARC effort.

## Sources of Funding

Grants were provided to Harvard Clinical Research Institute and Cardialysis to cover costs of travel, meeting rooms, and lodging for academic attendees at the Washington, DC, and Dublin meetings by Abbott Vascular, Biosensors International, Boston Scientific Corporation, Conor Medsystems, Cordis Corporation, Guidant, and Medtronic.

## Disclosures

None.

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# APPENDIX 1.2

## Clinical Event Committees in Coronary Stent Trials: Insights and Recommendations based on Experience in an Unselected Study Population

Vranckx P., Mc Fadden E., Mehran R,. Cutlip D .

*EuroIntervention.* 2012; **8**:368-74. [**technical report**]

# Clinical event committees in coronary stent trials: insights and recommendations based on experience in an unselected study population

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KEYWORDS

- stenting
- coronary
- endpoints
- clinical event committee

## Abstract

**Aims:** To introduce the interested reader to the concepts of the Clinical Event Committee (CEC) work process with a focus on the adjudication of major endpoints in contemporary coronary stent trials.

**Methods and results:** Endpoint adjudication by independent Clinical Events Committees (CEC) is critical to ensure the generation and recording of quality data in clinical outcome trials. CEC adjudication provides a standard, systematic and unbiased assessment of endpoints. For trials with relatively long-term clinical endpoints that span geographic regions and include diverse clinical presentations and practice patterns, this poses specific challenges. The recently published RESOLUTE All Comer coronary stent trial is used to illustrate some aspects of the CEC process.

**Conclusions:** Understanding the CEC review process is important to guide the design of future trials and allow meaningful comparisons of event rates among trials.

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## Introduction

In order to evaluate the effects of a particular treatment strategy on mortality and major morbidity within a disease entity, large, truly global clinical trial programmes with relatively long-term clinical endpoints have become the accepted standard. The critical challenge in the conduct of endpoint trials relates to the definition, collection and accurate assessment of endpoint data in a consistent timely manner.

In the context of coronary stent research, the need for uniform endpoint definitions and the harmonisation of clinical event adjudication has been addressed by the Academic Research Consortium (ARC) group.[1,2] These definitions were intended to be applied to relatively homogeneous populations with stable presentations of coronary disease. An important challenge in this process is to adapt the initial definitions, while maintaining accuracy and consistency across geographic areas and over the long course of the study. This may prove even more important while addressing minimally selected populations, including complex patients, reflecting routine clinical practice.[3] To serve this purpose a growing number of coronary device trials rely on the adjudication of safety and efficacy endpoints by independent Clinical Event Committees (CECs), also known as Clinical Endpoint Committees. Event and data adjudication by the CEC is a critical factor in generating and recording quality results, facilitating acceptance of the trial results by regulatory bodies, as well as the academic and medical communities.

It is the responsibility of the CEC to review all relevant and available data and provide an independent, blinded determination of trial specific endpoints or events utilising pre-specified criteria and considering the clinical scenario. CECs must be rigorous in their analysis of the data to ensure the highest potential value of the science. Since there are no accepted standards of what constitutes conclusive evidence, the process by which committee members arrive at their decisions must be made fully transparent. The quality of their work may be assessed on an on-going basis throughout the clinical trial and/or trial programme via internal and/or external validation.

In this article we will highlight the key concepts of the CEC process with a focus on the adjudication of major endpoints in coronary stent trials. The recently published RESOLUTE All Comer coronary stent trial (Resolute-AC) is used to illustrate some aspects of the CEC process.[4,5]

### CEC STRUCTURE AND PROCESS

A CEC should comprise three or more practising physicians with particular expertise in the subject of the research. Trial specific characteristics, such as the trial size, estimated event rates and number of endpoints, will dictate the number of committee members required. They should not be otherwise involved in the study (e.g., as investigators, members of the Data Safety Monitoring Board [DSMB], or Steering Committee) and should not have a financial interest in the sponsor. Ideally, the choice of CEC members and the operational aspects of the CEC process should be delegated by the sponsor to an independent academic research organisation (ARO). Where these tasks are undertaken by the sponsor, it is essential that pre-specified procedures, documented in the CEC charter, exist to ensure that the independence of the CEC is not compromised.

The different key components of the CEC process are depicted in **Figure 1**. They should be pre-specified in the CEC charter as a part of the study protocol. The CEC charter should provide a detailed description of the structure, the membership, and the role and responsibilities of the CEC. The workflow and working procedures, including all administrative as well as methodological aspects of the CEC work, should also be clearly outlined. The endpoints should be carefully defined and the the strictest possible criteria must be set. The criteria should also be simple in order to avoid misinterpretations.

The CEC must commit to conducting a paced and timely review of cases identified as having potential endpoints. This process should also allow for the generation of interim data that may be reviewed by DSMBs and the Steering Committee.[6] The total number of adjudicating members present at any meeting should be two

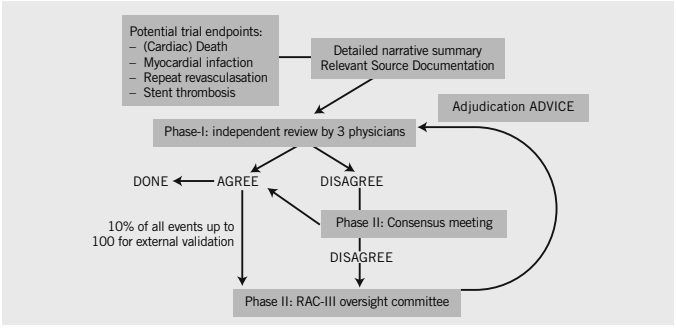


**Figure 1.** *The clinical event committee adjudication process. Caption: The key components of the CEC process are depicted here.*

or more and preferably odd in number to come to the final adjudication. In the Resolute-AC trial, both a web-based, independent review and the (face-to-face) consensus meeting methods were used. Given the complex patient population and the fact that several "teams" of reviewers were working in parallel, all potential events were first reviewed by three independent reviewers using a web-based system. When there was consensus agreement, then the adjudication was considered final. When there was disagreement, the event was discussed at a face-to-face consensus meeting, during which the CEC panel was asked to deliberate until every effort had been made to reach a unanimous decision whenever possible. In case of disagreement, the decision was by majority vote (>50%) of voting members present. For each case, a brief written justification of the reasons for a decision was provided. This allowed internal review of cases that had been decided by majority vote, to ensure consistency among CEC meetings with different members present.

Suspected endpoint events ("event triggers") are identified by using reports developed within the various study databases. Suspected endpoint events can be reported by the investigators at the clinical sites, identified through programmed queries based on triggers from the case report forms and other study data (e.g., angiographic or electrocardiographic core laboratory reports, specific patterns of release of biomarkers of myocardial damage) or following careful review of source data by the CEC. **Figure 2** shows the data source for the event triggers in Resolute-AC and their relationship to the final reported outcome. The CEC reviews endpoint triggers and all available data from case report forms and any accompanying source documentation as needed. This process is strongly dependent on the information provided by an investigator, including endpoint event reporting. This information should be complete, accurate and valid. Ideally, every item of data that appears in a case report form (CRF) should be documented somewhere else to allow verification, audit and reconstruction (see also: "data reporting and source data verification"). Source documentation packets should be blinded to both subject identification and treatment assignment. Clinical interpretation (from the Clinical Reviewer) and judgement (from the CEC) are important to cluster multiple event triggers correctly into one event (e.g., acute myocardial infarction [AMI] from multiple cardiac marker test results and ECGs, stent thrombosis adjudicated from AMI and from cardiac death). One final potential role of the CEC is to identify "problem" sites where there is a pattern of deviation from study mandated protocols (e.g., failure to collect the required biomarker data or systematic performance of follow-up angiography where there is no clear clinical indication).

Within a study or clinical trial programme (set of trials evaluating the same product) quality control (QC) procedures may be implemented to identify potential problems and areas for improvement in the CEC adjudication process. Given the consensus review method and high level of unanimous decisions, a formal intra- and inter-observer variability assessment at the individual CEC team level is not usually planned. Yet, a predefined percentage of randomly selected, previously adjudicated events may be resubmitted to other members within the same CEC committee (internal validation) or to another, independent, overseeing CEC committee (external validation). The latter will integrate a QC of CEC operations (e.g., the workflow and working procedures).

## EVENT ADJUDICATION BEYOND ANY REASONABLE DOUBT

The clinical adjudication process by itself should be highly specific, accurate and consistent, mainly driven by the application of pre-specified criteria for event definitions applied within a specific scenario. However, in cases where the minimal required data for event adjudication is permanently missing, event adjudication is based on interpretation of the available data, using a worst case scenario tempered by clinical judgement and, by consequence, more prone to variability.

## ENDPOINT DEFINITIONS

The effort of ARC with the objectives of establishing consistency among endpoint definitions and providing consensus recommendations for stent investigations in stable patients with *de novo* coronary

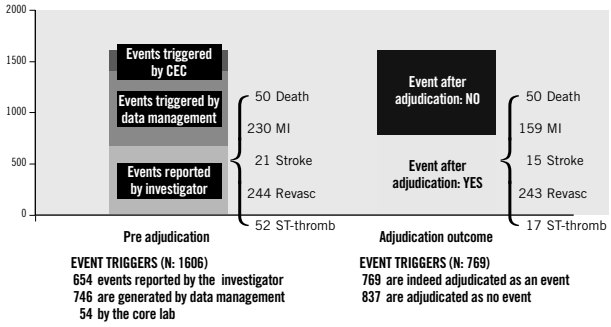


**Figure 2.** *Clinical event triggers in the Resolute-AC trial (RAC). The left panel shows the source for the suspected event ("triggers"), the right panel the final event adjudication.*

lesions was pursued and extended towards non-selected patient populations.[4,5,7,8]. A critical appraisal of the ARC endpoint definitions is beyond the scope of this paper and provided in a separate paper.[9] We will focus on those elements important to event adjudication and trial design in contemporary coronary stent trials including complex patient populations.

The ARC consensus proposed two composite endpoints for coronary device trials, one that is oriented towards procedure and device related risks and benefits (cardiac death, myocardial infarction attributed to the target vessel, clinically driven target lesion revascularisation), and a broader one that is oriented towards the overall patient-oriented clinical outcome. The emphasis should be on the latter.

In coronary stent studies with relatively long-term clinical endpoints, progression of coronary artery disease involving remote areas may become relevant. For protocols involving multivessel, multi-segment stenting, it may be problematic to attribute the event (e.g., myocardial infarction, stent thrombosis) directly to the prespecified target lesion and study stent.

When target-vessel and remote area events cannot be differentiated based on the available source documentation (e.g., ECG, coronary angiogram, autopsy findings) these events should be attributed to the study device.

## DEATH

ARC considered all-cause mortality the most unbiased method for reporting deaths in a clinical trial, even though it may be less specific than deaths adjudicated as due to cardiac aetiologies. All-cause death can be readily ascertained with minimal bias or need for adjudication. For situations when attribution to cardiac versus non-cardiac causes is desired, such as medium to long-term follow-up studies, ARC proposed a conservative approach considering the worst case scenario. Sudden or unexpected death even in patients with coexisting potentially fatal non-cardiac disease status (e.g., cancer or sepsis) should be classified as cardiac, including the "unknown", unless history related to the non-cardiac diagnosis indicates death was imminent. Clinical autopsies may help to establish the true cause of death and should be strongly recommended.[10] In Resolute-AC an additional category for classification of death, namely "unexplained" was available to the CEC, which defaulted to cardiac death for statistical analyses. This allowed the CEC to indicate that, were further source documentation provided, the cause could be reclassified as "non-cardiac" or, in the case of cardiac death within one month of the index procedure, further source documentation could clearly rule out a probable stent thrombosis. Commonly encountered situations were, firstly, death in patients undergoing primary percutaneous coronary intervention (PCI) at index, who were unwell but apparently stable in the subsequent days, but then died in circumstances where the source documentation did not establish a clear cause and did not allow the CEC to determine whether death was "expected". A second scenario, increasingly common after twelve months, was death where information from family members suggested the cause was non-cardiac (e.g., cancer) but where no source documentation was provided.

## MYOCARDIAL INFARCTION

The diagnosis of acute, evolving or recent MI requires, in the absence of pathologic confirmation, findings of a typical rise and/or fall of a biomarker of myocardial necrosis, in conjunction with clinical signs or symptoms that the cause of myocardial damage is ischaemia.[11]

After careful consideration, the ARC endorsed the joint ESC/ACCF/AHA/WHF (European Society of Cardiology, American College of Cardiology, American Heart Association and World Heart Foundation) Task Force 2007 universal definition of myocardial infarction for consistent application across investigational studies; however, they advised the use of creatine kinase-myocardial band (CK-MB) mass over cardiac specific troponin (cTn) as the primary marker of myocardial necrosis.[2,12] It has been contended that cTn may be overly sensitive, increasing the overall rates of PMI and exaggerating differences in clinical outcomes between treatments which are neither clinically nor prognostically relevant.[13-16] This may be even more of an issue in contemporary all-comer coronary stent trials allowing the unrestricted use of DES.[4-5] Moreover, and as illustrated in **Figure 3**, definition instability may be encountered while considering patients with acute coronary syndromes with or without on-going myocardial ischaemia at the time of the index procedure and/or while being confronted with missing biomarker sets.

Reinfarction following primary PCI, in patients with a presenting myocardial infarction, can only be assessed if there is a clear indication that the cardiac biomarker sample values were falling following the index event and were then rising again in the immediate periprocedural period of 48 hours **(Figure 3)**. Otherwise, there would be insufficient biomarker data to adjudicate a PMI. A 20% increase is considered significant, however, this value must exceed the appropriate threshold according to the timing of the event (post PCI or post coronary artery bypass grafting). Of note, the latter requirement was not included in the index publication.[12] In the case of reinfarction following elective PCI in patients with a recent MI (up to 48 hours, thrombolysed or not) and only one biomarker set available pre procedure, one may assume biomarkers to be falling, although this cannot be established with certainty. Here, judgement may be guided by the clinical scenario (e.g., timing of the procedure) and careful evaluation of serial 12-lead ECG and/or angiographic findings (e.g., occluded vessel, thrombus, or loss of side branch). The Resolute-AC Steering Committee decided to report endpoints both according to the 2007 universal definition of MI and also the modified historical WHO MI definition extended also to include acute coronary syndrome (ACS) patients.[4,5,16] For MI due to PCI, it is important to distinguish events defined by a threshold level of enzyme or biomarker elevation where the degree of elevation has a proven relationship to other more meaningful clinical outcomes.[17-19] The clinical relevance of the currently set thresholds levels of enzyme or biomarker elevation remains to be established.

Myocardial infarction after the predefined immediate periprocedural period of 48 hours (72 hours for coronary artery bypass grafting), and after the cardiac biomarkers used to detect myocardial

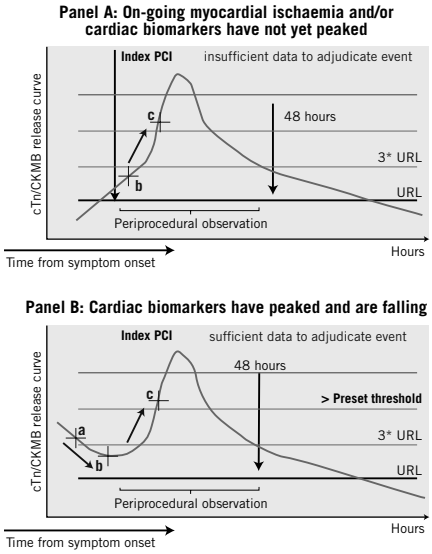


**Figure 3.** *ARC MI definition instability. ARC MI definition instability may be encountered in acute coronary syndromes with (scenario A) or without (scenario B) on-going myocardial ischaemia. *Scenario A: Patients with on-going signs and/or symptoms consistent with myocardial ischaemia and the cardiac biomarkers are not yet elevated and/or have not reached peak values. Two cardiac biomarker values were sampled post PCI: the first six hours post PCI (b), the second three to six hours later. There are insufficient data to adjudicate a new MI event following primary PCI considering the cardiac biomarkers. *Scenario B: cardiac biomarkers have reached peak values and are falling (cardiac biomarker sample values a-b). Any significant rise starting following the primary PCI will constitute a reinfarction (MI extension) (cardiac biomarker sample value c). The same criteria should be applied beyond 48 hours if the biomarker level has not yet returned below the upper reference limit. The criteria for spontaneous MI does not apply. URL denotes upper reference limit for the cardiac biomarkers used to detect myocardial injury.*

injury have returned below the 99th percentile of upper reference value in a normal reference population, may be secondary to late stent complications or progression of the native disease ("spontaneous"). ARC endorsed the 2007 universal definition of MI criterion for MI of any elevation of cTn above the upper range limit.

With sudden, unexpected cardiac death, involving cardiac arrest, especially when accompanied by clinical signs or symptoms of myocardial ischaemia, the CEC may adjudicate MI considering the clinical scenario including pathological findings, and new wall motion abnormalities on noninvasive imaging.

## REINTERVENTION

Approximately 50% of all repeat revascularisations in the RAC study were clinically justified target lesion revascularisation (TLR).[4,5] The ARC acknowledged the importance of clear and consistent definition of TLR to an understanding of variations in drug-eluting stent (DES) clinical effectiveness in reducing restenosis, whether across different patient populations, lesion categories or the tested devices themselves.[2] The clinical justification for TLR includes two fundamental components: the luminal measurement (angiographic component) and the clinical context. The quantitative pre-adjudication of coronary angiograms for lesion localisation, severity and visual intracoronary thrombus by an independent quantitative coronary angiographic (QCA) core laboratory should contribute to the quality of the process. The CEC is asked to judge the clinical justification in intermediate severity stenoses (50-70%) by assessing the presence of symptoms consistent with myocardial ischaemia in conjunction with the site-reported results of noninvasive functional testing. Protocol deviations with systematic follow-up angiography seem to be the norm in some geographic areas. In such cases, a cardiac basis for site-reported "symptoms" (if any) and their potential relation to the target vessel (in the presence of other untreated disease) mean that even "intermediate" restenoses are classified by default as clinically driven. While such events will not influence the results of a randomised DES trial, they have negative implications for the interventional community and for comparisons with surgery. An invasive functional (physiological) assessment by coronary pressure-derived fractional flow reserve (FFR) may provide important added value for intermediate lesions. However, where this is not pre-specified by protocol, for all such lesions, and subject to independent core lab validation, its value is dubious.

## STENT THROMBOSIS

Stent thrombosis is a catastrophic complication of coronary stenting, presenting as sudden death or nonfatal myocardial infarction (MI) in almost all cases. ST should not be considered an endpoint outside the overall clinical context. Concerns remain surrounding those events occurring beyond one year that may present as unexplained death. Limiting the ARC possible ST criteria to include death beyond 30 days due only to sudden death acute ischaemia may provide the best estimate of late and very late stent thrombosis rates.[10]

## DATA COLLECTION AND MONITORING

The strategy used to identify and adjudicate endpoint events is one of many factors to be considered when comparing event rates between clinical studies. Only a minority of coronary stent trials detail the techniques relating to the ascertainment of and data collection for hospitalised and non-hospitalised events. **Table 1** lists the minimum required data (coronary angiograms, autopsy reports, etc.) for CEC event adjudication for major outcome events in the Resolute-AC trial. For periprocedural MI, an analysable set of cardiac biomarkers (either CK, CK-MB or cTn) consisted of a baseline value and at least two subsequent measurements within 48 hours post procedure at ≥4 hour intervals. In patients with an inclusion MI, a minimum of three different samples is required (**Figure 3**,

**Table 1. Minimum required data for CEC event adjudication.**

| |
|---|
| DEATH<br>– Hospital discharge summary/letter (if applicable)<br>– Autopsy report<br>– Death certificate (describe circumstances of death)<br>– Relevant dated ECGs (admission, worst, last)<br>– Death certificate (for un-witnessed, out-of-hospital death)<br>– Recent (<30 d) coronary angiogram where applicable |
| ACUTE MYOCARDIAL INFARCTION<br>– Hospital discharge summary/letter (if applicable)<br>– Relevant dated ECGs (inclusion, admission, worst, last)<br>– All relevant cardiac marker details, including their or upper reference limit (URL) |
| RE-PCI<br>– Index PCI (angiogram)<br>– Diagnostic angiography preceding re-PCI<br>– Relevant clinical source documentation regarding myocardial ischaemia prior to re-PCI<br>– All relevant cardiac marker details (pre, post, after 8 – 12h), including their URL<br>– 12-lead ECG pre/post procedure<br>– Re-PCI (angiogram) with cathlab summary report |
| CABG<br>– Index PCI (angiogram)<br>– Diagnostic angiography preceding CABG<br>– Relevant clinical source documentation regarding myocardial ischaemia prior to CABG<br>– Hospital discharge summary/letter, including CABG surgery summary |
| Note: The adjudication of stent thrombosis is based on the underlying death, AMI and revascularise events. Info requirements, therefore, relate to these primary events. |

scenario B). As indicated earlier, clinical autopsies are vital to establish the true cause of death and should be strongly encouraged. This issue becomes even more critical in the late follow-up period when there may be a higher frequency of death and details are more likely to be inadequate for specifying a cause.[10]

In quantitative clinical research, the quality of CEC adjudication is highly dependent on the completeness and detail in individual patient accounts, including protocol-driven test results (laboratory examinations, standard 12-lead ECG). The potential underreporting of adverse events is an important limitation of large multicentre registries where data monitoring is only provided for a fraction of all events. An audit of a clinical trial provides the research sponsor with independent appraisal of the quality and completeness of the data generated by the trial. Although auditing alone cannot transform a poorly planned, executed, monitored, or analysed trial into a credible one, an active clinical trial audit programme will point out potential problem areas early, so that solutions can be put in place before it is too late. In addition to providing objective information about processes, audits can prevent future errors by identifying problematic work patterns or behaviors. Anticipation of an audit may be an important quality assurance mechanism, providing sites with an additional incentive to maintain data quality.

## Conflict of interest statement

The authors (PV, EMF, RM, DC) are all members of the Academic Research Consortium and have contributed equally to this document, drawing on their academic and clinical experience. All are involved in research work in collaboration with industry (i.e., the Medtronic Resolute coronary stent study programme), governmental or private health providers.

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# APPENDIX 1.3

# Zotarolimus-eluting or sirolimus-eluting coronary stent implantation: a randomised, multicentre, open-label, controlled trial

Camenzind E*, Wijns W, Mauri L, Kurowski V, Parikh K, Gao R, Bode C, Greenwood JP, Boersma E, Vranckx P, McFadden E, Serruys PW, O'Neil WW, Jorissen B, Van Leeuwen F, Steg PG*, for the PROTECT Steering Committee and Investigators

*Lancet*. 2012: **380**:1396-405 [**original research paper**]

# Stent thrombosis and major clinical events at 3 years after zotarolimus-eluting or sirolimus-eluting coronary stent implantation: a randomised, multicentre, open-label, controlled trial

*Edoardo Camenzind*, William Wijns, Laura Mauri, Volkhard Kurowski, Keyur Parikh, Runlin Gao, Christoph Bode, John P Greenwood, Eric Boersma, Pascal Vranckx, Eugene McFadden, Patrick W Serruys, William W O'Neil, Brenda Jorissen, Frank Van Leeuwen, Ph Gabriel Steg*, for the PROTECT Steering Committee and Investigators†*

## Summary

**Background** We sought to compare the long-term safety of two devices with different antiproliferative properties: the Endeavor zotarolimus-eluting stent (E-ZES; Medtronic, Inc) and the Cypher sirolimus-eluting stent (C-SES; Cordis, Johnson & Johnson) in a broad group of patients and lesions.

**Methods** Between May 21, 2007 and Dec 22, 2008, we recruited 8791 patients from 36 recruiting countries to participate in this open-label, multicentre, randomised, superiority trial. Eligible patients were those aged 18 years or older undergoing elective, unplanned, or emergency procedures in native coronary arteries. Patients were randomly assigned to either receive E-ZES and C-SES (ratio 1:1). Randomisation was stratified per centre with varying block sizes of four, six, or eight patients, and concealed with a central telephone-based or web-based allocation service. The primary outcome was definite or probable stent thrombosis at 3 years and was analysed by intention to treat. Patients and investigators were aware of treatment assignment. This trial is registered with ClinicalTrials.gov, number NCT00476957.

**Findings** PROTECT randomised 8791 patients, of whom 8709 provided consent to participate and were eligible: 4357 were allocated to the E-ZES group and 4352 patients to the C-SES group. At 3 years, rates of definite or probable stent thrombosis did not differ between groups (1·4% for E-ZES [predicted: 1·5%] *vs* 1·8% [predicted: 2·5%] for C-SES; hazard ratio [HR] 0·81, 95% CI 0·58–1·14, p=0·22). Dual antiplatelet therapy was used in 8402 (96%) patients at discharge, 7456 (88%) at 1 year, 3041 (37%) at 2 years, and 2364 (30%) at 3 years.

**Interpretation** No evidence of superiority of E-ZES compared with C-SES in definite or probable stent thrombosis rates was noted at 3 years. Time analysis suggests a difference in definite or probable stent thrombosis between groups is emerging over time, and a longer follow-up is therefore needed given the clinical relevance of stent thrombosis.

**Funding** Medtronic, Inc.

Published **Online** August 27, 2012 http://dx.doi.org/10.1016/S0140-6736(12)61336-1

See **Online/Comment** http://dx.doi.org/10.1016/S0140-6736(12)61385-3

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## Introduction

Drug-eluting stents substantially reduce the incidence of in-stent coronary restenosis through controlled release of an antiproliferative compound.[1–3] After their introduction, drug-eluting stents quickly replaced bare-metal stents in many countries, and were used in broad populations of patients and in complex coronary lesion subsets.[4,5] However, concern was raised that the reduction in restenosis associated with drug-eluting stents was achieved at the cost of a potential increase in adverse clinical events, including death and myocardial infarction.[6] Simultaneously, the routine use of early sirolimus-eluting or paclitaxel-eluting stents in broad clinical practice showed a persisting risk of stent thrombosis beyond 1 year that had not been noted with bare-metal stents.[7] Although rare, stent thrombosis is a serious and potentially fatal event.[8]

Subsequent clinical studies of drug-eluting versus bare-metal stents raised controversy about late outcomes;[6,9–12] these studies were, however, done in selected patient populations (single-vessel treatment, stable angina, elective procedures) and were not of sufficient size to adequately compare rates of stent thrombosis, death, or myocardial infarction.[13]

Currently available drug-eluting stents vary according to drug, polymer, and stent characteristics. It is plausible, given the effect of drug and polymer on vascular healing,[14] that these variations might be associated with differences in the risks of stent thrombosis and adverse clinical consequences over time.

The Patient Related OuTcomes with Endeavor versus Cypher stenting Trial (PROTECT)[15] was designed as a pragmatic, large, multicentre, randomised clinical trial. It compares two treatment modalities that are directly relevant to patient care, uses broad eligibility criteria, follows usual clinical practices, and is representative of real-world practice. PROTECT is unblinded and compares the incidence of stent thrombosis and late clinical events in a broad patient population with two widely used drug-eluting stents with very different potency profiles and vessel

healing characteristics: the Endeavor zotarolimus-eluting stent (E-ZES; Medtronic, Inc) and the Cypher sirolimus-eluting stent (C-SES; Cordis, Johnson & Johnson).[16,17] Both devices prevent restenosis, yet with different anti-proliferative potency.[18] Therefore, the key design element of PROTECT was the selection of two drug-eluting stent systems with different site-specific vascular healing responses, with the E-ZES being more similar to the vascular healing response after bare-metal stent implantation.[16,17] Pooled analysis of the E-ZES data showed that the rates of stent thrombosis in long-term follow-up were low.[19] Randomised studies comparing E-ZES stents to other drug-eluting stents were not, however, designed to compare stent thrombosis, or examine late outcomes per se.[18] External validity was sought by enrolling a broad group of patients and lesions, including stable and acute coronary syndrome patients with single-vessel or multivessel disease, and a mix of simple and complex lesions. We aimed to see if E-ZES was better than C-SES with respect to incidence of definite or probable stent thrombosis at 3 years after coronary stent implantation.

## Methods

### Study design and patients

PROTECT is a randomised, open-label, two-arm, multinational superiority trial, with the hypothesis being that E-ZES was superior to C-SES in respect of definite or probable stent thrombosis at 3 years, with a prospective randomised open-label blinded-endpoints design.[20]

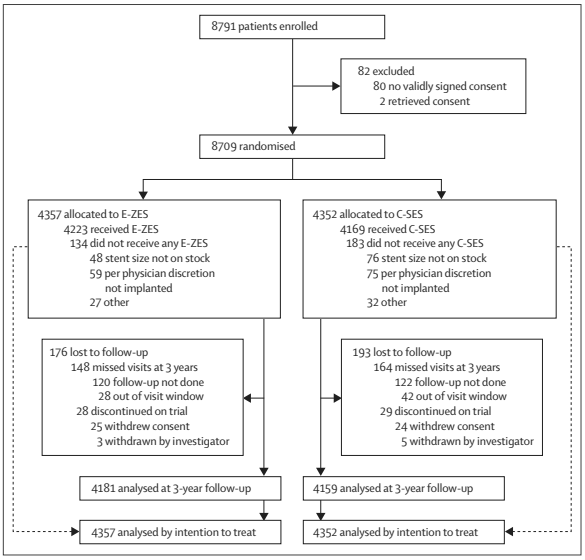


***Figure 1:*** **Trial profile**
C-SES=cypher sirolimus-eluting stent. E-ZES=endeavor zotarolimus-eluting stent. *No screening log was required for this trial.

The trial involved 196 participating hospitals in 36 countries across five continents.[15] Patients aged 18 years or older undergoing elective, unplanned, or emergency procedures in native coronary arteries were eligible for enrolment. Eligible patients provided written informed consent. Study design has been described previously.[15] Patients who had had bare-metal stent implantation in the preceding 12 months, a previous drug-eluting stent, or brachytherapy were excluded. The protocol was approved by the institutional ethical committee and/or centralised national ethical board in accordance with local regulations.

### Randomisation

Patients were randomly assigned to a stent type (1:1 ratio) shortly before or during the procedure after signed patient informed consent was obtained and all protocol inclusion and exclusion criteria were confirmed. Randomisation was stratified per centre with varying block sizes of four, six, or eight patients, and concealed with a central telephone-based or web-based allocation service. Patients and investigators were aware of treatment assignment. Assignment was concealed to the clinical event committee, core lab staff responsible for ECG and angiogram analyses, data management, and statistical analysis, and sponsor staff, excluding a small number responsible for vigilance reporting.

### Procedures

Treatment of coronary lesions was done in accordance with the manufacturer's instructions and local or national guidelines. Antiplatelet therapy with aspirin and clopidogrel (75 mg) or another thienopyridine derivative was started 3 days before the procedure or through a loading dose (clopidogrel 300–600 mg or its equivalent for other thienopyridine) for patients not yet taking these medications. Post procedure, aspirin was prescribed indefinitely and thienopyridine therapy for a minimum of 3 months up to 12 months, according to guidelines,[21] or for longer as per the physician's decision. Prolongation or reinstitution of thienopyridine therapy was allowed where clinically ated.

Three independent clinical contract research organisations (CROMSOURCE, Kraainem, Belgium; Pacific Clinical Research Group, Mosman, NSW, Australia; Vibgyor Scientific Research, Ahmedabad, India) were responsible for data collection, source document verification of all reported events, and on-site monitoring. Sites in the USA and Canada were monitored by Medtronic monitors. An electronic case report form (MedNet Solutions, Minneapolis, MN, USA) allowed paperless collection of the data entered directly by investigators and storage in an electronic web-based database.

Baseline characteristics, including angiographic characteristics, were site reported. All deaths and all triggers

for suspected myocardial infarction, stent thrombosis, or bleeding were adjudicated by the clinical events committee, comprising cardiologists who were not participating in the study and were not aware of the assigned treatment, and who had access to case records as provided by the investigators and source documents such as angiograms, electrocardiographs, autopsy reports, and discharge letters. Revascularisations and strokes (not related to a bleeding) were not adjudicated.

Cardiac biomarker data (creatine kinase, creatine kinase myocardial-band if creatine kinase was outside of the normal range, and troponin) were to be obtained within 72 h of the procedure and at least once after the procedure. Centres were instructed to report all obtained biomarker values for event adjudication. A 3-year follow-up visit with electrocardiograph was mandatory. Patient informed consent and source documentation of all reported events were monitored in all patients. Other data monitoring was done in 30% of randomly selected patients at all participating centres.

### Statistical analysis

The primary outcome was the composite of definite or probable stent thrombosis, according to the Academic Research Consortium definition,[22] at 3 years post-procedure in the intention-to-treat population. The main secondary outcomes were chosen to identify sequelae of stent thrombosis that would be of greatest concern to patients,[6] and included combinations of death and myocardial infarction at 3 years in the intention-to-treat population: (1) total death and large non-fatal myocardial infarction, (2) total death and non-fatal myocardial infarction, (3) cardiac death and large non-fatal myocardial infarction, and (4) cardiac death and non-fatal myocardial infarction. Cardiac death was defined according to the Academic Research Consortium definition as any death unless an unequivocal non-cardiac cause could be established.[22] Myocardial infarctions are reported according to the historical WHO and the Academic Research Consortium[22] (or 2007 Universal[23]) definitions. By contrast with the WHO definition, which is based on total creatine kinase measurements, the Academic Research Consortium definition primarily applies the more specific, but also more sensitive, troponin for the identification of myocardial injury.[24] For the primary endpoint of stent thrombosis, the Academic Research Consortium[22] criteria for myocardial infarction were applied. The WHO definition was used for the related composite endpoints to be consistent with other contemporary studies comparing drug-eluting stents.[24]

A large myocardial infarction was defined as acute ST-elevation myocardial infarction, new pathological Q-waves not present on the baseline electrocardiograph, or creatine kinase more than five times the upper limits of normal. Other secondary outcomes have been listed previously.[15] We obtained prospective data on bleeding complications, according to the Thrombolysis In Myocardial Infarction criteria,[25] using a descriptive form that included bleed location, provocation of bleeding, and results of bleeding. Lesion success was defined as the attainment of less than 50% residual stenosis of the target lesion with any percutaneous method; device success as the attainment of less than 50% residual stenosis of the target lesion with only the assigned device; and procedure success as the attainment of less than 50% residual stenosis of all the target lesions and no inhospital major adverse cardiac events.

The sample size was calculated assuming an incidence of stent thrombosis of 2·5% for the C-SES arm and 1·5% for the E-ZES arm (relative risk 0·60) at 3 years.[15] A sample size of 8800 patients would provide statistical power of 90%, with a 2-sided α level of 0·05 assuming no more than 5% lost to follow-up.

Dichotomous and categorical variables are reported as counts and percentages; between-group differences were assessed with Fisher's exact test for dichotomous variables and Cochran-Mantel-Haenszel Modified Ridit Scores for categorical variables. Continuous variables are

| | E-ZES stent (n=4357) | C-SES stent (n=4352) | p value |
|---|---|---|---|
| Age (years) | 62·3 (10·6) | 62·1 (10·7) | 0·50 |
| Male sex | 3340/4357 (77%) | 3308/4352 (76%) | 0·48 |
| Body-mass index (kg/m$^2$) | 27·8 (4·4) | 27·9 (4·5) | 0·24 |
| Diabetes mellitus | 1174/4357(27%) | 1236/4352 (28%) | 0·13 |
| Insulin dependent | 285/4357 (7%) | 323/4352 (7%) | 0·11 |
| Hypertension | 2814/4357 (65%) | 2759/4352 (63%) | 0·26 |
| Hyperlipidaemia | 2694/4357 (62%) | 2734/4352 (63%) | 0·34 |
| History of smoking | 2515/4357 (58%) | 2500/4352 (57%) | 0·80 |
| Current smoker | 1084/4357 (25%) | 1098/4352 (25%) | 0·71 |
| Premature coronary artery disease in first-degree relative (n=7540) | 1288/3768 (34%) | 1312/3772 (35%) | 0·59 |
| Previous myocardial infarction | 884/4357 (20%) | 907/4352 (21%) | 0·53 |
| Previous coronary artery bypass graft | 199/4357 (5%) | 224/4352 (5%) | 0·21 |
| Previous percutaneous coronary intervention | 534/4357 (12%) | 556/4352 (13%) | 0·48 |
| Previous stroke | 133/4357 (3%) | 136/4352 (3%) | 0·85 |
| Procedure indication | | | |
| All (acute) myocardial infarctions | 1123/4357 (26%) | 1130/4352 (26%) | 0·85 |
| ST elevation myocardial infarction | 356/4357 (8%) | 384/4352 (9%) | 0·28 |
| Non-ST-elevation myocardial infarction | 767/4357 (18%) | 746/4352 (17%) | 0·57 |
| Unstable angina | 796/4357 (18%) | 842/4352 (19%) | 0·21 |
| Stable angina | 2156/4357 (49%) | 2101/4352 (48%) | 0·27 |
| Silent ischaemia | 282/4357 (6%) | 279/4352 (6%) | 0·93 |
| Left ventricular ejection fraction (%; n=4489) | 58·8% (12·6) | 58·3% (12·6) | 0·17 |
| Serum creatinine (μmol/L; n=8152) | 87·6 (31·5) | 88·3 (38·4) | 0·37 |
| Complex patients* | 2526/4357 (58%) | 2528/4352 (58%) | 0·93 |

Data are n/N (%) or mean (SD). E-ZES=Endeavor zotarolimus-eluting stent. C-SES=Cypher sirolimus-eluting stent. *Defined as placement of a stent in a patient with at least one of the following clinical or lesion characteristics: renal insufficiency (creatinine level ≥140 μmol/L [1·6 mg/dL]), ejection fraction <30%, acute myocardial infarction ≤72 h, more than one lesion per vessel, more than two vessels with stents, lesion length >27 mm, bifurcation lesion, lesion in bypass graft, in-stent restenosis, unprotected left main artery, lesion with thrombus, or total occlusion.[26]

***Table 1:*** **Patient characteristics at baseline**

| | E-ZES stent (n=4357 patients; n=6151 lesions) | C-SES stent (n=4352 patients; n=6140 lesions) | p value |
|---|---|---|---|
| **Lesion characteristics** | | | |
| Vessel location (by lesion) | .. | .. | 0·13 |
| Left anterior descending | 2901/6151 (47%) | 2827/6140 (46%) | |
| Left circumflex | 1416/6151 (23%) | 1380/6140 (22%) | |
| Right coronary artery | 1776/6151 (29%) | 1851/6140 (30%) | |
| Left main | 43/6151 (<1%) | 61/6140 (1%) | |
| Bypass graft | 15/6151 (<1%) | 21/6140 (<1%) | |
| Restenosis after previous PTCA | 18/6150 (<1%) | 26/6140 (<1%) | 0·23 |
| In-stent restenosis | 63/6150 (1%) | 65/6140 (1%) | 0·86 |
| Chronic total occlusion* | 177/6149 (3%) | 168/6139 (3%) | 0·66 |
| Bifurcation | 1038/6149 (17%) | 977/6139 (16%) | 0·15 |
| Moderate or severe calcification (*vs* none or mild) | 1708/6149 (28%) | 1851/6139 (30%) | 0·004 |
| Moderate or severe tortuosity (*vs* mild) | 1394/6146 (23%) | 1414/6139 (23%) | 0·65 |
| TIMI flow 0 or 1 | 956/6149 (16%) | 887/6139 (14%) | 0·09 |
| Thrombus | 467/6149 (8%) | 486/6139 (8%) | 0·52 |
| ACC/AHA lesion class B2/C | 3300/6147 (54%) | 3421/6139 (56%) | 0·024 |
| Reference vessel diameter (mm) | 2·98 (0·47) | 2·96 (0·47) | 0·031 |
| Minimum luminal diameter (mm) | 0·5 (0·4) | 0·5 (0·4) | 0·98 |
| Diameter stenosis (%) | 82·8 (13·0) | 82·8 (12·8) | 0·80 |
| Lesion length (mm) | 17·7 (9·3) | 17·7 (9·0) | 0·73 |
| **Procedure characteristics** | | | |
| Number of vessels treated per patient | 1·20 (0·45) | 1·20 (0·46) | 0·46 |
| Number of lesions treated per patient | 1·40 (0·71) | 1·39 (0·71) | 0·85 |
| Number of stents per patient | 1·63 (0·99) | 1·59 (0·96) | 0·06 |
| Total stent length per patient (mm) | 31·28 (20·80) | 31·20 (20·77) | 0·86 |
| Number of stents per lesion | 1·16 (0·49) | 1·13 (0·46) | 0·001 |
| Lesions with predilatation | 4152/6151 (68%) | 4262/6140 (69%) | 0·023 |
| Periprocedure medication | .. | .. | .. |
| Unfractionated heparin | 4011/4356 (92%) | 4003/4351 (92%) | 0·91 |
| Low-molecular-weight heparin | 216/4356 (5%) | 234/4351 (5%) | 0·38 |
| Direct thrombin inhibitor | 182/4356 (4%) | 167/4351 (4%) | 0·44 |
| Glycoprotein IIb/IIIa inhibitor | 780/4356 (18%) | 799/4351 (18%) | 0·60 |
| Post-procedure characteristics | .. | .. | .. |
| Residual stenosis (%) | 1·9 (9·2) | 2·2 (10·1) | 0·10 |
| TIMI 2/3 | 6116/6151 (99%) | 6104/6139 (99%) | 1·00 |
| Lesion success† | 6032/6055 (>99%) | 6006/6044 (99%) | 0·06 |
| Device success‡ | 5869/6055 (97%) | 5773/6044 (96%) | <0·0001 |
| Procedure success§ | 4145/4272 (97%) | 4135/4266 (97%) | 0·80 |

Data are n/N (%) or mean (SD). E-ZES=Endeavor zotarolimus-eluting stent. C-SES=Cypher sirolimus-eluting stent. PTCA=percutaneous coronary angioplasty. TIMI=thrombolysis in myocardial infarction. ACC/AHA=American College of Cardiology/American Heart Association. *TIMI 0, no unstable angina, no myocardial infarction within 72 h. †Attainment of less than 50% residual stenosis of the target lesion with any percutaneous method. ‡Attainment of less than 50% residual stenosis of the target lesion with only the assigned device. §Attainment of less than 50% residual stenosis of all the target lesions and no in-hospital major adverse cardiac events.

***Table 2:*** **Baseline lesion and procedure characteristics**

| | E-ZES stent (n=4357) | C-SES stent (n=4352) | p value |
|---|---|---|---|
| Aspirin | 4251 (98%) | 4253 (98%) | 0·72 |
| Clopidogrel | 4278 (98%) | 4271 (98%) | 0·81 |
| Ticlopidine | 10 (<1%) | 9 (<1%) | 1·00 |
| Other antiplatelet and/or antithrombin agent | 137 (3%) | 155 (4%) | 0·29 |
| Dual antiplatelet therapy* | 4199 (96%) | 4195 (96%) | 1·00 |

Data are number of patients (%). E-ZES=Endeavor zotarolimus-eluting stent. C-SES=Cypher sirolimus-eluting stent. *Aspirin and thienopyridine.

***Table 3:*** **Use of antiplatelet and antithrombin medications at discharge**

reported as means (SD) and were compared with the use of a two-sample t test. We did the analysis according to the intention-to-treat principle in the entire enrolled study population. We used the Kaplan-Meier method to study the time to clinical outcomes and applied the log-rank test to time-to-event between groups. We also analysed clinical events in the same manners for early (0–1 month), late (1 month to 1 year), and very late (more than 1 year) time intervals, and for combined early and late (0 to 1 year) time intervals as prespecified in the statistical analysis plan. For all outcomes, a two-sided p value lower than 0·05 represented statistical significance. We prespecified 12 subgroups in the statistical analysis plan for tests of interaction with treatment on the primary outcome. We did these tests using logistic regression, with the main effect and a variable generated by multiplying the status of randomised treatment group by the status of the subgroup (interaction term) where a two-sided p value of less than 0·05 on this interaction term would be interpreted as a signal of possible heterogeneity of the treatment effect within the subgroup. We made no formal adjustment for multiple testing. We did the analyses with SAS, version 9.2 (SAS Institute Inc, Cary, NC, USA). This trial is registered with Clinicaltrials.gov, number NCT00476957.

### Role of the funding source

Project management for PROTECT was the responsibility of Medtronic Bakken Research Center (Maastricht, the Netherlands) and was sponsored by Medtronic, Inc (Santa Rosa, CA, USA). The Steering Committee designed the study, in collaboration with the sponsor. An independent academic research organisation (Cardialysis, Rotterdam, the Netherlands), blinded to the patients' study stent assignment, was responsible for the organisation of meetings involving the clinical events committee and data safety monitoring board, and for the data analysis. Access to the unblinded database was provided to a limited number of Medtronic staff not involved in the study for vigilance and regulatory reporting requirements. Members of the Steering Committee wrote the manuscript and vouch for the completeness and accuracy of the data gathering and analysis. The authors were not restricted from disclosing the study results. All data collection (except for sites in Canada and the USA where the sponsor's staff did the monitoring visits), data analysis, data interpretation, and writing of the report were done by independent groups, and the sponsor had only oversight

of these activities. The corresponding author had full access to all data in the study and final responsibility to submit for publication.

## Results

Between May 21, 2007 and Dec 22, 2008, we recruited 8791 patients from 36 recruiting countries (appendix). Two patients withdrew consent before the procedure; for 80 others the consent was not validly signed. In total, 8709 patients provided a valid signed consent and were eligible for inclusion in the analysis: 4357 were randomly assigned to receive E-ZES (6151 lesions) and 4352 patients to receive C-SES (6140 lesions; figure 1). 8340 (95·8%) of patients were available for follow-up at 3 years.

The baseline clinical characteristics were similar between the E-ZES and C-SES groups (table 1). 2253 (26%) patients presented with (acute) myocardial infarction, 2410 (28%) had diabetes, and 5054 (58%) were classified as complex. Lesion characteristics were similar between groups with the exception of moderate to severe calcification and B2/C lesions, which were more common in the C-SES group, and reference vessel diameter, which was smaller in the C-SES group (table 2). Procedure characteristics were similar between groups, with the exception of number of stents per lesion, which was greater in the E-ZES group, device success, which was higher in the E-ZES group and use of predilatation, which was higher in the C-SES group (table 2). The use of antiplatelet drugs at discharge and at all follow-up intervals was similar in both groups (table 3, figure 2). Dual antiplatelet therapy was used in 8402 (96%) patients at discharge, 7456 (88%) at 1 year, 3041 (37%) at 2 years, and 2364 (30%) at 3 years.

The primary outcome of definite or probable stent thrombosis at 3 years did not differ (table 4 and figure 3A). The rate of definite or probable stent thrombosis was similar over the first 30 days (figure 4), but was higher for E-ZES between 31 and 360 days (figure 4), and higher for C-SES between 1 and 3 years (figures 4 and 5A). No significant interactions were noted between stent type and any of the prespecified subgroups, with the exception of geographic region and multivessel disease (figure 6).

In a post-hoc analysis, the primary endpoint did not differ significantly between the two treatment groups in patients in North America (Medtronic-monitored sites) and patients in the other regions (non Medtronic-monitored sites; p value for interaction=0·397).

Rates of death or large non-fatal myocardial infarction did not differ between groups, nor did any of the various composites of death or myocardial infarction or other secondary outcomes (death, myocardial infarction, stroke, or major bleeding; table 4, figure 3B). However, the rate of definite stent thrombosis was lower with E-ZES, while rates of target-lesion revascularisation and target-vessel revascularisation were lower with C-SES than with E-ZES (table 4, figures 3C, 3D). The rate of target-vessel revascularisation was lower with C-SES than with E-ZES up to 1 year but higher than with E-ZES from 1 to 3 years (figure 5D).

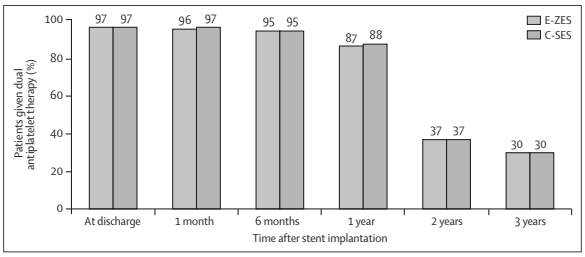


*Figure 2:* **Use of dual antiplatelet therapy from hospital discharge to 3 years**
E-ZES=Endeavor zotarolimus-eluting stent. C-SES=Cypher sirolimus-eluting stent. No significant difference was noted between groups at any timepoint.

| | E-ZES stent (n=4357) | C-SES stent (n=4352) | Hazard ratio (95% CI)* | p value |
|---|---|---|---|---|
| **Primary endpoint** | | | | |
| Definite or probable stent thrombosis† | 61 (1·4%) | 75 (1·8%) | 0·81 (0·58–1·14) | 0·22 |
| **Main secondary endpoints** | | | | |
| Total death and large non-fatal MI | 225 (5·3%) | 255 (6·0%) | 0·88 (0·73–1·05) | 0·16 |
| Total death and non-fatal MI | 331 (7·7%) | 360 (8·4%) | 0·92 (0·79–1·06) | 0·25 |
| Cardiac death and large non-fatal MI | 157 (3·7%) | 174 (4·1%) | 0·90 (0·72–1·11) | 0·33 |
| Cardiac death and non-fatal MI | 265 (6·2%) | 282 (6·6%) | 0·94 (0·79–1·11) | 0·45 |
| **Other secondary endpoints** | | | | |
| All deaths | 181 (4·2%) | 186 (4·4%) | 0·97 (0·79–1·19) | 0·76 |
| Cardiac death | 109 (2·6%) | 105 (2·5%) | 1·03 (0·79–1·35) | 0·81 |
| MI‡ | 179 (4·2%) | 203 (4·8%) | 0·88 (0·72–1·08) | 0·21 |
| Large MI | 64 (1·5%) | 85 (2·0%) | 0·75 (0·54–1·04) | 0·08 |
| MI§ | 625 (13·8%) | 628 (13·9%) | 1·00 (0·89–1·12) | 1·00 |
| Definite stent thrombosis† | 31 (0·7%) | 51 (1·2%) | 0·61 (0·39–0·95) | 0·03 |
| Probable stent thrombosis† | 30 (0·7%) | 25 (0·6%) | 1·20 (0·70–2·03) | 0·51 |
| Possible stent thrombosis† | 68 (1·6%) | 68 (1·6%) | 1·00 (0·71–1·39) | 0·98 |
| Definite or probable or possible stent thrombosis† | 127 (3·0%) | 139 (3·3%) | 0·91 (0·72–1·16) | 0·45 |
| Target lesion revascularisation | 249 (5·6%) | 156 (3·5%) | 1·65 (1·34–2·03) | <0·0001 |
| Target vessel revascularisation | 364 (8·2%) | 310 (7·1%) | 1·19 (1·02–1·39) | 0·03 |
| Non-target vessel revascularisation | 347 (8·2%) | 347 (8·2%) | 1·00 (0·86–1·16) | 0·97 |
| MACE | 529 (12·3%) | 461 (10·8%) | 1·16 (1·03–1·32) | 0·02 |
| MACCE | 579 (13·5%) | 507 (11·8%) | 1·16 (1·03–1·30) | 0·02 |
| Stroke | 77 (1·5%) | 72 (1·4%) | 1·04 (0·73–1·50) | 0·81 |
| Bleeding events (TIMI)¶ | 201 (4·7%) | 184 (4·4%) | 1·09 (0·89–1·33) | 0·38 |
| Major | 75 (1·8%) | 67 (1·6%) | 1·12 (0·08–1·55) | 0·51 |
| Major + minor | 108 (2·5%) | 104 (2·5%) | 1·04 (0·79–1·36) | 0·79 |

Data are number of patients (%). E-ZES=Endeavor zotarolimus-eluting stent. C-SES=Cypher sirolimus-eluting stent. MI=myocardial infarction. MACE=major adverse cardiac events. MACCE=major adverse cardiac and cerebrovascular events. TIMI=thrombolysis in myocardial infarction. *Cox model, assuming proportional hazards. †Based on the Academic Research Consortium definition. ‡Based on the extended historical definition. §Based on the Academic Research Consortium definition. ¶TIMI bleed[2] consists of major+minor+minimum.

*Table 4:* **Incidence of clinical outcomes at 3 years according to Kaplan-Meier estimates**

See **Online** for appendix

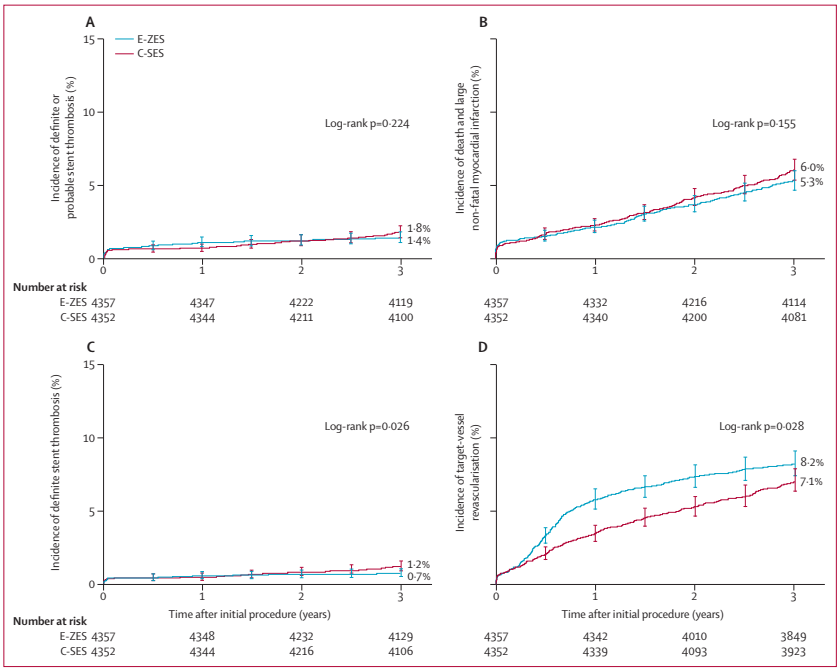


***Figure 3:*** **Incidences of endpoints at 3 years according to Kaplan-Meier estimates**
E-ZES=Endeavor zotarolimus-eluting stent. C-SES=Cypher sirolimus-eluting stent. (A) Definite or probable stent thrombosis according to the Academic Research Consortium definition. (B) Total death and large non-fatal myocardial infarction. (C) Definite stent thrombosis according to the Academic Research Consortium definition. (D) Target vessel revascularisation. Error bars indicate a point-wise two-sided 95% CI.

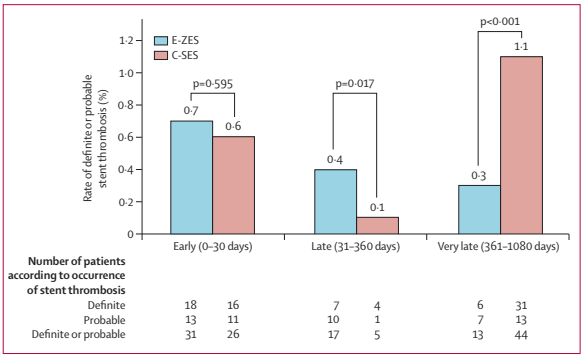


***Figure 4:*** **Rate of definite or probable stent thrombosis by temporal category and treatment group**
E-ZES=Endeavor zotarolimus-eluting stent. C-SES=Cypher sirolimus-eluting stent.

## Discussion

PROTECT is the largest randomised trial to date comparing stent devices in a broad population of patients undergoing coronary stenting in Asia, Australia and New Zealand, Europe, the Middle East, and North and South America (panel); the population did not differ from those reported in worldwide registries, particularly with respect to lesion-related and patient-related prothrombotic characteristics (appendix) and is thought to portray a moderately complex patient population.[27,28] Based on different reported pathophysiological responses to different drug and polymer constituents, the PROTECT study hypothesis was designed as a superiority trial, with E-ZES postulated to be superior to C-SES, for safety outcomes of two drug-eluting stent systems with different potency and vessel healing characteristics.[16,17] This contemporary trial assessed stent thrombosis and patient-oriented safety outcomes instead of focusing primarily on vessel or stent outcomes.[15] No overall difference was noted in event

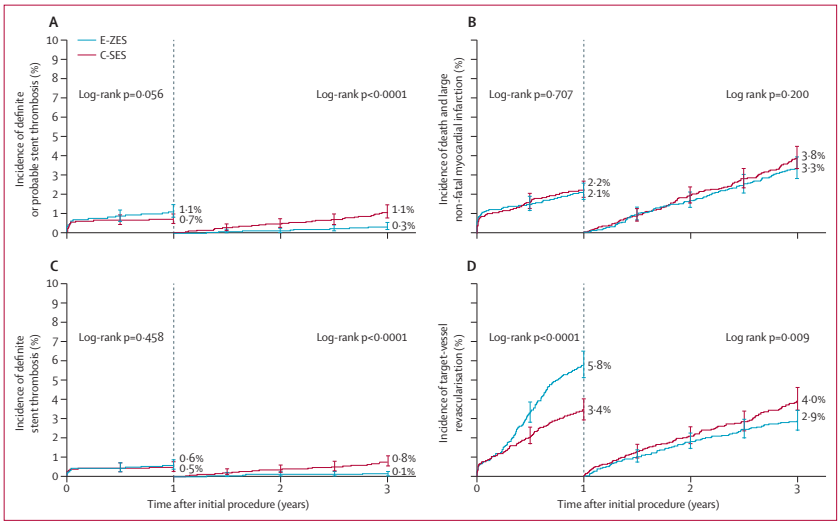


***Figure 5:*** **Incidence of endpoints at 0–1 years and at 1–3 years according to Kaplan-Meier estimates**
E-ZES=Endeavor zotarolimus-eluting stent. C-SES=Cypher sirolimus-eluting stent. (A) Definite or probable stent thrombosis according to the Academic Research Consortium definition. (B) Total death and large non-fatal myocardial infarction. (C) Definite stent thrombosis. (D) Target-vessel revascularisation. Error bars indicate a point-wise two-sided 95% CI.

| | Number of patients | E-ZES rate | C-CES rate | Risk ratio (95% CI) | p value |
|---|---|---|---|---|---|
| Male | 6366 | 0·02 | 0·02 | 0·88 (0·60–1·29) | 0·510 |
| Female | 1974 | 0·01 | 0·02 | 0·59 (0·28–1·24) | 0·159 |
| Age ≥75 years | 1070 | 0·03 | 0·02 | 1·53 (0·69–3·37) | 0·290 |
| Age <75 years | 7270 | 0·01 | 0·02 | 0·70 (0·48–1·02) | 0·062 |
| European | 6075 | 0·02 | 0·02 | 0·97 (0·66–1·44) | 0·894 |
| Non-European | 2265 | 0·01 | 0·02 | 0·48 (0·24–0·95) | 0·031 |
| Diabetes mellitus | 2297 | 0·02 | 0·03 | 0·91 (0·55–1·52) | 0·728 |
| Non-diabetes mellitus | 6043 | 0·01 | 0·01 | 0·75 (0·48–1·18) | 0·210 |
| Renal dysfunction | 235 | 0·03 | 0·05 | 0·50 (0·13–1·97) | 0·315 |
| Non-renal dysfunction | 8105 | 0·01 | 0·02 | 0·84 (0·59–1·18) | 0·310 |
| ACS | 2756 | 0·01 | 0·02 | 0·61 (0·32–1·14) | 0·118 |
| Non-ACS | 5584 | 0·02 | 0·02 | 0·91 (0·61–1·35) | 0·634 |
| AMI | 1190 | 0·02 | 0·02 | 0·86 (0·38–1·99) | 0·732 |
| Non-AMI | 7150 | 0·01 | 0·02 | 0·80 (0·55–1·15) | 0·230 |
| STEMI | 220 | 0·04 | 0·03 | 1·38 (0·32–6·03) | 0·666 |
| Other | 8120 | 0·01 | 0·02 | 0·79 (0·56–1·11) | 0·171 |
| Multivessel | 1586 | 0·01 | 0·03 | 0·43 (0·21–0·90) | 0·021 |
| Single vessel | 5754 | 0·01 | 0·02 | 0·98 (0·67–1·45) | 0·935 |
| RVD ≤2·75 mm | 3343 | 0·02 | 0·03 | 0·69 (0·44–1·08) | 0·103 |
| RVD >2·75 mm | 4997 | 0·01 | 0·01 | 1·01 (0·61–1·68) | 0·968 |
| Lesion length >18 mm | 3701 | 0·02 | 0·03 | 0·65 (0·41–1·01) | 0·053 |
| Lesion length ≤18 mm | 4639 | 0·01 | 0·01 | 1·07 (0·64–1·79) | 0·800 |
| Simple | 3492 | 0·01 | 0·01 | 0·77 (0·41–1·44) | 0·410 |
| Complex | 4848 | 0·02 | 0·02 | 0·83 (0·56–1·23) | 0·343 |



***Figure 6:*** **Risk of definite or probable stent thrombosis in prespecified subgroups after E-ZES or C-SES implantation**
E-ZES=Endeavor zotarolimus-eluting stent. C-SES=Cypher sirolimus-eluting stent. ACS=acute coronary syndrome. AMI=acute myocardial infarction. STEMI=ST-segment elevation myocardial infarction. RVD=reference vessel diameter.

rates for the primary outcome—definite or probable stent thrombosis at 3 years—between E-ZES and C-SES. Rates of death or large myocardial infarction did not differ between groups either. E-ZES reduced the risk of definite stent thrombosis and C-SES reduced the overall risk of target vessel revascularisation. However,

***Panel:* Research in context**

**Systematic review**

To put the results from PROTECT into perspective, we searched Medline for randomised clinical trials comparing E-ZES and C-SES and reporting stent thrombosis rates and clinical outcomes. Seven trials were identified, all of which had been assessed for quality and combined in a very recent meta-analysis, totalling 5983 patients, albeit with follow-up truncated at 1 year and with no information about duration of dual antiplatelet use.[26] The meta-analysis of the seven existing randomised trials showed no difference between C-SES and E-ZES with respect to the incidence of definite stent thrombosis or of any safety outcomes. No difference was noted between stents in terms of cardiac death or myocardial infarction, but revascularisation rate was lower after C-SES than after E-ZES, as measured by target-lesion revascularisation, with target-vessel revascularisation showing no difference between groups.[26] The authors indicated that "all included studies were neither designed nor powered to assess the long-term risk of late and very late (>1 year) definite ST [stent thrombosis], and we await the results of the PROTECT study to resolve the issue. The use of SES provides superior 1-year clinical and angiographic outcomes compared with ZES. However, some long term follow-up studies suggest that ZES are not inferior to or even better than SES with respect to clinical outcomes".

PROTECT includes, in a single randomised study design, a large population of patients (n=8709), with detailed information on dual antiplatelet use (96% at discharge, 88% at 1 year, 37% at 2 years, and 30% at 3 years) and a follow-up of 3 years. Despite this, PROTECT did not find evidence of superiority in stent thrombosis rates between E-ZES and C-SES at 3 years or in the secondary endpoint of death or myocardial infarction between groups. A trial enrolling more than 30 000 patients would have been needed to show a difference between the two treatment groups at 3 years under the present dual antiplatelet therapy. However, according to current practice, definite stent thrombosis was lower at 3 years with E-ZES and efficacy, as measured by target vessel revascularisation (TVR), was slightly superior with C-SES versus E-ZES.

**Interpretation**

PROTECT was designed to compare the incidence of stent thrombosis between two devices with different healing characteristics, and did not find evidence of superiority in definite and probable stent thrombosis rates between E-ZES and C-SES at 3 years and the rates of stent thrombosis were lower than anticipated. However, prespecified time analysis suggests a difference is emerging over time. Differences between devices emerged during the period of 1–3 years, when use of dual antiplatelet therapy was lowest, suggesting a possible important role for the use of dual antiplatelet therapy. Thus information about stent thrombosis rate with a given drug-eluting device has to be assessed with caution and always in perspective of the concomitant dual antiplatelet therapy treatment and duration of follow-up.

rates of definite or probable stent thrombosis, adverse clinical outcomes, and revascularisation were low up to 3 years in both study groups.

PROTECT followed a randomised open-label design, in which patients were treated according to clinical practice and data collection was selective. Despite this simple design, and by contrast with previous stent studies using administrative data,[29–31] the ability to discriminate differences in stent thrombosis was preserved in PROTECT by detailed data collection, high follow-up rates, and independent adjudication focused on stent thrombosis and the key clinical outcomes. As such, the PROTECT trial had a pragmatic design while ensuring high-quality outcome data.[32,33] The main secondary outcome was selected to account for the most important clinical presentations of stent thrombosis—death and large myocardial infarction. By contrast with many previous trials, the size of PROTECT allowed us to assess separately safety and efficacy. Additionally, revascularisation was clinically driven and not triggered by protocol-mandated repeat angiography.

The rate of stent thrombosis noted with E-ZES matched the expected rate (expected 1·5%; observed 1·4%), whereas the rate with C-SES was lower than that anticipated (expected 2·5%; observed 1·8%). PROTECT did not find a significant difference in rates of definite or probable stent thrombosis in the current clinical therapeutic setting at 3 years as the study was not powered to detect a 20% reduction in the risk of definite or probable stent thrombosis. The result cannot be explained by a potentially less complex patient selection, as this would have affected both groups. This finding might have been related to the more common use of continuous dual antiplatelet therapy in both study groups compared with earlier studies of C-SES. Given the seriousness of the clinical manifestation of stent thrombosis, typically death or myocardial infarction, any reduction has clinical relevance. Furthermore, hundreds of thousands of patients worldwide have been implanted with these devices.

Interestingly, the pattern of events over time was distributed differentially, with both devices having the same incidence of early stent thrombosis, but C-SES having fewer late, but more very late, stent thrombosis (definite or probable) than E-ZES. The higher incidence of late stent thrombosis in the E-ZES was driven by an increased rate of probable stent thrombosis. In the C-SES group, the higher incidence of very late stent thrombosis events than that in the E-ZES group was driven by an increased incidence of definite stent thrombosis. It remains speculative whether a different mechanism of myocardial infarction (ie, occlusive restenosis in the E-ZES group *vs* non-covered stent struts in the C-SES group) contributed to this result.

In the context of clinical interest is the low incidence of definite stent thrombosis in the C-SES group between 30 days and 1 year (four events) when use of dual antiplatelet therapy was higher than 85%, and a more than three-fold increase in the rate of definite stent thrombosis per year when use of dual antiplatelet therapy decreased to less than 40%. In the E-ZES group, the incidence of definite stent thrombosis rate per year decreased from late to very late by two-fold despite decreasing regimen of dual antiplatelet therapy, suggesting that use of dual antiplatelet therapy has a different long-term clinical relevance according to the type of stent used. We also noted an increase in definite stent thrombosis at 3 years with C-SES, the most specific thrombotic endpoint.

The analysis at 1 year versus 1–3 years compared the two devices under high (>80%) versus low (<40%) regimen of dual antiplatelet therapy, respectively, and

showed a consistently increased incidence of very late events in the C-SES group, which would be consistent with an increased propensity for very late stent thrombosis due to delayed healing with this device.[6] A similar pattern of events has been noted in long-term follow-up of pooled analyses of small randomised comparisons of C-SES with bare-metal stents.[12,13]

Up to 3 years, and from 1 to 3 years (the period of low use of dual antiplatelet therapy use), the main clinical safety endpoints (composite of total death and large myocardial infarction) paralleled the curves of definite thrombotic events. Follow-up to 5 years, currently in progress, will show whether curves of definite and definite or probable stent thrombosis further diverge and will translate into differences in clinical safety outcomes.

A very late increase of target-vessel revascularisation with C-SES was noted, which might be driven by the increased incidence of definite stent thrombosis. PROTECT at 3-years follow-up suggests that there is a trade-off between revascularisation and stent thrombosis with these two drug-eluting stents, albeit smaller in magnitude than that between bare-metal stents and early drug-eluting stents and potentially modulated by long-term use of dual antiplatelet therapy.[34] The optimum duration of dual antiplatelet therapy after drug-eluting stent placement cannot be identified from PROTECT, as duration of dual antiplatelet therapy was not assigned randomly. The value of prolonged dual antiplatelet therapy is being investigated in ongoing large trials such as the Dual Antiplatelet Therapy Study.[35] PROTECT data suggest that the optimum duration of dual antiplatelet therapy might vary according to the device characteristics.

There are a number of limitations to this study. Operators were aware of the assigned study device and might have chosen specific treatment strategies or procedural techniques on the basis of their experience with these devices. Patients were not masked to the study device; however, the main study outcomes were chosen for their objectivity and were adjudicated by an independent, blinded clinical events committee. Reflecting clinical practice, vessel and lesion characteristics were not analysed by a core laboratory, and revascularisation events were not adjudicated centrally. Overall, the study procedures in PROTECT were designed to represent current practice.[32] Since the trial was designed, one of these devices is no longer manufactured. The long-term clinical outcomes reported are, however, still very relevant to the millions of patients worldwide permanently implanted with either of these devices.

This trial is unique in drug-eluting stent trials through its hypothesis-driven concept, investigating the safety of two drug-eluting stents with different vessel healing characteristics and antiproliferative properties; through its pragmatic design, focused on patient-oriented clinical outcomes; and from its size, designed to be powered for small absolute differences in rates of stent thrombosis.

**Contributors**

EC, WW, LM, and PGS were the principal investigators, participated in the study design and data analysis, and cowrote the manuscript. VK, KP, RG, CB, and JG participated in data collection, critical revision of the manuscript. EB participated in the statistical analysis and data analysis. PV, EMcF, BJ, and FvL participated in study organisation, data collection, and provided comments on the report. PWS and WWO provided scientific advice and critical revision of the manuscript.

**Conflict of interest**

LM has been a consultant for Medtronic and Cordis and has received research grants (to institution) from Medtronic, Cordis, Boston Scientific, Abbott, Bristol-Myers Squibb, Dandified-Adventist, Eli Lilly, Daichii. CB has been advisor and speaker for Bayer, AstraZeneca, and Sanofi-Aventis. EMcF has received honoraria from Medtronic, Abbott Vascular, and Cordis for participation in Clinical Events Committees and travel grants from Medtronic, Boston Scientific, AstraZeneca, Sanofi-Aventis, and Boehringer Ingelheim. PGS has received research grants (to institution) from NYU School of Medicine, Sanofi-Aventis, Servier; has been a consultant or in advisory board for Ablynx, Amarin, Astellas, Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo-Lilly, GlaxoSmithKline, Medtronic, MSD, Novartis, Pfizer, Roche, Sanofi-Aventis, Servier, and The Medicines Company; and has stockholding for Aterovax. All other authors declare that they have no conflicts of interest.

**Acknowledgments**

We thank Tessa A M Rademaker-Havinga (Cardialysis, Rotterdam, the Netherlands) who assisted with the statistical programming. Sophie Rushton-Smith assisted with preparation of the figures and references, and editing of the manuscript, and was funded by Medtronic Inc.

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# APPENDIX 1.4

## FAME and coronary stent investigations: is there a kink in the wire?

Cutlip DE, Mehran R, Vranckx P. *J Am Coll Cardiol*.

2010;**57**:115-6; author reply 116. [**technical report, only provided as a reference**]

We read with interest the report by Tonino et al. (1) on behalf of the FAME (Fractional Flow Reserve [FFR] Versus Angiography in Multivessel Evaluation) investigators. They concluded that "angiography is inaccurate in assessing the functional significance of a coronary stenosis when compared with the FFR, not only in the 50% to 70% category but also in the 70% to 90% angiographic severity category" (1). The FAME study, including this more detailed analysis, provides a strong foundation for moving toward ischemia-directed stent therapy in patients with symptomatic coronary artery disease (2,3), and we agree with this in principle.

We are concerned, however, with the lack of clarity for how the percent diameter stenosis was determined in this study and whether the conclusions are related to the fallibility of angiography or the methods of angiographic analysis. Although it is valid to consider a visual estimate of angiographic severity for purposes of the FAME trial, it should be clarified if this is the case before conclusions regarding the value of angiography are made. It is well known that visual estimates generally overestimate lesion severity as determined by quantitative coronary angiographic (QCA) methods. Furthermore, QCA lesion severity has been the standard for determination of clinically indicated revascularization in coronary stent clinical trials, on which the safety and effectiveness of these devices are based (4). With this background, more detailed information on the angiographic analysis used in FAME becomes of interest. We did not find this information in any of the original FAME publications. We kindly request that the FAME investigators provide the details of how angiographic severity was determined. If QCA was not available, what methods were used to verify standardization of reporting among investigators? We also invite the FAME investigators to express their expert opinion if this additional information would impact their conclusions (if divergent from the index paper) and what would be the repercussions for clinical practice and future stent investigations, if any.

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# [ PART 2 ]

## PATENCY-2 : CONCOMITANT PHARMACOLOGICAL ENVIRONMENT. BALANCING PREVENTION OF ISCHEMIC COMPLICATIONS AND BLEEDING.

# CHAPTER 2.1

## Does the site of bleeding matter. A stratified analysis on location of TIMI-Bleedings and their impact on 12 month outcome in patients with ST-segment elevation myocardial infarction

Vranckx P, Valgimigli M, Gianluca Campo G, Percoco G, Bolognese L,Vassanelli C, Colangelo S, de Cesare N, E. Rodriguez E, Ferrario M, Moreno R, Piva T, Sheiban I, Pasquetto G, Prati F, Nazzaro MS, Parrinello G, Ferrari

R. *EuroIntervention* 2012: 15;**8**:71-8 [**original research paper**]

# Does the site of bleeding matter? A stratified analysis on location of TIMI-graded bleedings and their impact on 12-month outcome in patients with ST-segment elevation myocardial infarction

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**KEYWORDS**

- haemorrhage
- access-site
- percutaneous coronary intervention
- acute myocardial infarction

## Abstract

**Aims:** While bleeding in patients with STEMI undergoing primary percutaneous coronary intervention (pPCI) is known to be associated with poor outcomes, the differential prognostic impact of access-site related versus non access-site related bleedings is unknown. We aimed to assess the relative impact of access-site related bleeding, as compared to non access-site related, on 12-month clinical outcome in patients undergoing intervention for STEMI.

**Methods and results:** Thirty-day bleeding endpoints, stratified into access-site versus non access-site, were examined according to the TIMI scale in 744 patients with STEMI enrolled in the MULTISTRATEGY trial. TIMI major or minor bleeding complications occurred in 56 (7.5%) patients within 30 days, 46% had an access-site related bleed and 34% required blood transfusion. Bleeding severity and the need for transfusion were equally distributed between site access- versus non-site access-related bleeds. After adjustment, patients with any TIMI rated bleed were more likely to die or develop recurrent MI within 12 months (HR 2.1 [95% CI: 1.13-3.8]; p=0.02). This ratio was entirely driven by non-site access-related bleeds (adjusted HR: 2.66 [95% CI: 1.21-5.8]; p=0.007), whereas site-access bleeds were not associated with worse outcomes (HR: 0.74 [95% CI: 0.16-3.4]; p=0.70).

**Conclusions:** While bleeds of any TIMI severity within 30 days were independently associated with worse cardiovascular outcomes at 12 months, thus confirming previous analyses, this relationship was entirely driven in our study by non access-site related haemorrhagic events. Investigation on whether the site of bleeding complications may preferentially impact cardiovascular outcomes is warranted.

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## Introduction

The combined use of anticoagulants, potent anti-platelet agents (e.g., glycoprotein IIb/IIIa [Gp IIb/IIIa] receptor inhibitors[1-7]) and an invasive strategy in patients with STEMI reduces ischaemic coronary events but also increases bleeding[8-9].

The Janus (Roman god of gates and doors, of beginnings and endings, represented as a double-faced head looking in opposite directions) nature of refined concomitant antithrombotic therapies may reveal itself under highly (pro−) thrombogenic conditions, such as contemporary pPCI. On the one hand, periprocedural and deferred (athero-) thrombotic events are a real concern while stenting in a vessel with visible thrombus, especially when using active stents10. On the other hand, we face bleeding and its attendant risks of death and MI[8,11].

There is a paucity of data on whether the site of bleeding, access-site related or not, affects cardiovascular outcomes after PCI. This information has relevant clinical and pathophysiological implications. Although not all bleeding can be directly attributed to complications at the procedure access-site, the latter remain a significant factor in post-procedural bleeding[8]. They can largely be prevented by technical refinements during puncture or implementing a routine radial approach. Non access-site bleeding complications mainly reflect co-morbidity and intensity/duration of anti-thrombotic therapy. Thus, strategies to prevent bleeding complications, targeting different pathophysiological components, may have different impacts on preventing access-site versus non access-site bleeding events.

As part of a pre-specified sub-analysis of the MULTISTRATEGY trial, we investigated the relative impact of access-site related bleeding, as compared to non access-site related, on one-year clinical outcome in patients undergoing pPCI.

## Methods

The rationale, design and methodology of the MULTISTRATEGY study have been detailed in a previous publication and are outlined below[12,13]. Briefly, patients were randomly assigned with the use of a two-by-two factorial design to one of four interventional strategies of reperfusion: abciximab with an uncoated stent, abciximab with a sirolimus-eluting stent, tirofiban with an uncoated stent, or tirofiban with a sirolimus-eluting stent. The study protocol, including this pre-specified "bleeding" sub-analysis, was approved by the ethics committee at each institution and was conducted according to the principles of the Declaration of Helsinki. All patients provided written informed consent before enrolment. Follow-up visits were scheduled at one month, four months, eight months and 12 months.

## Study population and study protocol

### PATIENT POPULATION

Patients in the MULTISTRATEGY study were enrolled at 16 centres in Italy, Argentina and Spain. Patients who entered MULTISTRATEGY had to be ≥18 years of age, be admitted for1 chest pain for longer than 30 minutes with either an electrocardiographic ST-segment elevation of 1 mm or greater in two or more contiguous electrocardiogram leads or with a new left bundle-branch block, and2 admission either within 12 hours of symptom onset or between 12 and 24 hours after onset with evidence of continuing ischaemia. The exclusion criteria included administration of thrombolysis in the previous 30 days, major surgery within 15 days, and active bleeding or previous stroke in the last six months.

### CONCOMITANT ANTICOAGULATION TREATMENT

Immediately after checking eligibility criteria and before the visualisation of coronary angiographic anatomy, the local site investigators performed open-label assignments of study treatments via sealed envelopes. Randomisation was achieved with a 1:1:1:1 computer-generated random sequence supplied by an academic statistician, without stratification, in permuted blocks of 30. Either tirofiban or abciximab was administered at first medical contact before an arterial sheath insertion during the angiography procedure. Tirofiban was given as a bolus of 25 µg/kg, followed by an 18- to 24-hour infusion at 0.15 µg/kg/min. Abciximab was administered as a bolus of 0.25 mg/kg, followed by a 12-hour infusion at 0.125 µg/kg/min. Unfractionated heparin (UFH) was given at 40 to 70 U/kg, targeting an activated clotting time of at least 200 seconds. All patients received aspirin (160-325 mg orally or 250 mg intravenously, followed by 80-125 mg/d orally indefinitely) and clopidogrel (300 mg orally and then 75 mg/d for at least three months). Stenting was the default strategy in all patients with a reference vessel diameter of 2.5 mm or larger at visual estimation.

### DATA COLLECTION AND MANAGEMENT

Clinical data were prospectively collected at each site by research nurses or treating physicians using a standardised case report form (CRF). Demographic and clinical characteristics, treatment practices, and hospital outcome data, including information on occurrence and timing of major bleeding, were collected. Medications and procedures received in hospital were categorised into those received during the "first 48 hours of admission (periprocedural)" or those received "anytime during hospitalisation." Independent study monitors employed by the University of Ferrara verified 100% of the data in the CRFs. End points, including bleeding events, were adjudicated and classified by a blinded clinical events committee (CEC). Independent adjudication of an event trigger, including bleeding, was performed separately by two CEC members; in case of disagreement, the opinion of a third member was obtained, and the final decision taken by consensus.

Standardised definitions of all patient-related variables, clinical diagnoses, selected hospital complications, and outcomes were used[2]. In-hospital bleedings were graded according to the TIMI trials criteria[14]. A bleeding complication was defined as major if it was intracranial or if clinically overt signs of haemorrhage were associated with a drop in haemoglobin concentration of more than 5.0 g/dl (or, when a haemoglobin value was not available, an absolute drop in the haematocrit of at least 15%). Minor bleeding was defined as a clinically overt haemorrhage (including that seen on imaging) associated with a fall in haemoglobin concentration of 3.0 to 5.0 g/dl

(or, when a haemoglobin value was not available, a fall in the haematocrit of 9% to <15%). Patients were classified as having received a transfusion if they received whole blood or packed red cells at any point during their index hospitalisation.

TIMI study definitions take into account blood transfusions, therefore haemoglobin and haematocrit values are adjusted by 1 g/dl or 3%, respectively, for each unit of blood transfused. Therefore, the true change in haemoglobin or haematocrit is calculated as follows: if there has been an intervening transfusion between two blood measurements: Δ haemoglobin (Hgb) = [baseline Hgb – post-transfusion Hgb] + [number of transfused units]; Δ haematocrit (Hct) = [baseline Hct – post-transfusion Hct] + [number of transfused units×3][15]. Date and site of each episode of major bleeding were recorded. Bleeding that occurred after coronary artery bypass graft surgery was not included in this analysis.

We defined major life-threatening bleeding as fatal bleeding, intracranial bleeding, intrapericardial bleeding with cardiac tamponade, hypovolaemic shock or severe hypotension due to bleeding and requiring vasoactive drugs or surgery, a decline in the haemoglobin level of 5.0 g/dl or more, or the need for a transfusion of at least four units of red blood cells (RBC).

### STATISTICAL ANALYSIS

Categorical variables are expressed as percentages, and continuous variables are expressed as mean and standard deviation. Baseline characteristics were compared with $\chi^2$ or Fisher exact tests for categorical variables and the t-test for continuous variables.

Kaplan-Meier analysis was used to illustrate 12-month event-free survival for patients with and without combined TIMI major and minor bleeding within 30 days.

We compared unadjusted rates of the composite end point of death and non-fatal recurrent MI among patients with no TIMI "significant" (major/minor: major and minor combined) bleeding and those with TIMI "significant" bleeding severity and separately for the categories of access-site and non access-site related bleeding. To determine the association between access-site and non access-site related bleeding, we constructed separate models for each category. The first model incorporated "access-site related TIMI major/minor bleeds within 30-days" as a time-dependent covariate and used "no access-site related TIMI major/minor bleeds within 30-days" as the reference. The second model incorporated "non access-site related TIMI major/minor bleeds plus unknown (significant drop in haemoglobin without overt bleeding) within 30-days" as a time-dependent covariate and used "no non access-site related TIMI major/minor bleeds plus unknown within 30-days" as the reference.

A Cox proportional hazards model was used to test the association between TIMI major/minor bleeds within 30 days after the PCI and one-year mortality or non-fatal MI while adjusting for confounding demographic and clinical variables. Baseline differences that were not uniformly distributed in patients with and without bleeding complications based on a p-value of 0.1 or less were considered significant and entered into the multivariable model; these differences include gender, diabetes, baseline creatinine clearance, haemoglobin level at presentation, femoral access, intra-aortic balloon pump (IABP) use, KILLIP class greater than one, right coronary artery as target vessel, vessel size (MLD post-PCI) and final TIMI 3 flow, as well as need for transfusion. Age was not separately entered into the model to avoid co-linearity with creatinine clearance, whose formula includes age.

All analyses, carried out based on the intention to treat principle, were performed using STATA, version 9.2 (Stata Corp., College Station, TX, USA).

## Results

Of the 744 patients enrolled in the MULTISTRATEGY trial, 565 (76%) patients were male, and 357 (48%) patients were ≥65 years of age. One hundred and eight (15%) patients suffered from diabetes, and fifteen (3%) patients had documented peripheral artery disease. **Table 1** shows the baseline and angiographic characteristics of the patients stratified based on the occurrence of a TIMI major/minor bleed within 30 days. Patients who bled were older and more often female, with a higher prevalence of diabetes, and they presented more frequently with clinical signs of heart failure than patients without significant bleeding, despite similar left ventricular ejection fraction at transthoracic echocardiogram. A higher proportion of patients who experienced a TIMI major/minor bleed within 30 days had a femoral access approach and the use of an IABP. Interestingly, the peak ACT values did not differ in patients with than those without bleeding complications. Fifteen (2.0%) patients experienced a TIMI major bleed, whereas 41 (5.5%) patients fulfilled the TIMI minor bleeding criteria, such that 56 (7.5%) patients experienced a TIMI major or minor bleed within 30 days. Twenty-three bleeding events (3.1%) were judged as life-threatening by the investigators and none were intracranial or intra-ocular.

The incidence of bleeding within the various categories of TIMI bleeding severity (major, minor and major-minor combined) did not differ between the Abciximab- and Tirofiban-treated patient groups **(Table 2)**. However, significantly more patients in the Abciximab treatment group had a nadir haemoglobin (Hb) value <8.5 g/dl. This was offset by a slight trend towards more transfusion of at least one unit in the Tirofiban-treated patients; however, equal patient numbers were transfused with >2 units of blood in both treatment arms. Access-site bleeding complications were equally represented in both treatment arms.

The location of TIMI major/minor bleeding at 30 days was at the site of the vascular access, including retroperitoneal in 26 (46%) patients, gastrointestinal in eight (14%), genitourinary in six (11%), pericardial in three (5%), pulmonary in three (5%), other sites in three (5%) or without overt bleeding site identified in seven (13%). Nineteen out of 56 (34%) patients with TIMI major/minor bleed within 30 days underwent blood transfusion during the hospitalisation; six (11%) patients required surgery to repair or explore the bleeding site. Approximately half the TIMI major/minor bleeds occurred within 48 hours of the pPCI (data not shown). The severity (major versus minor) of TIMI bleeds is shown in **Figure 1** and did not differ based on location (site-access versus non site-access).

**Table 1. Baseline characteristics in patients with or without TIMI major/minor bleeding within 30 days.**

| Characteristics | TIMI major/minor within 30 days | | |
|---|---|---|---|
| | No | Yes | *p*-values |
| Age (yr) | 63.6±11.8 | 65.5±11.8 | 0.07 |
| Male sex, (%) | 77 | 64 | 0.05 |
| Body Mass Index (kg/m$^2$) | 30.4±39 | 26.6±5 | 0.46 |
| Diabetes, (%) | 14 | 23 | 0.084 |
| Hypertension, (%) | 57 | 63 | 0.74 |
| Current cigarette use, (%) | 37 | 39 | 0.95 |
| Creatinine Clearance (ml/min) | 85.5±37.7 | 73.1±31.7 | 0.017 |
| Hb at presentation (gr/dl) | 13.7±3.2 | 14.7±2 | 0.022 |
| Peripheral vascular disease, (%) | 4 | 2 | 0.24 |
| Prior myocardial infarction (%) | 8 | 7 | 0.92 |
| Prior percutaneous coronary intervention (%) | 6 | 2 | 0.34 |
| Prior coronary bypass surgery (%) | 1 | 0 | 0.89 |
| Prior stroke or transient ischaemic attack (%) | 4 | 9 | 0.32 |
| Killip class ≥II (%) | 15 | 25 | 0.07 |
| Use of intra-aortic balloon pump (%) | 2 | 11 | 0.001 |
| Left ventricular ejection fraction within 48 hours after presentation (%) | 45.5±10 | 45.7±12 | 0.91 |
| Femoral access (%) | 89 | 98 | 0.04 |
| Number of disease vessel (%) | 1.7±0.8 | 1.8±0.9 | 0.23 |
| Infarct-related vessel (%) | | | |
| Left anterior descending coronary artery | 44 | 32 | 0.12 |
| Left circumflex artery | 16 | 11 | 0.41 |
| Right coronary artery | 38 | 54 | 0.03 |
| Left main coronary artery | 1 | 4 | 0.16 |
| Saphenous-vein graft | 1 | 0 | 0.35 |
| TIMI Flow before intervention (%; 0/1/2/3) | 59/7/13/21 | 70/4/7/20 | 0.45 |
| TIMI 3 flow after intervention (%) | 94 | 88 | 0.092 |
| Quantitative coronary analysis | | | |
| Reference vessel diameter, pre (mm) | 2.90±0.55 | 2.98±0.57 | 0.31 |
| MLD, pre | 0.38±0.59 | 0.33±0.63 | 0.61 |
| Reference vessel diameter, post (mm) | 2.92±0.47 | 3.02±0.57 | 0.15 |
| MLD, post | 2.66±0.49 | 2.53±0.78 | 0.07 |

Hb: haemoglobin; MLD: minimal lumen diameter

**Table 2. Thirty-day bleeding endpoint and the individual components as counts and percentages.**

| Outcome at 12 months | Abciximab (n=372) | Tirofiban (n=372) | *p*-values |
|---|---|---|---|
| Death | 17 (4.6%) | 14 (3.8%) | 0.71 |
| Re-infarction | 13 (3.5%) | 17 (4.6%) | 0.57 |
| Death or re-infarction | 30 (8.1%) | 27 (7.3%) | 0.78 |
| Clinical driven target-vessel revascularisation | 28 (7.5%) | 26 (7.0%) | 0.89 |
| Safety analysis at 30 days | | | |
| TIMI major bleed | 6 (1.6%) | 9 (2.4%) | 0.60 |
| TIMI minor bleed | 23 (6.2%) | 18 (4.8%) | 0.52 |
| Fatal bleeds | 0/372 (0%) | 1 (0.3%) | >0.99 |
| Haemodynamic compromise | 10 (2.7%) | 13 (3.5%) | 0.67 |
| Intracranial bleed | 0 | 0 | … |
| Intraocular bleed | 0 | 0 | … |
| Retroperitoneal bleed | 2 (0.5%) | 2 (0.5%) | 0.61 |
| Requiring surgical intervention | 3 (0.8%) | 3 (0.8%) | 0.68 |
| ≥3 g/dl drop in Hb * | 29 (7.8%) | 22 (5.9%) | 0.42 |
| ≥3 g/dl drop in Hb* without observed blood loss | 3 (0.8%) | 4 (1.1%) | 0.99 |
| ≥4/dl drop in Hb * | 19 (5.1%) | 17 (4.6%) | 0.86 |
| ≥4/dl drop in Hb without observed blood loss | 4 (1.1%) | 2 (0.5%) | 0.69 |
| Red blood cell transfusion ≥1 Units | 8 (2.2%) | 14 (3.8%) | *p*=0.28 |
| Red blood cell transfusion ≥2 Units | 8 (2.2%) | 9 (2.4%) | *p*>0.99 |
| Any access-site bleeding | 24 (6.4%) | 28 (7.5%) | 0.66 |
| Hb admission <10 g/dl | 19 (5.1%) | 15 (4.0%) | 0.59 |
| Hb nadir <8.5 g/dl | 15 (4.0%) | 3 (0.8%) | 0.009 |

* Correction for every unit of whole blood/packed cells transfused (one unit is counted for 1 g/dl); SAE: serious adverse events

## IMPACT OF BLEEDS ON 12-MONTH OUTCOMES

In the MULTISTRATEGY trial the overall rate of death and the composite of death or myocardial infarction within 12 months was 4.2% and 7.7% respectively.

In the univariate Cox proportional hazards model, patients with TIMI major or minor bleeds within 30 days had more than a two-fold increase in the composite of death or MI at 12 months (HR: 2.45 [95% CI: 1.21-4.97]; p=0.012) **(Figure 2)**. After adjusting for all potential confounders in the multivariable Cox proportional hazards model, including all clinical and angiographic variables that were not uniformly distributed based on bleeding status as reported in **Table 2**, as well as need for transfusion, TIMI major/minor bleed was still associated with a two-fold increase in the composite of death or MI within 12 months (HR: 2.1 [95% CI: 1.13-3.8]; p=0.02). Similarly, when transfusion was restricted to patients receiving at least two red blood cell units, the multivariable analysis yielded identical results.

When TIMI major or minor bleeding events were stratified based on their location, access-site bleeding complications were not associated

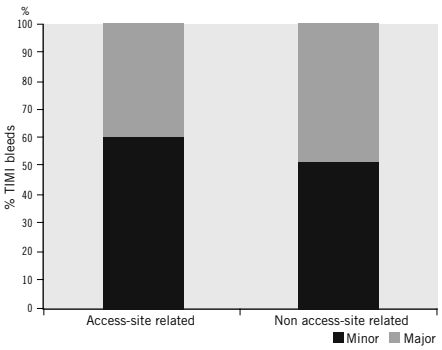


**Figure 1.** *TIMI bleedings stratified, based on site and severity in the MULTISTRATEGY trial. The severity of bleeds according to the TIMI scale did not differ based on the site of haemorrhage.*

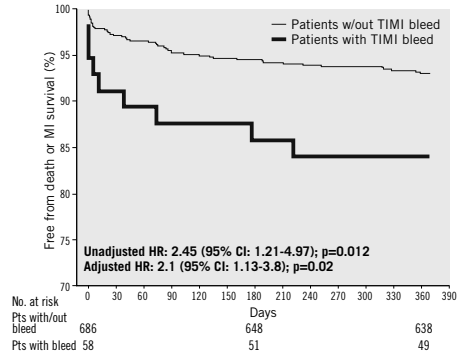


**Figure 2.** *Cumulative Kaplan–Meier estimates of mortality and reinfarction rates during follow-up based on bleeding status. Cumulative risk of death and reinfarction at 370 days in patients with or without TIMI-defined major or minor bleeding complications within 30 days of pPCI. Overall four patients were lost to follow-up between eight and 12 months.*

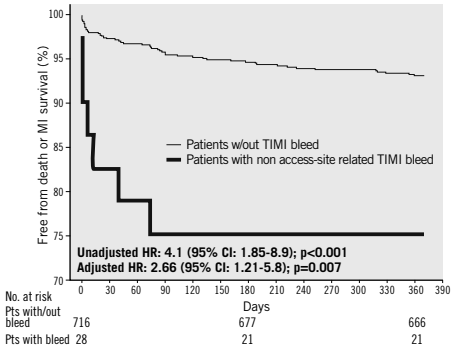


**Figure 3.** *Cumulative Kaplan–Meier estimates of mortality and reinfarction rates during follow-up based on non access-site bleeding status. Cumulative risk of death and reinfarction at 370 days in patients with non-site access-related TIMI major or minor complications or without any bleeds within 30 days of pPCI. Overall four patients were lost to follow-up between eight and 12 months.*

with a worse 12-month outcome (adjusted HR: 0.74 [95% CI: 0.16-3.4]; p=0.70), whereas non access-site related bleeds were associated with a worse 12-month outcome **(Figure 3)**, both after univariate analysis (HR: 4.1 [95% CI: 1.85-8.9]; p<0.001) and multivariable adjustment (HR: 2.66 [95% CI: 1.21-5.8]; p=0.007) **(Figure 4; Table 3)**. Excluding bleeds from unidentified sites yielded identical

**Table 3. Multivariable Cox models for the association between bleeding events and mortality or reinfarction within 12 months.**

| Variables | *p*-values | Wald statistics | Hazard ratios (95%) CI | $\chi^2$ |
|---|---|---|---|---|
| Impact of any TIMI major or minor bleed on death or re-MI at 1 year | | | | 32 |
| Final TIMI 3 | 0.01 | 5.98 | 0.39 (0.18-0.82) | |
| Killip class greater than 1 | 0.02 | 5.16 | 2.1 (1.1-3.7) | |
| Any TIMI major or minor bleeds | 0.02 | 5.07 | 2.1 (1.13-3.8) | |
| LVEF (%) | 0.03 | 4.7 | 0.97 (0.95-0.99) | |
| Creatinine clearance (ml/min) | 0.09 | 2.8 | 0.99 (0.98-1.00) | |
| Impact of site access-related TIMI major or minor bleed on death or re-MI at 1 year | | | | 30 |
| Final TIMI 3 | 0.008 | 7.06 | 0.37 (0.18-0.76) | |
| Killip class greater than 1 | 0.016 | 5.72 | 2.1 (1.15-3.9) | |
| LVEF (%) | 0.03 | 4.54 | 0.97 (0.94-0.99) | |
| Creatinine clearance (ml/min) | 0.06 | 3.29 | 0.99 (0.98-1.00) | |
| Access-site TIMI major or minor bleeds | 0.70 | 0.15 | 0.74 (0.16-3.4) | |
| Impact of non-site access-related TIMI major or minor bleed on death or re-MI at 1 year | | | | 33 |
| Final TIMI 3 | 0.01 | 5.88 | 0.39 (0.19-0.83) | |
| Access-site TIMI major or minor bleeds | 0.007 | 5.46 | 2.66 (1.21-3.4) | |
| LVEF(%) | 0.039 | 4.24 | 0.97 (0.94-0.99) | |
| Killip class greater than 1 | 0.041 | 4.16 | 1.9 (1.03-3.6) | |
| Creatinine clearance (ml/min) | 0.12 | 2.32 | 0.99 (0.98-1.00) | |

The following variables were entered into the models: Creatinine clearance; sex; haemoglobin at presentation; diabetes; KILLIP class coded as dummy variable (one versus greater than one); use of intra-aortic balloon pump; right coronary artery as culprit vessel; final TIMI 3 flow versus lower; minimal lumen diameter post-stenting; left ventricular ejection fraction assessed through transthoracic echocardiogram performed within 48 hours; red blood cell transfusion (coded as dummy variable) together with any; site access only or non-site access only TIMI major or minor bleed. (To avoid co-linearity, age and creatinine clearance, which included ages in the formula, have not been entered simultaneously in the models. The impact of bleeding on 12-month death or MI were identical if age or creatinine clearance were used in the multivariable models).

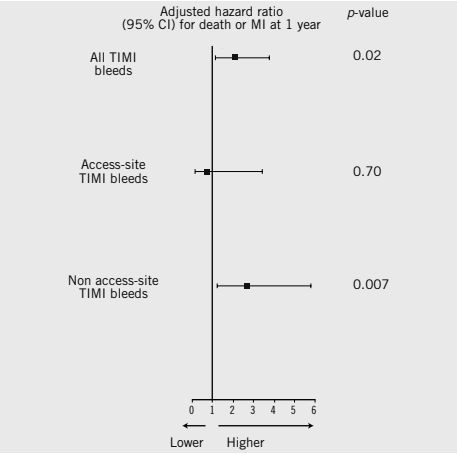


**Figure 4.** *Stratified analysis on the site of bleeding. Adjusted hazard ratios for death or reinfarction within 370 days according to whether any TIMI major/minor bleed (access-site related or non access-site related) occurred within 30 days of pPCI.*

results. Similarly, adding any transfusion or blood transfusion of at least two blood units failed to influence our model (data not shown).

## Discussion

The analysis of the relationship between bleeds within 30-day and 12-month outcomes can be summarised as follows:

1. TIMI major/minor bleed within 30 days were independently associated with worse cardiovascular outcomes, including overall death and non-fatal MI within 12 months, confirming previous analyses.
2. While both severity according to the TIMI scale and the need for RBC transfusion were equally distributed between access-site and non access-site related bleeding events, only the latter were associated with a higher death or MI rate after one year of follow-up in both the univariate and multivariable-adjusted regression analysis.

The main results of the MULTISTRATEGY trial have been reported and discussed elsewhere[13]. The actual sub-analysis implementing the TIMI bleeding grading was pre-specified. The differential clinical impact of bleeding by different classifications among patients with ACS must be recognised[14]. Of interest, the overall incidence of both TIMI major and/or minor bleeding grading events within 30 days on the basis of clinical and laboratory findings was lower in the MULTISTRATEGY trial as compared to the Harmonising Outcomes with Revascularisation and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, and mirror the results of the Tirofiban arm in Ongoing Tirofiban in Myocardial Evaluation (On-TIME) 2 trial[15-18]. These findings may partly be explained by a less strict heparin protocol used in the HORIZONS-AMI trial, which had a target activated clotting time of 250 seconds but reached a median value in the GPI arm of 265 as compared to 232 seconds in our study. Moreover, patients with a recent (within six months), history of active bleeding were not eligible for participation in the MULTISTRATEGY trial[12,13].

In our trial, nearly half of all TIMI major/minor bleeds within 30 days were access-site related, including retroperitoneal bleeds. However, they only independently contributed for about 1% of the deaths observed within 12 months. Our data are consistent with a recent observation by the STEEPLE trial investigators but contrast with the 4% mortality risk attributable to femoral access-related bleeding observed in a large contemporary PCI cohort[19,20]. While considering the large upper boundary of the 95% CI for the adjusted HR of 12-month mortality or MI by access-site related bleed **(Figure 4)**, we acknowledge that we may have missed this signal by a lack of statistical power. Routine implementation of a transradial approach was previously demonstrated to dramatically reduce access-site bleedings, including TIMI major and minor bleedings[21-23]. However, whether and to which extent a transradial approach would independently translate into a mortality benefit in pPCI still merits further scrutiny. To this extent, the recently published RIVAL study, embedded within the CURRENT-OASIS 7 trial, already provided a strong signal towards a differential benefit of the transradial over the transfemoral vascular access strategy among patients undergoing primary, rescue, or urgent PCI for STEMI[22]. However, patients with STEMI comprised only one third of the RIVAL study population, and the broad confidence interval for the primary endpoint weakened the robustness of the data.

In contrast, in our study, non access- (versus access-) site related bleeding following pPCI contributed four to five times more to mortality. Early upper gastrointestinal (GI) bleed is a serious condition in ACS and is often associated with multiple-unit blood transfusion (90% of the patients with upper GI bleed in our trial had a transfusion, data not shown[23]). It was the most common source of non access-site related bleeding. Because patients at high bleeding risk were excluded from participation in MULTISTRATEGY, the true incidence of GI bleed in an unselected, more elderly, population may be even higher. Early concomitant use of proton blockers may prove effective in reducing bleeding events without any safety penalty towards an increase in ischaemic complications[24]. Several reasons could explain why bleeding leads to higher rates of cardiovascular events and deaths[25]. Non access-site bleeding may be more frequent in patients with high rates of co-morbidity, who therefore have intrinsically increased risks of adverse events.

Of interest, packed red blood cell transfusion at any or higher quantity was not causally related to mortality at 12 months in the MULTISTRATEGY trial. Again, this lack of relationship may reflect the insufficient power of a low signal-to-noise ratio considering the complex relationship between transfusion, bleeding and mortality. The direct link between transfusion and mortality was questioned in the APEX-AMI trial, which failed to demonstrate a dose–response effect of transfusion[26].

Our findings on the predictors, risks and consequences of bleeding are in accordance with the literature[27]. Increasing age, gender, diabetes, renal dysfunction and IABP use have repeatedly been reported as independent predictors for significant bleeding in ACS or PCI. We also found that clinical signs of heart failure (KILLIP class) were associated with the occurrence of significant bleeding. Assessing the individual patient bleeding risk may inform decisions regarding bleeding avoidance strategies including the choice of the appropriate periprocedural antithrombotic regimen[28,29].

Several limitations of the present study must be emphasized. We should acknowledge that MULTISTRATEGY is a relatively small, randomised controlled trial. The limited patient sample and the exclusion of patients at high risk of bleeding may limit the robustness of some of our findings. However, consistency of most of our results with previous work may substantiate the validity of our analysis. The logistic complexities of this trial imposed an open-label design with a potential for bias. We attempted to mitigate this potential for bias with the requirement that all ischaemic and bleeding events were adjudicated by independent committees unaware of the treatment assignments. In up to one quarter of patients, no overt bleeding source could be identified. These patients were classified as non access-site related bleeding. In all patients, there was a significant drop in haemoglobin; there was no confirmed retroperitoneal bleeding in any of them. However, whether asymptomatic decreases in haemoglobin and/or haematocrit that do not require transfusion impact prognosis is questionable[14].

In conclusion, the results of our study indicate that TIMI major and minor grade bleedings that occur within 30 days following pPCI identify patients who are at risk for intermediate-term death or MI. However, access-site related bleeding, while substantially contributing to the total bleeding events, did not contribute to 12-month mortality and MI to the same extent as non access-site related bleeding in this analysis. Understanding the mechanisms by which bleeding is causally related to adverse clinical events is crucial in developing strategies to reduce the risks of adverse outcomes in ACS.

## Conflict of interest statement

The authors have no conflicts of interest to declare.

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# CHAPTER 2.2

## Clinical development of bivalirudin (Angiox™): rationale for thrombin-specific anticoagulation in percutaneous coronary intervention and acute coronary syndromes. International Journal of Clinical Practice

Serruys PW, Vranckx P, Allikmets K.

*Int J Clin Pract*. 2006;**60**:344-50. [ **technical report** ]

# Clinical development of bivalirudin (Angiox®): rationale for thrombin-specific anticoagulation in percutaneous coronary intervention and acute coronary syndromes

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## SUMMARY

As the pathophysiology of acute coronary syndromes (ACS) has been clarified in recent years, major advances have been made in the management of the disease. The magnitude of the thrombotic process triggered upon plaque disruption is modulated by different elements that determine plaque and blood thrombogenicity. Thrombin plays a pivotal role in ACS because of its extensive procoagulant and prothrombotic actions. Antithrombotic therapy and powerful antiplatelet therapies, in addition to early percutaneous coronary intervention (PCI), have become central in the management of ACS. A number of options for anticoagulation regimens are available. However, many agents currently used have significant limitations, recognition of which has led to the development, evaluation and clinical introduction of the class of thrombin-specific anticoagulant agents. This paper will discuss the clinical development of the direct thrombin inhibitor bivalirudin as the core anticoagulant in the contemporary PCI setting and the implications for its use in ACS.

**Keywords:** Bivalirudin; thrombin; thrombin-specific anticoagulation; direct thrombin inhibitors; percutaneous coronary intervention; clinical trials; acute coronary syndromes



## INTRODUCTION

During the last decades, the complexity of acute coronary syndromes (ACS) has been appreciated and to a great extent unraveled. It is now apparent that the 'ACS', namely unstable angina (UA) and evolving myocardial infarction (MI), share a common anatomical substrate. ACS evolve due to an acute or subacute primary reduction of myocardial blood flow (and oxygen supply), provoked by disruption of an atherosclerotic plaque associated with thrombosis, inflammation, vasoconstriction and microembolisation. Depending on the extent and duration of coronary artery obstruction, clinical manifestations range from UA to acute MI (1).

Most ACS are caused by intracoronary thrombus superimposed on disrupted atherosclerotic plaque. Platelets adhere to subendothelial proteins exposed at sites of plaque disruption where they become activated, release vasoactive and procoagulant substances, and aggregate (1). The magnitude of the thrombotic process triggered upon plaque disruption is modulated by different elements that determine plaque and blood thrombogenicity. Tissue factor (TF) in the lipid-rich core of the plaque initiates coagulation process, leading to thrombin generation. A potent platelet agonist, thrombin, recruits additional platelets to the site of vascular injury. Thrombin also converts fibrinogen to fibrin, which serves to stabilise platelet-rich thrombi formed at sites of plaque disruption.

As the physiopathology of ACS has been clarified in recent years, major advances have been made in the management of the disease. Antithrombotic therapy and powerful antiplatelet therapies, in addition to early percutaneous coronary intervention (PCI), have become central in the management of patients presenting with UA as well as with ST-segment elevation and non-ST-segment elevation ACS. Cardiologists are faced with a number of options for anticoagulation regimens. However, many agents currently used have significant limitations, recognition of which has led to the development, evaluation and clinical introduction of the active site-directed thrombin inhibitor class of agents. This paper will discuss the clinical development of the direct thrombin inhibitor bivalirudin as the core anticoagulant in the contemporary PCI setting and the implications for its use in ACS.

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## ANTITHROMBIN THERAPY FOR ACS

### The Central Role of Thrombin in the Coagulation Process

Thrombin is an important molecule in ACS because of its extensive procoagulant and prothrombotic actions. Thrombin

represents the culmination of coagulation as it converts fibrinogen to clottable fibrin by releasing fibrinopeptides A and B (2). Thrombin is also responsible for its own nonlinear generation caused by positive feedback activation, whereby thrombin enhances neoformation of thrombin. Besides its central role in coagulation, thrombin is the most potent naturally occurring platelet agonist and thus constitutes an interesting target for drugs that would prevent the formation of fibrin- and platelet-rich thrombi induced by thrombin. The important role of thrombin in generating acute platelet-rich thrombus and promoting vascular healing after arterial injury is well documented.

Exposure of TF in the atherosclerotic plaque to flowing blood leads to increased thrombin generation, resulting in platelet- and fibrin-rich thrombus formation. Such platelet aggregates can occur in response to spontaneous disruption of a vulnerable plaque but can also develop during PCI in response to (high-pressure) balloon inflations and deployment of coronary stents (3). Thrombin binds to its specific receptor on platelets ultimately leading to the expression of activated glycoprotein IIb/IIIa (GP IIb/IIIa) receptors on the platelet surface. Ligands such as fibrinogen cross-link activated platelets via the GP IIb/IIIa receptor forming platelet aggregates. In addition to contributing to thrombus formation, such platelet aggregates increase the surface area for the prothrombinase complex by providing a phospholipid membrane platform on which a complex of activated factors V and X and calcium ions can form (4), thereby amplifying thrombin generation. When bound to fibrin (5,6), fibrin degradation products (7) or subendothelial matrix (8), thrombin becomes resistant to inactivation by the heparin/antithrombin complex. In vessels with diseased endothelium, thrombin promotes the release of the vasoconstrictor endothelin-1. Thrombin also potentiates the proliferative effects of multiple growth factors and is a key mediator of early smooth-muscle-cell proliferation following arterial injury (9).

Because of thrombin's central role in arterial thrombogenesis, the goal of most anticoagulant treatment regimens during PCI or in the management of ACS is to block thrombin generation or inhibit its activity.

### Current Anticoagulants: Room for Improvement?

Inhibiting thrombin is a key treatment strategy for ACS. For nearly 50 years, the standard for antithrombotic therapy in clinical practice has been unfractionated heparin (UFH). Although familiar to the vast majority of the clinicians, UFH has the disadvantage of a variable anticoagulant effect due to its nonlinear pharmacokinetics and variable binding to blood proteins [necessitating frequent activated partial thromboplastin time (aPTT) monitoring], neutralisation by platelet factor-4, the potential to cause thrombocytopenia and heparin-induced thrombocytopenia (HIT) and a relative inability to inhibit clot-bound thrombin (10).

An important limitation of UFH is its platelet-activating effect, necessitating the concomitant use of potent antiplatelet agents. Because platelets have a pivotal role in the pathogenesis of thrombosis after plaque rupture, it is not surprising that various antiplatelet agents [aspirin, the thienopyridines and the glycoprotein IIb/IIIa inhibitors (GPIs)] have proved to be effective in reducing the incidence of adverse events that are associated with plaque rupture. The currently available antiplatelet agents differ in their modes of action, antiplatelet potency, time of onset of action, cost and the specific circumstances and temporal framework in which they should be used.

Thienopyridines (ticlopidine and clopidogrel), which inhibit stimulation of the adenosine diphosphate receptor ($P2Y_{12}$) and aspirin, which inhibits thromboxane $A_2$ ($TxA_2$) production resulting in decreased stimulation of the $TxA_2$ receptor, interfere with steps leading to activation of GPIIb/IIIa receptors. In combination, they have been proved superior to aspirin alone and to oral anticoagulation for prevention of major adverse cardiac events after coronary stenting (11). A major benefit of dual antiplatelet therapy is a lower rate of stent thrombosis. Concordantly, this combination also has been shown to prevent death and ischaemic complications in patients with UA or MI without ST-segment elevation (12) and recently also when added to fibrinolytic therapy for ST-elevation MI (STEMI) (13).

GPIs (abciximab, tirofiban and eptifibatide) directly inhibit platelet aggregation at the GPIIb/IIIa receptor and are the most potent (and expensive) antiplatelet agents. Patients considered to be at high risk of intracoronary thrombotic complications and treated according to an invasive strategy within 1–2 days after hospitalisation appear to obtain the most benefit from them (14,15). In a cost-conscious environment, the increased cost of a prolonged intravenous infusion (up to 12–24 h post procedure) and significant bleeding complications remain a problem. As the GPIs do not completely block the platelet activation pathway, they are routinely used concomitantly with aspirin.

To overcome some of the limitations of UFH, two main approaches were taken to develop new anticoagulants. Heparin preparations have been partially digested to produce low-molecular-weight heparins (LMWH), which have been extensively studied and are replacing UFH in many clinical settings. The second approach took its cue from the medicinal leech, *Hirudo medicinalis*, which produces hirudin, a direct thrombin inhibitor.

### Direct Thrombin Inhibitors: Mode of Action and Rationale for Clinical Use

Direct thrombin inhibitors (DTIs) were developed primarily to overcome the inability of the heparin/antithrombin

complex to inactivate the clot-bound thrombin. In contrast to heparin and LMWH which catalyse the inactivation of thrombin by antithrombin (16,17), DTIs bind directly to the enzyme (thrombin) and block its interaction with all its substrates. All of the direct antithrombins exhibit a concentration-dependent anticoagulant effect. For none of the specific site-directed inhibitors is an antidote available to reverse their anticoagulant effect.

The first DTI in clinical use was recombinant hirudin (desulphatohirudins), a 65-amino acid peptide that nearly encircles the thrombin molecule, the prototype of direct thrombin inhibitors. It binds to thrombin with high affinity, forming an essentially irreversible 1:1 stoichiometric complex, and can be detected as the hirudin-thrombin complex at least 18 h after the administration has been stopped (18). The terminal half-life of desulphatohirudins in healthy volunteers is 60 min. Desulphatohirudins are cleared via the kidneys and may accumulate in patients with renal insufficiency.

Coupling of peptides that mimic the carboxyterminal of hirudin to peptides that are specific for the inhibition of the catalytic site of thrombin has led to the development of a synthetic molecule termed bivalirudin, in which the amino-terminus consists of the catalytic site-directed tetrapeptide, whereas the carboxyterminus consists of the 12 terminal residues of hirudin (19). Bivalirudin binds to thrombin molecule at two sites, both active catalytic site and exosite-1 (20). The binding of bivalirudin to thrombin is reversible because thrombin can slowly cleave an Arg3–Pro4 bond in bivalirudin with resultant re-exposure of the catalytic centre of thrombin, thus restoring the active site functions of the enzyme and, by consequence, the haemostatic capacity of thrombin (21). This mechanism could explain the lower rates of bleeding observed in trials of bivalirudin. Bivalirudin has a half-life of 25 min in PCI (22). Lower molecular-weight direct thrombin inhibitors, such as bivalirudin (a 20-amino acid peptide), are better able to inhibit thrombin bound to fibrin clots than hirudin. This ability probably reflects size-restricted diffusion of hirudin into intact thrombi because once thrombi are solubilised, hirudin and smaller inhibitors have equivalent activity against bound thrombin.

Additional features of bivalirudin that make it an attractive agent for clinical use include its lack of binding to plasma proteins and its lack of neutralisation by platelet factors. Because of its stable antithrombotic effect, bivalirudin can be administered as a constant infusion, adjustments in response to haemostasis monitoring are not recommended. In contrast to hirudin, renal excretion is not the only route of bivalirudin clearance. Instead, bivalirudin is to large extent also degraded by endogenous peptidases (23). Consequently, bivalirudin may be safer than hirudin in patients with renal impairment. Another important feature of bivalirudin is its lack of platelet-activating potential (contrary to UFH) (24). Furthermore, by inhibiting thrombin in an efficient way, bivalirudin prevents the thrombin-mediated platelet activation and thus might obviate the need for additional potent antiplatelet drugs such as GPIs that are often used with UFH.

The potential advantages of direct thrombin inhibitors over heparin have prompted comparisons of these agents and have been the inspiration for several randomised trials.

## CLINICAL EVIDENCE WITH DIRECT THROMBIN INHIBITORS

### Early Clinical Studies with DTIs: Proof of Concept

The efficacy and safety of intravenous direct thrombin inhibitors, in comparison with UFH, has now been evaluated in more than 40 clinical trials for ACS without ST segment elevation, in acute MI and in PCI indications.

The early trials in STEMI patients, where direct antithrombins recombinant hirudin or hirulog (the former name for bivalirudin) were added to the thrombolytic therapy, did not show any additional benefits for the DTIs (25–27). Bleeding complications were a major concern, emphasising the strong antithrombotic properties of these drugs. By careful adjustment of the dose of both hirudin and UFH, major bleeding could be reduced. Pooled data from GUSTO-IIb and TIMI-9B showed that hirudin was more effective at achieving and managing the target aPTT range (28). In patients with ACS without ST-segment elevation, hirudin, in general, has shown a superiority over UFH during the period of administration but no statistically significant advantages in the longer term in their primary end points and proved at least as effective as heparin in patients undergoing coronary angioplasty (29–31). In the Hirudin in a European restenosis prevention trial VErsus heparin Treatment In PTCA patients (HELVETICA) study, hirudin produced a significant reduction in the primary composite outcome (absence of death, CABG, target lesion revascularisation, MI) at 96 h that was preserved at 30 days (29). The time-to-event curves converged thereafter, possibly reflecting the development of restenosis in both groups. That hirudin failed to prevent restenosis is not surprising, because none of the antithrombotic agents tested to-date has influenced this process. However, the observation that hirudin was superior to heparin at 96 h, and that this benefit was maintained at 30 days, is consistent with the results of other studies (OASIS II, GUSTO-IIb) supporting the hypothesis that potent antithrombotic drugs are needed to prevent thrombosis after mechanical injury to the coronary artery.

Overall cost/effectiveness and safety issues, with a narrow margin between efficacy and risks of bleeding, have precluded the routine clinical application of hirudin.

### Clinical Studies with Bivalirudin

Bivalirudin has been extensively investigated in several clinical trials involving very different patient populations. On the basis of the currently available clinical trials, the European Society of Cardiology task force for percutaneous coronary interventions adjudicated bivalirudin a level IIa C classification as anticoagulant to reduce bleeding complications in stable CAD (32). Planned and ongoing studies should provide grounds for further recommendation regarding the potential use of this drug in high-risk populations (NSTE-ACS, STEMI).

In the Bivalirudin Angioplasty Trial (BAT), bivalirudin was compared with heparin in 4098 patients undergoing coronary angioplasty for unstable or postinfarction angina. In an initial per protocol analysis, results suggested that there was a benefit with bivalirudin (33), a finding that was supported in a later re-analysis using an intention-to-treat analysis (34). This FDA-endorsed reanalysis used the same closed database as the initial study. It provided more complete follow-up information and a more contemporary definition of the endpoints. When this additional information was included, bivalirudin significantly reduced the combined endpoint of death, MI or repeat revascularisation in the entire cohort ($n = 4312$) at 7 days (OR 0.78, 95% CI: 0.62–0.99, $p = 0.04$) and at 90 days (OR 0.82, 95% CI: 0.70–0.96, $p = 0.01$), mainly owing to an effect on the need for revascularisation. At 7 days, major bleeding events were significantly less frequent with bivalirudin than with heparin (3.5% and 9.3%, respectively; $p < 0.001$). The BAT was the basis for the approval of bivalirudin in the US in 2000. Considering the results from BAT trial, bivalirudin could provide a safer platform on which to add other antithrombotic agents, such as GPIIb/IIIa antagonists. Alternatively, by better inhibiting thrombin-mediated platelet aggregation, bivalirudin might obviate the need for additional antiplatelet therapy in well-specified patient groups.

The BAT trial had certain limitations as it was performed in the era when the GPIs and thienopyridines were not used. Also, the control arm in the trial utilised rather high UFH doses as per clinical practice at the time. To bring the clinical development of bivalirudin to a more contemporary setting of PCI, it was further evaluated in the Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial (CACHET) and in the Randomised Evaluation of PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-I and REPLACE-II trials. The CACHET trial suggested, that bivalirudin and preprocedural oral platelet inhibition with planned or provisional abciximab may be at least as safe and effective as low-dose heparin plus planned abciximab during PCI (35). In this small ($n = 264$) pilot trial, the rates of the composite end point (death, MI, target lesion revascularisation or major bleeding) at 7 days were 3.4% for bivalirudin and 10.6% for heparin and abciximab ($p = 0.018$). Abciximab was necessitated on a provisional basis in 24% of the patients in both bivalirudin arms (B and C).

Further evidence of the safety and efficacy of this combined antithrombotic approach was provided in a second large-scale ($n = 1056$) pilot trial: the REPLACE-1 trial (36). The main objective of REPLACE-1 was to gain experience with bivalirudin at revised, lower doses and to estimate the rate of complications with bivalirudin in the contemporary PCI setting. In REPLACE-I, where provisional GPIs were used at the physicians discretion bivalirudin was found to be at least as effective as heparin, with numerically lower rates of ischaemia and major bleeding in the bivalirudin arm. The composite efficacy endpoint of death, MI or repeat revascularisation before hospital discharge or within 48 h occurred in 5.6 and 6.9% of patients in the bivalirudin and heparin groups, respectively ($p = 0.40$). Major bleeding occurred in 2.1 vs. 2.7% of patients randomised to bivalirudin or heparin, respectively ($p = 0.52$). Most patients (72%) received GPIs, enabling the safety of the combined antithrombotic approach to be determined. This trial represents the largest prospective dataset of bivalirudin administered concomitantly with GPIIb/IIIa blockade and provides evidence of the safety and efficacy of this combined antithrombotic approach.

Given the small sample size and the limited statistical power of the CACHET and REPLACE-1 studies, the efficacy of bivalirudin with provisional GPIIb/IIIa blockade, with regard to protection from peri-procedural ischemic and haemorrhagic complications, was reassessed in the large ($n = 6010$) REPLACE-2 trial (37). Aspirin was prescribed to all patients, and the use of clopidogrel encouraged. At 30 days, based on prespecified statistical criteria, bivalirudin was shown to be non-inferior to heparin plus planned GPIIb/IIIa blockade for acute ischaemic endpoints (composite and individual endpoints) and was associated with a highly significant 41% relative reduction of in-hospital major bleeding rates (2.4 vs. 4.1%; $p < 0.001$). The 6-month and 1-year findings of the REPLACE-2 trial validated the durable efficacy of bivalirudin (38). By 6 months, no significant differences between treatment groups emerged in rates of death, MI or repeat revascularisation. A trend towards better survival with bivalirudin developed over 6 months and was sustained through 1 year. Although this difference in mortality was not statistically significant, the possible benefit with bivalirudin was seen across all pre-specified subgroups, including patients at highest risk of long-term death. A subanalysis of this trial confirmed the similar efficacy and the lower incidence of bleeding for bivalirudin, regardless of renal function (39). Coupled with the advantages of bivalirudin with regard to cost savings and ease of administration, the long-term analysis of REPLACE-2 data establishes bivalirudin plus provisional GPIIb/IIIa inhibition as an attractive antithrombotic strategy for patients undergoing elective or urgent PCI. The clinical trial data are supported by a large consecutive patient registry

of nearly 7000 patients undergoing 'real-world' angioplasty at a US tertiary care centre (40).

### Bivalirudin in ACS with PCI: Work in Progress

Early angiography followed by revascularisation is considered the treatment of choice for moderate- to high-risk patients with ACS. However, despite the integration of newer therapies including stents, GPIs and thienopyridines, the rate of adverse ischaemic cardiac events and bleeding complications still remains quite high. These considerations and the results of preliminary data in this patient setting obtained from the BAT and both the TIMI 7 (Phase II) and TIMI 8 (Phase III) trial (34,41,42) provided the background for the Acute Catheterisation and Urgent Intervention Triage strategY (ACUITY) trial (43).

The ACUITY trial is a large ($n = 13{,}800$) project performed in patients of moderate- to high-risk ACS undergoing an early (<72 h) invasive strategy (43). In addition to evaluating the utility of bivalirudin in ACS, this study will also provide important guidance regarding the necessity for and timing of GPIIb/IIIa inhibitor administration. In parallel, the large-scale HORIZONS trial will assess the use of bivalirudin as adjunctive therapy in modern day primary PCI for STEMI, comparing bivalirudin plus bail-out GP IIb/IIIa inhibitor with heparin plus planned GPIIb/IIIa inhibitor treatment.

## ADDITIONAL THOUGHTS

As there is no antidote for rapidly reversing the effects of DTIs, monitoring these drugs is of importance for patients who have high risk of bleeding, such as patients with renal impairment. Bivalirudin can be monitored with the use of the activated clotting time. However, there is no need for routine monitoring due to the predictable anticoagulant activity of bivalirudin. Future studies should provide additional data on the use of DTIs in the subset of patients with renal failure.

## CONCLUSION

The clinical studies to date support the concept that bivalirudin has the potential to replace heparin and become the anticoagulant of choice during PCI. Recent guidelines of both European Society of Cardiology and American college of Cardiology recommended bivalirudin as an alternative to UFH during PCI in stable coronary artery disease (44). Bivalirudin can also be considered the alternative anticoagulation strategy in patients who cannot tolerate UFH and is approved by the FDA for use in patients with HIT/HITTS undergoing PCI (45). The ongoing trials involving bivalirudin are aimed to further define the optimum management strategies in the area of atherothrombosis and its complications, providing clinicians with the best treatment option and ensuring that the best possible outcome for the patients is achieved. The results of ongoing trials, as well as the cost and ease of use of new agents, will influence the transition towards new treatment strategies.

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*Paper received July 2005, accepted December 2005*

# CHAPTER 2.3

## Looking Back into the Future: Desirudin in ACS and Coronary Stenting

Vranckx P, Valgimigli M, Kurz M, Bell D, Serruys P.W.J.C..

*EuroIntervention*. 2011; **7**: 263-9 [**technical report** ]

# Looking back into the future: desirudin in acute coronary syndromes and coronary stenting

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**KEYWORDS**

- desirudin
- iprivask
- revasc
- acute coronary syndrome
- percutaneous coronary intervention
- direct thrombin inhibitors

## Abstract

Although percutaneous coronary intervention (PCI) is a highly effective modality for the management of acute coronary syndromes, it can potentiate the existing prothrombotic state around lesion areas and lead to ischaemic complications. Adjunctive pharmacologic treatment with heparin reduces the risk of ischaemic events, but the utility of heparin is limited by its unpredictable pharmacodynamic effects and its inability to modulate fibrin-bound thrombin. Additionally, a potential risk of heparin-induced thrombocytopenia is associated with heparin use. Direct thrombin inhibitors (DTIs) have emerged as potential alternatives to heparin in patients undergoing PCI. Bivalirudin is a DTI indicated for use in PCI. Results from various studies have suggested clinical benefit associated with the use of bivalirudin, driven primarily by the reduction in bleeding risks compared with the standard treatment regimens. Of concern, however, is a significant increase in acute stent thrombosis with bivalirudin monotherapy compared with heparin plus GPIIb/IIIa inhibitors following primary PCI for ST-segment elevation myocardial infarction (STEMI). Desirudin is a highly potent DTI with greater binding affinity than bivalirudin for thrombin. This report provides a comparative overview of the pharmacology and clinical utility of desirudin and bivalirudin in the setting of PCI.

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## Introduction

The majority of acute coronary syndromes (ACS) are caused by intracoronary thrombus superimposed on disrupted atherosclerotic plaque[1]. Platelets adhere to subendothelial proteins exposed at sites of plaque disruption where they become activated, release vasoactive and procoagulant substances, and aggregate[2]. The magnitude of the thrombotic process triggered upon plaque disruption is modulated by different elements that determine plaque and blood thrombogenicity. Exposure of tissue factor in the atherosclerotic plaque to flowing blood leads to increased thrombin generation, resulting in platelet- and fibrin-rich thrombus formation[2]. Such platelet aggregates can occur in response to spontaneous disruption of a vulnerable plaque, but they can also develop during percutaneous coronary intervention (PCI) in response to high-pressure balloon inflations and deployment of coronary stents[3,4].

Modulation of thrombotic and coagulation potential is a key factor in improving early (<30 days) clinical outcomes and in preventing complications in patients undergoing PCI[4,5]. There is clear evidence that anticoagulation in addition to platelet inhibition is effective and the combination of the two therapies is more effective than either treatment alone[6-8]. To minimise the risk of ischaemic complications during and shortly after PCI, many adjunctive antithrombotic regimens targeting thrombin generation and/or activity have been investigated and are currently in use[7-9].

Unfractionated heparin (UFH) has been widely used as the standard anticoagulant during PCI for more than two decades[5]. Heparin exerts its anticoagulant effect indirectly by binding to antithrombin, thereby dramatically enhancing the ability of antithrombin to inhibit coagulation system enzymes, particularly thrombin and factor Xa[10]. Yet there are several important disadvantages associated with the use of UFH. Due to its unpredictable, nonlinear pharmacokinetics, UFH exhibits a variable anticoagulant effect, variable binding to blood proteins and the vessel wall, and sensitivity to the inhibitory effects of platelet factor-4[10,11]. Further, the heparin-antithrombin complex is not very effective in neutralising clot-bound thrombin and, in some patients, heparin causes an immunologic thrombocytopenia (i.e., heparin-induced thrombocytopenia [HIT]), which can result in immune-mediated thrombosis[10,11]. These limitations of heparin have spurred the development of anticoagulants with different mechanisms of action, with the goal of improving outcomes and safety for patients undergoing PCI.

One approach to overcoming some of the limitations of UFH took its cue from the European leech, Hirudo medicinalis, which produces hirudin, a direct thrombin inhibitor (DTI). Direct thrombin inhibitors comprise a class of anticoagulants that bind directly to thrombin and block its interaction with its substrates[12,13]. While UFH has the potential to induce platelet aggregation, DTIs indirectly inhibit platelet activity[10,14-17]. Potential advantages associated with the use of DTIs compared with heparin include increased efficacy via the ability to bind to and inhibit fibrin-bound thrombin[12,13,18].

Several DTIs are currently approved for use by the European Medicines Agency (EMEA), namely the bivalent DTIs desirudin, lepirudin, and bivalirudin, along with the univalent DTIs argatroban and dabigatran **(Table 1)**[19-30]. Results from a recent meta-analysis of data from nearly 36,000 patients in 12 clinical trials indicated that DTIs were more effective than heparin in reducing death or myocardial infarction (MI) in patients with ACS, particularly in patients undergoing early PCI[31].

Bivalirudin (Angiox®, The Medicines Company, Parsippany, NJ, USA) is currently the most widely investigated DTI in patients undergoing PCI[32-36]. When used in place of heparin plus planned glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, it has consistently demonstrated a reduction in protocol-defined major and minor bleeding[36-38]. Major periprocedural bleeding has been identified as an important predictor of increased mortality[36,38,39]. Whether this apparent relationship between bleeding and risk of death is a cause-and-effect relationship or merely an association based on shared risk factors remains unclear. In the Harmonising Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, bivalirudin with provisional GPIIb/IIIa inhibitors significantly reduced all-cause and cardiac mortality at 30 days and at 12 months compared with heparin and planned

**Table 1. Main properties and pharmacokinetic characteristics of currently approved direct thrombin inhibitors[19-30].**

| | Desirudin | Bivalirudin | Lepirudin | Argatroban | Dabigatran etexilate |
|---|---|---|---|---|---|
| Route of administration and dosing | – Fixed BID SC dosing<br>– Single IV bolus (ongoing head-to-head trial vs. bivalirudin) | IV bolus followed by continuous IV infusion | IV bolus followed by continuous IV infusion | IV bolus followed by continuous IV infusion | Orally administered capsules taken once daily |
| Plasma half-life | ≈60 minutes | ≈25 minutes | ≈80 minutes | ≈45 minutes | ≈12-17 hours |
| Thrombin binding | Bivalent | Bivalent | Bivalent | Univalent | Univalent |
| Ki | $10^{-13}$ M | $10^{-9}$ M | $10^{-14}$ M | $10^{-8}$ M | $10^{-9}$ M |
| Primary route of metabolism and clearance | Renal (80%) and renal (20%) | Enzymatic | Renal | Hepatic | Renal |

aPTT: activated partial thromboplastin time; BID: twice daily; IV: intravenous; SC: subcutaneous

GPIIb/IIIa inhibitors; however, these reductions occurred at the cost of a significant increase in stent thrombosis immediately following the acute intervention (first 24 hours). There are residual concerns about increased stent thrombosis in patients with ST segment elevation myocardial infarction (STEMI) undergoing primary angioplasty and cost issues associated with bivalirudin. The other DTI that has already been tested in PCI, desirudin administered as an IV bolus, may provide a valuable alternative.

Desirudin (Revasc®, Canyon Pharmaceuticals, Hunt Valley, MD, USA) is a selective and potent thrombin inhibitor that is currently approved for prophylaxis of deep venous thrombosis in patients undergoing orthopaedic surgery[40]. Results from completed studies showed that intravenous (IV) desirudin, with or without subcutaneous desirudin, reduced ischaemic events compared with heparin in patients undergoing PCI[41-43]. More studies are under way to further investigate the clinical utility of desirudin in this patient population. In this technical report, we examine the pharmacologic basis for considering desirudin over bivalirudin in patients undergoing PCI. The framework for further clinical evaluation of this issue is presented.

## Rationale for desirudin in the management of patients undergoing PCI

Desirudin, a recombinant 65 amino-acid protein, has a binding affinity for thrombin greater than 10,000 times that of bivalirudin (desirudin, ki=10-13 moles; bivalirudin ki=10-9 moles)[26,27]. The mean terminal half-life of desirudin when given as an IV bolus is approximately 60 minutes[22,44-46], allowing bolus-only administration in PCI, without the need for a continuous infusion. Desirudin has low allergic/immunogenic potential, even with repeated exposure[47,48].

A high binding affinity for thrombin, rapid onset of action, and a modestly longer half-life compared with bivalirudin are characteristics that make desirudin well suited for use in patients undergoing PCI. These pharmacologic properties may be especially advantageous in high-risk patient populations with a high thrombin load.

Furthermore, the current cost of desirudin is approximately one third of the cost of bivalirudin per procedure[49]. As the use of desirudin is expected to involve simpler administration regimens with no need for monitoring, the pharmacoeconomic considerations may be even more favourable for the use of desirudin compared with bivalirudin, provided clinical outcomes are comparable.

## Overview of desirudin PCI trials

Several key interventional trials have investigated the use of desirudin in patients undergoing PCI **(Table 3)**. These studies were conducted during the early to mid-1990s when postprocedural anticoagulation was common and adjunctive use of GP IIb/IIIa inhibitors or thienopyridines was not[41-43]. Van den Bos and colleagues[41] conducted a phase II trial in 113 patients with stable angina randomised to desirudin 20 mg bolus followed by continuous infusion at a rate of 0.16 mg/kg/hr, or to UFH 10,000 U administered as a bolus and continued at a rate of 12 U/kg/hr for 24 hours. The incidence of MI and/or emergency coronary bypass surgery was higher in the UFH group compared with the desirudin group (10.3% vs. 1.4%, respectively; RR, 7.6; 95% CI, 0.9-65.6). At 24 hours post procedure, complete perfusion was present in all patients in the desirudin group compared with 91% in the UFH group, and ST-segment displacement was present in 4% of the patients treated with desirudin compared with 11% of UFH-treated patients[41].

The Hirudin with Heparin in the Prevention of Restenosis after Coronary Angioplasty (HELVETICA) trial was a pivotal, multicentre, randomised, double-blind trial that randomised 1,154 patients with unstable angina undergoing PCI to either: (1) desirudin 40 mg IV bolus plus 0.2 mg/kg/h infusion for 24 hours; (2) desirudin 40 mg IV bolus plus 0.2 mg/kg/h infusion for 24 hours, followed by desirudin 40 mg subcutaneously twice daily for three days; or (3) UFH 10,000 U IV bolus plus 15 U/kg/h for 24 hours (Table 3)[42]. The primary efficacy outcome was event-free survival (absence of death, nonfatal MI, coronary artery bypass graft [CABG] surgery, use of bailout procedures such as stenting, or second angioplasty at previously dilated sites) at 30 weeks after angioplasty. Other clinical end points included incidence of early cardiac events and measures of safety, tolerability, and luminal renarrowing. The study investigators reported that desirudin was as effective as UFH in event-free survival at 30 weeks. Importantly, desirudin was associated with a significantly reduced incidence of early clinical events (within 96 hours of PCI) compared with UFH (RR in combined hirudin groups, 0.61; 95% CI, 0.41-0.90; $p$=.023) **(Table 2)**. This benefit was particularly pronounced in the most unstable patients (those with Braunwald class III angina; RR in combined hirudin groups, 0.41; 95% CI, 0.21-0.78; $p$=.006). There were no significant differences observed between the treatment groups in the incidence of major or minor bleeding events.

**Table 2. Incidence of clinical events for the intent-to-treat patient population (HELVETICA Trial). Reprinted with permission from Serruys 1995.[42]**

| | Desirudin-1* (n=381) n (%) | Desirudin-2¶ (n=378) n (%) | Heparin‡ (n=382) n (%) |
|---|---|---|---|
| Events at 96 hours | | | |
| Death | 0 | 0 | 2 (0.5) |
| MI | 13 (3.4) | 9 (2.4) | 16 (4.2) |
| CABG | 6 (1.6) | 3 (0.8) | 9 (2.4) |
| Re-PTCA | 12 (3.1) | 8 (2.1) | 18 (4.7) |
| Any event | 30 (7.9) | 21 (5.6) | 42 (11.0) |

CABG: coronary artery bypass graft; MI: myocardial infarction; PTCA: percutaneous transluminal coronary angioplasty; *Desirudin-1: 40 mg intravenous bolus +0.2 mg/kg/h intravenous infusion for 24 hours; ¶Desirudin-2: 40 mg intravenous bolus +0.2 mg/kg/h intravenous infusion for 24 hours followed by the subcutaneous administration of desirudin 40 mg bid for 3 consecutive days; ‡Heparin: 10,000 IU intravenous bolus +15 IU/kg/h for 24 hours.

**Table 3. Summary of desirudin trials in patients undergoing percutaneous coronary intervention[41-43,50].**

| Study | Design and population | Treatments | | Efficacy endpoints | Safety endpoints |
|---|---|---|---|---|---|
| | | Desirudin | Heparin | | |
| van den Bos 1993[41] | Double-blind, randomised trial in patients with unstable angina undergoing PCI (N=113) | – IV bolus: 20 mg<br>– Continuous IV infusion: 0.16 mg/kg/h | – IV bolus: 10,000 IU<br>– Continuous IV infusion: 12 IU/kg/h | Myocardial infarction and/or emergency coronary bypass surgery within 24 h following PTCA<br>– Desirudin: 1.4%<br>– Heparin: 10.3% | Major bleeding[d]<br>– Desirudin: 5%<br>– Heparin: 0% |
| HELVETICA[42] | Double-blind, randomised trial in patients with unstable angina and coronary stenosis warranting PCI (N=1154) | Group A: desirudin 40 mg IV bolus + desirudin 0.2 mg/kg/h IV infusion for 24 h + desirudin 40 mg SC BID for 3 d<br><br>Group B: desirudin 40 mg IV bolus + desirudin 0.2 mg/kg/h IV infusion for 24 h + placebo | Group C: heparin 10,000 U + heparin 15 IU/kg/h 24-h IV infusion + placebo | Event-free survival at 30 wk post-angioplasty[a]<br>– Desirudin: Group A, 68%; Group B, 63.5%<br>– Heparin: Group C, 67.3%<br>– No significant differences among the 3 groups ($p$=.61)<br><br>Any event within 96 h of treatment initiation[b]<br>– Desirudin: Group A, 5.6%; Group B, 7.9%<br>– Heparin: Group C, 11.0%<br>– Significant reduction with desirudin (groups A and B) vs. heparin ($p$=.023) | Major bleeding[c]<br>– Desirudin: Group A, 7.7% Group B, 5.5%<br>– Heparin: Group C, 6.2%<br>– No significant differences between the 3 groups<br><br>Minor bleeding<br>– Desirudin: Group A, 15.1% Group B, 13.1%<br>– Heparin: Group C, 11.3%<br>– No significant differences between the 3 groups |
| Roe 2001[43] | *Post hoc* subgroup comparison analysis of PCI patients in GUSTO IIb, a prospective, randomised, multicentre, double-blind study investigating ACS patients with or without fibrinolytic therapy (N=1410)[43,50] | – Bolus: 0.1 mg/kg (≤15 mg total)<br>– Continuous IV infusion: 0.1 mg/kg/h (≤15 mg/h total) for 3-5 d[50] | – Bolus: 5,000 U<br>– Continuous IV infusion: 1,000 U/h for 3-5 d[50] | Death or nonfatal MI or reinfarction within 30 d<br>– Desirudin: 6.8%<br>– Heparin: 9.6%<br>– No significant differences between the groups ($p$=.06)<br><br>Death or nonfatal MI or reinfarction within 6 mo<br>– Desirudin: 9.5%<br>– Heparin: 12.3%<br>– No significant differences between the groups ($p$=.08)<br><br>Death or nonfatal MI or reinfarction within 48 h<br>– Desirudin: 2.2%<br>– Heparin: 3.9%<br>– No significant differences between the groups ($p$=.06) | In-hospital bleeding<br>– Desirudin: 9.7%<br>– Heparin: 7.5%<br>– No significant differences between the groups ($p$=.14) |

ACS: acute coronary syndromes; IV: intravenous; PCI: percutaneous coronary intervention; PTCA: percutaneous transluminal coronary angioplasty; a. Absence of death and MI, and no further coronary interventions required; b. Incidence of death, MI, or further coronary interventions ; c. Overt bleeding, resulting in decreased haemoglobin level ≥2 g/dL, requiring transfusion of ≥2 units whole blood or packed cells; or intracranial or retroperitoneal bleeding or bleeding occurring in a major joint; d. Any intracranial and retroperitoneal bleeding, as well as bleeding at any other site requiring transfusion of ≥2 units of blood.

Finally, the GUSTO-IIb study randomised 12,142 patients with ACS to 72 hours of therapy with either IV heparin or desirudin[50]. Roe and colleagues conducted a subanalysis of 1,410 patients in GUSTO-IIb who underwent PCI while on study drug, comparing the incidence of MI and death between patients receiving desirudin versus UFH[43]. They reported that desirudin was associated with a trend toward a reduction in the primary endpoint (composite endpoint of death or nonfatal MI) compared with UFH within 48 hours post-PCI (2.2% vs. 3.9%; odds ratio [OR], 0.55; 95% CI, 0.29-1.03; $p$=.06). Treatment with desirudin was also associated with a lower risk than UFH of nonfatal MI at 30 days (4.9% vs. 7.6%, respectively; OR, 0.63; 95% CI, 0.40-0.98; $p$=.04) and at six months (6.7% vs. 9.7%; OR, 0.67; 95% CI, 0.45-0.99; $p$=.04), with no significant increase in procedure-related bleeding (2.8% for desirudin

vs. 2.3% for UFH; $p$=.53). The results from these studies in patients undergoing PCI indicate that IV infusion of desirudin provides a potentially valuable alternative to UFH in PCI.

## Future development of desirudin in contemporary PCI

An urgent or early invasive mechanical (reperfusion) strategy is recommended in patients with ST segment elevation acute coronary syndromes (STE-ACS) and with non-STE-ACS considered to be at high risk for developing major myocardial necrosis, or in those at risk for rapid progression to vessel occlusion. In patients with a high thrombus burden, facilitation of coronary intervention with potent "upstream" pharmacotherapy and thrombus debulking devices appears promising. Desirudin may be well suited to this interventional strategy because of its high affinity for thrombin, (including clot-bound thrombin) and a balanced risk of major bleeding, along with the practical advantages of a single-bolus only administration and an economical price. Further research is focused on the development of desirudin for contemporary PCI. Positive results from these trials may result in establishing desirudin as the anticoagulant of choice in PCI.

First, a dose-ranging study will evaluate two dosing levels of single-bolus desirudin (30 mg or 45 mg) compared with standard regimens of UFH or bivalirudin. The primary efficacy outcome measure will include the 7-day combined incidence of death from any cause, non-fatal MI, and urgent target vessel revascularisation (coronary bypass surgery or PCI) due to myocardial ischaemia. In addition, non-CABG major bleeding occurring up to 48 hours after PCI will be assessed. Repeated blood sampling should allow for a detailed study of the coagulation profile and drug pharmacodynamics. In addition, secondary outcome measures will include area under the curve for high-sensitivity troponin. It is anticipated that this sensitive measure of myocardial damage may unmask important differences between the desirudin bolus regimens and bivalirudin. Our hypothesis is that the optimal desirudin bolus dose will provide superior ischaemic protection compared with bivalirudin owing to its higher binding thrombin-binding affinity and modestly prolonged half-life[19,22,23,26,27,29]. This study will aim to determine the optimal bolus dose of desirudin, balanced against UFH or bivalirudin, to pursue in a phase III outcomes trial.

## Conclusions

Establishment of optimal antithrombotic and anticoagulant protocols remains a major goal for patients undergoing PCI, balancing the risk of ischaemic and iatrogenic bleeding complications. The short-acting nature of bivalirudin may contribute to a favourable safety profile compared with UFH plus GPIIb/IIIa inhibitors, but it may also limit its effectiveness in the prevention of acute stent thrombosis following PCI. The relative safety profiles of currently approved DTIs are unknown, as clinical studies involving direct comparisons of these agents have not yet been conducted.

Desirudin may prove to be a valuable competitor to bivalirudin in the management of patients undergoing PCI. Potential advantages of desirudin include ease of use, potential for increased efficacy owing to its increased binding affinity for thrombin, a modestly longer half-life, and its considerably lower costs. Because of these advantages, desirudin has the potential to become the anticoagulant of choice for the interventional community. Future studies will help to further characterise the advantages of desirudin in patients undergoing PCI.

## Conflict of interest statement

Editorial support for this article was provided by Peloton Advantage LLC. No author received an honorarium or other form of financial support related to the development of this manuscript.

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# CHAPTER 2.4

## Dabigatran, a novel, oral, direct thrombin inhibitor, to support Elective Percutaneous Coronary Intervention. (*the D-Fine study*)

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*EuroIntervention* 2012. [**original research paper**]

Dabigatran to support Elective Percutaneous Coronary Intervention

## ABSTRACT

Aims: Patients receiving long-term anticoagulant treatment with dabigatran may need to undergo a percutaneous coronary intervention (PCI). It is well known that coagulation activation occurs in patients undergoing elective PCI. We studied markers of coagulation activation during elective PCI in patients using dabigatran in order to investigate whether coagulation activation is suppressed by dabigatran without additional heparin treatment .

Methods and results: This phase-IIa, exploratory, multi-center, randomized, open-label study included 50 stable patients having an elective PCI. Patients on standard dual antiplatelet therapy (DAPT) were randomized (2:2:1) to either pre-procedural dabigatran 110mg BID (n=19) or 150mg BID (n=21), as compared to standard intra-procedural unfractionated heparin (UFH) (n=10). During PCI and stent placement the levels of prothrombin fragment 1+2 were consistently higher in the dabigatran-groups as compared to the UFH-group (levels at 2 hr. after start PCI: 270.6 pmol/l (1.7)(geometric mean(gSD)) vs.179.0 pmol/l (2.1), respectively), however not significant (p: 0.2499). Also thrombin-antithrombin complexes trended to be higher in the dabigatran-group compared to UFH-group (levels at 2 hr: 8.5 µg/l (2.3)) vs 4.5 µg/l (3.8), p: 0.0612).

Five out of 40 (12.5%) patients required bail-out anticoagulation in the dabigatran-group, of whom 4 experienced a procedural myocardial infarction (MI), versus 1 out of 10 in the UFH-group, who had a stent thrombosis without MI prior to the study-PCI. One minor access-site bleeding occurred in the dabigatran group.

Conclusion: Dabigatran treatment (110 mg or 150 mg BID) may not provide sufficient anticoagulation during PCI.

Clinical Trial Registration: URL: EudraCT. Unique identifier: No: 2007-007536-25.

Key Words: angioplasty, anticoagulation, coronary artery disease, thrombosis.

## INTRODUCTION

Patient populations at risk of venous or arterial thrombosis, including patients with atrial fibrillation (AF), often receive long-term anticoagulant treatment. Many of these patients suffer co-existing atherosclerotic coronary artery disease (CAD) and may be in need of an urgent percutaneous coronary intervention (PCI) during the treatment period. (1-3)

During PCI more intensified anticoagulation may be needed to perform the procedure safely, because balloon inflation and stent placement can potentiate an existing pro-thrombotic state around lesion areas and lead to ischemic complications. (4-7) The choice of the concomitant pharmacological environment is critical, as is the dosage of the drugs. The value of a peri-procedural antithrombotic regimen depends on the balance between prevention of ischemic and bleeding complications. (8)

Dabigatran etexilate, an orally available, potent, direct inhibitor of thrombin, given at a dose of 150mg twice daily, is more effective than warfarin in prevention of stroke and systemic embolism in patients with AF. (3) Dabigatran etexilate has little interaction with food and drugs and can therefore be prescribed in a fixed dose without the requirement of frequent monitoring. (9) It is yet unknown whether patients who are on stable long-term anticoagulation with dabigatran are adequately anticoagulated to perform a PCI procedure safely or need additional (unfractionated) heparin to suppress coagulation activation during the procedure.

The primary goal of this study was to investigate whether dabigatran treatment, mimicked by giving a short course of 110 mg or 150 mg BID dabigatran before the procedure, on the background of standard dual antiplatelet therapy (DAPT) adequately suppresses coagulation activation during elective PCI.

## METHODS

### Study design and population

The D-fine clinical trial is a phase 2a prospective, randomized, exploratory study conducted in 4 hospitals in the Netherlands. Clinical Trial Registration: URL: EudraCT. Unique identifierNo: 2007-007536-25. Patients were considered for the study if planned for a non-urgent PCI via femoral approach to treat symptomatic, obstructive CAD (demonstrated silent ischemia, stable angina, unstable angina, or non–ST-segment–elevation myocardial infarction). The cardiac specific troponin (cTn) at the time of the index PCI had to be below the 99$^{th}$ percentile of the upper reference limit (URL). Patients were excluded for lesion specific conditions, if they were hemodynamic unstable or at increased bleeding risk (See Supplementary Appendix-2 for inclusion and exclusion

criteria). Patients were followed for a maximum period of two weeks after the index PCI for this study.

An independent external safety physician (FV) was charged to monitor patient safety and advised the Steering Committee on potential issues that might have occurred during the trial conduct. Special emphasis was placed on capturing thrombotic intraprocedural complications such as abrupt vessel closure, no reflow, and formation of clots on or within the interventional equipment (catheters and wires i.e.). The trial was approved by the ethics committee at each participating institution, and all patients provided written informed consent.

### Randomization and Study Treatments

Patients were randomly assigned through pre-prepared sealed envelopes, in an open-label fashion respecting a 2:2:1 ratio to either pre-procedural dabigatran (Boehringer Ingelheim Pharma GmbH & Co. KG, Germany) 110mg twice daily (n=19), dabigatran 150mg twice daily (n=21) or intra-procedural unfractionated heparin (UFH) 70IU per kilogram of body weight with subsequent boluses targeted to achieve an activated clotting time (ACT) of 250 to 300 (n=10). Dabigatran was started 24 hours before the index PCI for a total of 3 doses pre-PCI (respectively 24 hours, 12 hours and 2 hours before the index PCI). All patients were pre-treated with 75 to 325mg aspirin, and clopidogrel (loading dose 300mg) administered no less than 12 hours before the index PCI.

Given the overall low to medium risk patient group included in this trial, glycoprotein IIb/IIIa inhibitor (abciximab: bolus of 0.25 mg per kilogram followed by an infusion of 0.125 µg per kilogram per minute; maximum dose, 10 µg per minute, for a maximum of 12 hours) use was restricted to bail-out situation, as defined below, in addition to an additional bolus of heparin (50 U/kg maximum 3,500 U). Coronary stenting with either bare-metal or drug-eluting stents, according to the choice of the physician, was the preferred method of PCI.

## LABORATORY COAGULATION ASSAYS

The coagulation assay panel included the thrombin time performed with 10 units of thrombin (TT 10U, Thromboclotin, Siemens), prothrombin time (PT) and international normalized ratio (INR)(Tromborel S, Siemens) , activated clotting time (ACT), activated partial thromboplastin time (aPTT, Triniclot, Trinity Biotech), fibrinogen according to Clauss (Thrombin Reagent (Siemens)), thrombin-antithrombin (TAT)-complex (Enzygnost® TAT micro, Siemens), prothrombin fragment 1+2 (F1+2, Enzygnost® F1+2, Siemens) and D-Dimer levels (AutoDimer, Biopool® International). Dabigatran plasma levels were

measured at screening (blank sample), just before 2nd dose (12 hours pre-PCI), just before 3rd dose (2 hours pre-PCI), just before the index PCI (2h post dose, around peak), 6-8h post index PCI (8-10h post dose).

Blood samples for coagulation testing were collected in 3.2% trisodium citrate (0.105 M) using a vacutainer system (Becton Dickinson, Plymouth, UK). Blood samples for pharmacokinetic analysis were collected in K-EDTA (potassium ethylene-di-aminetetra-acetic acid). All samples were centrifuged within 30 minutes after collection at 4°C for 10 minutes at 2,000 *g*. Platelet-poor plasma was prepared frozen in small pre-labeled cryo vials and frozen immediately at -80°C until processing. Shipment of the frozen (-80°C) plasma samples from the clinical site to the central analytical laboratory was on dry ice. All coagulation testing was performed (in bath) at the department of haematology, Erasmus Medical Centre, Rotterdam, the Netherlands. The dabigatran plasma levels were measured by Boehringer Ingelheim, Biberach, Germany.

## CLINICAL OUTCOME MEASURES

The 'primary' clinical outcome measure was the number of patients who needed bail-out anticoagulant treatment for ischaemic cardiac events and/or had clinical or angiographic signs of catheter related thrombosis during the PCI procedure such as abrupt vessel closure, new thrombus with reduced flow, no-reflow; or clot formation on or within the interventional equipment (guiding catheter, guide wire i.e.).

We also assessed the occurrence of major and clinically relevant non-major in hospital bleeding events or up to 3 days (whatever came first). Major bleeding events, clinically relevant non-major bleeding events, and minor bleeding events were classified on the basis of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) (3) and the Thrombolysis in Myocardial Infarction (TIMI) scales. (10) The occurrence of other adverse events up to 14 days following the index PCI were captured. Myocardial infarction (MI) was defined according to the 2007 Universal Definition. (11)

The protocol issued for the performance of standard 12-lead electrocardiogram (before the PCI; 6-8 hours and 18-24hours post PCI; at discharge and during the 7-14 days follow-up visit) and the collection of blood samples for measurements of cardiac enzyme levels (before the PCI; 6-8hours and 18-24 hours after the PCI ) and haemoglobin levels.

## STATISTICAL ANALYSIS

This is an exploratory trial and no formal sample size calculation has been performed. Mainly descriptive statistics were carried out. For the comparison of coagulation parameters over time, analysis of repeated measures were performed. The repeat measures model of the log transformed laboratory values contained treatment, visit (time) and visit interaction as fixed classification effects, along with the log transformed baseline laboratory value and log baseline lab value by visit interaction as linear covariates. An unstructured covariance structure was used to model the within-patient errors. For the lab values the repeated measures models reported results in adjusted geometric means and the comparison of the ratio of these means between the treatments. The ratio was accompanied by a confidence interval and p-value. Ratios were presented due to log transformations to achieve normality in the skewed distribution on the original scale. Clinical outcome data were analysed according to a modified intention-to-treat principle, whereby patients who did not receive any study drug were excluded from all analyses, as was pre-specified in the protocol. Differences between the treatments were expressed in Odds ratios and their matching 95% confidence intervals. Interpolation of missing data was not conducted. Categorical outcomes were compared with the chi-square test or Fisher's exact test. Continuous variables were compared using the Wilcoxon rank-sum test. Statistical analyses were performed with the use of SAS software, version 9.2 by dedicated statistician.

## RESULTS

### Patient population and treatment allocation

A total of 53 patients were randomized between August 2009 and April 2010. Three patients in the dabigatran 110mg dose group were excluded from the study: Two had predefined major exclusion criteria (left main coronary artery disease, severe anaemia: both patients were excluded before the intake of any study medication) and one was not compliant to the intake of study medication. All other patients (n=50) completed the planned observation period.

Baseline demographics are presented in table-1. Median age was 65 (25th and 75th percentiles, 59 and 71 years), 68% were male. The cardiac specific troponin measurement at baseline was below the upper reference limit in all patients. The median estimated glomerular filtration fraction (eGFR) calculated by means of the Cockcroft–Gault formula was 95.4ml/min (25th and 75th percentiles, 83.1 and 118.3 ml/min). (12) The details of the procedural characteristics are listed in supplementary table-1. All patients

undergoing PCI (n=50) were pre-treated with DAPT. Of the 59 attempted lesions, all were successfully dilated. Three patients had a functional (Fractional flow reserve >0.80) and the lesions were left untouched. Drug eluting stents were used in all except one patient (98%) and 2-vessel stenting was performed in 9 (18%) cases.

## COAGULATION LABORATORY MEASUREMENTS.

A selection of coagulation parameters are presented in figure-1 and table-2. The aPTT was significantly higher on heparin ($p<0.0001$ within the first 2 hours) as compared to the dabigatran groups. The APTT (seconds) increased from 28.8 (1.1)(geometric mean (gMean), standard deviation (gSD)) to a maximum of 51.8 (1.5 gSD) seconds at 1 hour following the start of PCI in the dabigatran group and an increase from 29.2 (1.1 gSD) to a maximum of 240 (1.0 gSD) seconds at one hour in the UFH group. A similar pattern was observed for ACT (see table-2). The INR was hardly influenced by dabigatran and remained below 1.5. The thrombin time ($TT_{10U}$, seconds) at baseline was not different between the treatment groups. In the dabigatran group the $TT_{10U}$ increased from 13.3 (1.1 gSD) to 60 (1.0 gSD) seconds after one hour. Also in the heparin group, the $TT_{10U}$ increased from 14.6 (1.5 gSD) to 60 (1.0 gSD) seconds after an hour. During the interventional procedure a similar pattern was observed between dabigatran and UFH. However, after 18 hours, in the heparin group the $TT_{10U}$ was normalized, whereas in the dabigatran group the $TT_{10U}$ was still slightly prolonged (23.8 (1.5 gSD) seconds).

The relationship between dabigatran plasma concentrations and the coagulation parameters (INR, $TT_{10U,}$ aPTT and ACT,) are presented in figure 2, panel A-D. This includes all blood samples taken during the study. We observed a weak correlation between dabigatran plasma levels and INR ($r^2=0.4029$, p value<0.0001) and ACT ($r^2=0.2981$, p value=0.0104). No correlation was found with $TT_{10U}$ ($r^2=0.0270$, p value=0.0818). The thrombin time was unmeasurable (>60 seconds, maximum) in most patients with high plasma concentrations of dabigatran (figure 2B).

For the markers indicating coagulation activation, including F1+2 and TAT, there were no differences in baseline values (figure 1, panel C-D). A strong rise of both thrombin generation markers was observed in the dabigatran treated patients as compared to the UFH group. At 2 hours after following the start of PCI, F1+2 was higher in the dabigatran-group compared to UFH-group 270.6 pmol/L (1.7gSD) vs.179.0 (2.1gSD) respectively, however not significant (p-value=0.2499). Baseline concentrations of TAT complexes in the dabigatran groups were slightly lower than in the heparin group: 3.23 ug/l ($95^{th}$ percentile 14.2 gSD 1.9) versus 3.89 ($95^{th}$ percentile 19.5 gSD=2.0). TAT complexes trended to be higher in the dabigatran-groups compared to UFH-group [e.g. levels at 2 hr: 8.5

ug/l (2.3gSD) vs 4.5 (3.8gSD), p-value 0.0612]. D-dimer levels were similar between the dabigatran and UFH groups and were not strongly increased during and after PCI.

## PHARMACOKINETIC MEASUREMENTS

The dabigatran plasma concentrations within 2 hours prior to PCI ("trough": 10-16h post-2nd dose and immediately before third dose) were 36.9 ng/ml (gMean) (45.1%gCV) for the 110mg dose group and 64.2 ng/ml (44.0%gCV) for the 150mg dose group. The levels remained within the same range at the time of PCI ("around peak": 1-3h post-3rd dose) (98.4 ng/ml, 89.9%gCV; 161 ng/ml, 65.2%gCV respectively) and 6-8hours following PCI (36.6 ng/ml, 84.9%gCV; 63.1 ng/ml, 57.5%gCV respectively). In patients with mild renal impairment (eGFR 30-80ml/min) (5/43, 12%) dabigatran trough levels were approximately 42 % higher (0.669 ng/mL/mg vs. 0.470 ng/mL/mg) and peak concentrations approximately 60% (1.86 ng/mL/mg vs. 1.16 ng/mL/mg) higher than in patients with an eGFR □ 80ml/min.

## CLINICAL OUTCOMES

The overall proportion of patients who required rescue anticoagulant medication and/or have clinical signs of catheter related thrombosis did not significantly differ between groups (odds ratio 1.25, 95%CI: 0.128-12.252) (supplementary table-3). Two patients in the dabigatran group experienced a procedural flow limiting thrombus formation imposing bail-out anticoagulation, one was a case of procedural stent thrombosis while an intravascular ultrasound examination was performed. Additional (on top of the primary outcome) major adverse cardiac events up to 14 days occurred in 2 patients in the dabigatran groups, all were peri-procedural myocardial infarction, versus none in the UFH group. One patient in the dabigatran 110mg dose group developed new symptoms consistent with myocardial ischemia after the patient left the catheterisation suite, but within 12 hours after the index PCI, a peri-procedural MI was diagnosed. There were no deaths. For a full description of the individual patient narratives see supplementary table 4. Major and clinically relevant bleeding events did not occur. The overall incidence of adverse events was similar in both treatment groups: 34.1% in the combined dabigatran group, 30.0% in the UFH group and of mild intensity.

## DISCUSSION

The D-fine study is the first to investigate whether pre-procedural dabigatran provides sufficient antitcoagulant effect to obviate the need for adjunctive heparin in case of PCI. Our results suggest that a short course of dabigatran, plus standard DAPT, but without concomitant intra-procedural UFH, prior to an elective PCI was insufficient to suppress coagulation activation during balloon inflation and stent expansion as compared to intra-procedural UFH.

Patients on oral anticoagulants in the need for an (urgent) PCI represent a clinical conundrum, as management guidelines for revascularisation are based on clinical trials that have largely excluded patients who receive long-term anticoagulation therapy. Dabigatran etexilate is a new generation oral direct thrombin inhibitor that decreases thrombo-embolic events in patients with atrial fibrillation. (3, 13-14) The pharmacokinetic profile of dabigatran etexilate is characterized by maximum plasma concentrations at approximately 2 hours after oral administration, a bi-exponential distribution phase and a terminal half-life of about 11 hours in healthy volunteers above 65 years. (9) The total and peak exposure increase linearly and are dose proportional after single and multiple oral dosing of the drug. Dose selection of dabigatran in this trial was based phase-II and III clinical trial data (i.e. RE-LY trial). (15-16) In our study three doses of dabigatran (110 or 150mg) were given before the PCI. This resulted in trough and peak dabigatran plasma concentrations that were 43% and 10% lower, respectively, than steady state concentrations achieved in the previously reported RE-LY trial. (3) The trough concentrations were closer to those encountered in VTE treatment study. (17) These differences in pharmacokinetics may be explained by both the short treatment course and by differences in study populations, mainly driven by differences in estimated glomerular filtration. (3,9)

In this in mechanistic study the main focus was the peri-procedural results of coagulation tests and levels of markers of coagulation activation in both the UFH and dabigatran treated patients. Levels of F1+2 and TAT complexes, which are both markers of thrombin generation, trended to be higher in patients treated with dabigatran than those treated with UFH. This may be caused by the fact that UFH inhibits the coagulation system not only via thrombin, but also via factor Xa and, to a lesser extent also via other coagulation factors. Both dabigatran dosing groups had elevated TAT-complex values as compared to UFH, suggesting more coagulation activation than in the heparin group. This seemed to be dabigatran-dose dependent, since patients treated with dabigatran 110 mg bid had F1+2 and TAT values that were even more increased than in those treated with dabigatran 150 mg bid ( figure-1).

Although our study was not powered to detect a difference in clinical outcome measures between UFH and dabigatran, the number of adverse events of 13 % of patients is higher than seen in general practice and previous studies with other anticoagulants may raise caution flags. (18-19) It is of importance to mention the recent report by Uchino et al , whom reported an 30 % increased incidence of AMI in patients treated with dabigatran compared to vitamin K antagonists in a meta-analysis of all major dabigatran trials for various indications (20)

The reported laboratory data, coupled with the cases of flow limiting thrombus in the dabigatran groups, indicate that the differences between UFH and dabigatran with regard to the attenuation of coagulation activation may be clinically relevant. Whether higher doses of dabigatran etexilate, with or without an additional bolus of UFH, could support PCI remains subject for further investigation. Pending further data, an in analogy with the OASIS-5 trial and the horizons-AMI trial, one may consider an additional bolus of heparin in patients in the need of urgent PCI while being anti-coagulated with dabigatran. (21-22)

This study has several limitations. First, the limitations of an open label study design, only the dabigatran dose was blinded, should be acknowledged. However, the laboratory technicians were not aware of the treatment the individual patients have received. This study was limited to elective PCI in stable patients. This consists up to 60% of patients in routine PCI practice. (23) Patients with more complex lesion morphology and on-going myocardial ischemia may be at higher risk of peri-procedural thrombotic complications (complex lesion morphology, STEMI) and in the need of even more intense peri-procedural anticoagulation. (4-5) As indicated earlier, the D-Fine study was only exploratory by design. D-fine was not powered to show a difference in clinical or angiographic thrombotic complications among its three arms. Overall the trial is too small to draw any conclusion regarding differences in clinical outcome. A definitive non-inferiority study versus UFH in an all-comers PCI setting will require a considerable number of patients and may not be achievable

In conclusion, in the setting of PCI, a short course of dabigatran prior to the procedure, without intra-procedural heparin, may not be sufficient to suppress coagulation activation compared to intra-procedural unfractionated heparin.

## AKNOWLEDGEMENTS

The authors recognise the valuable input of drs K. Metzman PhD (Pharmacokinetic data analysis and interpretation), L.M.C. van Campen MD (Source verification of the data) and

P Gobbels (statistical data analysis). We thank dr. GA Van Es for his critical revision of the intellectual content of the manuscript. We thank the study staff at the participating centres for their efforts in collecting the data and the patients who volunteered to participate in the study.

## ROLE OF THE FUNDING SOURCE

The members of the Steering Committee, including the sponsor representatives, were responsible for the design and conduct of the study and writing of the paper. The sponsor was responsible for collection and source verification of the data, with oversight by an independent clinical events committee. Analyses were performed by the sponsor and were verified by an independent statistician (AG).

## DISCLOSURES

JF, PR, and RJ report being employees of Boehringer Ingelheim. No other potential conflict of interest relevant to this article was reported

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Table 1: Base-Line Characteristics of Each Treatment Group

| | Dabigatran 110mg (n:22 ) | Dabigatran 150mg (n:21) | Dabigatran 110 or 150mg (n:43) | Heparin (n:10) |
|---|---|---|---|---|
| Age (yr), mean | 65.5 | 63.0 | 64.3 | 67.0 |
| Male sex (%) | 63.6 | 71.4 | 67.4 | 70.0 |
| BMI (kg/m$^2$), mean (SD) | 27.8 (3.5) | 27.4 (3.9) | 27.6 (3.6) | 29.6 (4.4) |
| BSA (m$^2$), mean (SD) | 2.0 (0.2) | 2.0 (0.2) | 2.0 (0.2) | 2.0 (0.2) |
| Previous MI (%) | 22.7 | 23.8 | 23.3 | 10.0 |
| Previous PCI (%) | 36.4 | 33.3 | 34.9 | 60.0 |
| Previous CABG (%) | 4.5 | 14.3 | 9.3 | 10.0 |
| Hypertension | 63.6 | 71.4 | 67.4 | 70.0 |
| Diabetes Mellitus | 18.2 | 23.8 | 20.9 | 20.0 |
| Current smoker (%) | 9.1 | 9.5 | 9.3 | 0.0 |
| Creatinine Clearance Class ml per minute per 1.73 m$^2$ of BSA | | | | |
| □30 and <50 | 3 | 0 | 3 | 0 |
| □50 and <80 | 2 | 4 | 6 | 3 |
| □80 ml | 14 | 17 | 31 | 7 |
| Unknown | 3 | 0 | 3 | 0 |
| Silent ischemia N(%) | 1 (4.5) | 0 (0.0) | 1 (2.3) | 0 (0.0) |
| Stable angina (%) | 21 (95.5) | 21 (100.0) | 42 (97.7) | 10 (100.0) |
| Non-ST-ACS (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

Categorical variables are presented in absolute values and percent N (%)

Non-ST-ACS: non ST segment elevation acute coronary syndrome was defined as: unstable angine class I-III according to Braunwald classification with or without elevation of troponin I.

Stable angina was defined according to the classification of the Canadian Cardiovascular Society.

BMI denotes body mass index

BSA denotes body surface area

eGFR denotes estimated glomerular filtration rate

MI denotes myocardial infarction

Non-ST-ACS denotes non ST segment elevation acute coronary syndrome

PTCA denotes percutaneous trans-luminal coronary angiography

CABG denotes coronary artery bypass grafting

**Figure 1: Markers of coagulation activation for dabigatran vs. heparin.**

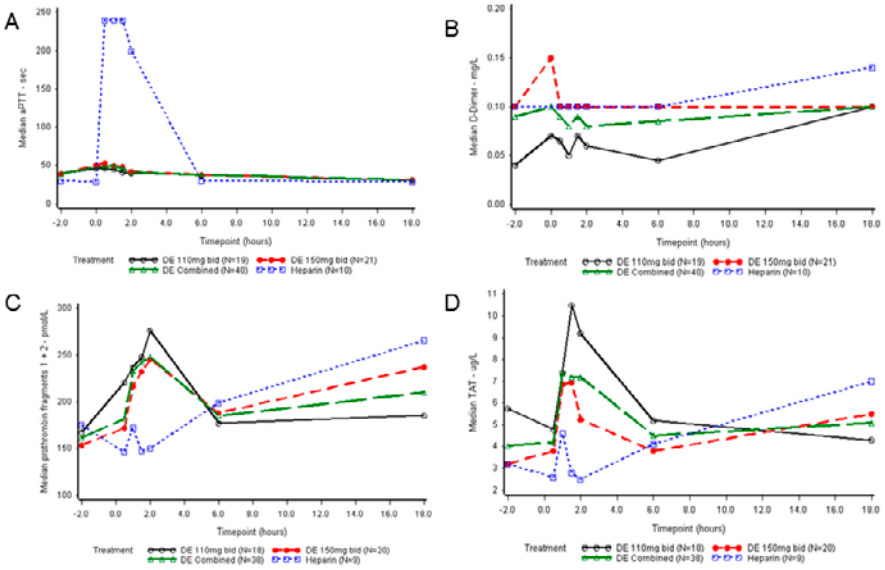
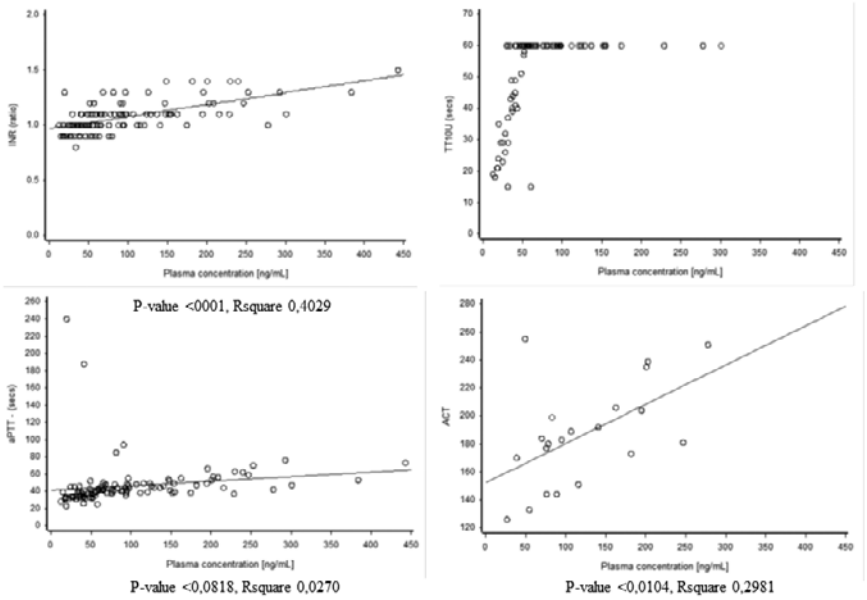



Figure 1 and 2 are represented in a separate document.

Figure 1 A-G: markers of coagulation activation for dabigatran vs heparin.

CAPTION: Results of markers of coagulation related to the index PCI. F1+2: prothrombin fragments 1 and 2, aPTT: activated partial thromboplastin time, TAT: thrombin-antithrombin III, D-Dimers.

Figure 2: Relationship between dabigatran plasma concentrations and the result of ACT, aPTT, INR and TT10U.




P-value <0,0818, Rsquare 0,0270

P-value <0,0104, Rsquare 0,2981

Figure 2 A-D: Relationship between dabigatran plasma concentrations and the result of INR, TT10U, aPTT and ACT.

Caption: Relationship between dabigatran plasma concentrations and INR, TT10U, aPTT and ACT.. INR: International Normalized Ratio (INR), TT: Thrombin time (thrombin concentration 10IU/ml), aPTT: activated partial thromboplastin time, ACT: activated clotting time.

Table 2: Geometric means (gSD) of Coagulation Measures over time.

| | | pre- PCI | | During PCI | | | Post PCI | | |
|---|---|---|---|---|---|---|---|---|---|
| | | baseline | <2hrs | 0.5hrs | 1.0hr | 1.5hrs | 2hrs | 6-8hrs | 18-24hrs |
| aPTT$^{ratio}$ | D110mg | 1.0 (0.0) | 1.3 (1.1) | 1.6 (1.2) | 1.6 (1.2) | 1.5 (1.2) | 1.4 ( 1.3) | 1.4 (1.6) | 1.0 (1.1) |
| | D150mg | 1.0 (0.0) | 1.5 (1.2) | 1.8 (1.3) | 2.0 (1.7) | 2.0 (1.7) | 1.8 ( 1.9) | 1.4 (1.5) | 1.1 (1.2) |
| | Combined | 1.0 (0.0) | 1.4 (1.2) | 1.7 (1.3) | 1.8 (1.5) | 1.7 (1.5) | 1.6 ( 1.7) | 1.4 (1.5) | 1.1 (1.2) |
| | UFH | 1.0 (0.0) | 1.0 (0.0) | 8.2 (1.1) | 7.4 (1.4) | 7.3 (1.2) | 5.5 ( 1.5) | 1.1 (1.2) | 1.0 (1.0) |
| ACT* seconds | D110mg | ND | 172.6 (1.2) | 186.3 (1.5) | 193.8 (1.2) | 177.3 (1.4) | 179.1 ( 1.2) | ND | ND |
| | D150mg | ND | 163.3 (1.4) | 187.6 (1.2) | 211.7 (1.3) | 191.6 (1.2) | 186.7 ( 1.1) | ND | ND |
| | Combined | ND | 168.1 (1.3) | 187.0 (1.4) | 203.2 (1.3) | 184.1 (1.3) | 182.6 ( 1.2) | ND | ND |
| | UFH | ND | 147.0 (1.1) | 187.3 (1.4) | 243.6 (1.2) | 199.4 (1.1) | 177.0 ( 1.2) | ND | ND |
| INR | D110mg | 0.9 (1.1) | 1.0 (1.1) | 1.1 (1.2) | 1.1 (1.1) | 1.1 (1.2) | 1.1 ( 1.1) | 1.0 (1.1) | 1.0 (1.1) |
| | D150mg | 1.0 (1.3) | 1.1 (1.1) | 1.3 (1.2) | 1.2 (1.2) | 1.2 (1.2) | 1.2 ( 1.2) | 1.1 (1.1) | 1.0 (1.1) |
| | Combined | 0.9 (1.3) | 1.0 (1.1) | 1.2 (1.2) | 1.2 (1.2) | 1.2 (1.2) | 1.2 ( 1.2) | 1.1 (1.1) | 1.0 (1.1) |
| | UFH | 1.0 (1.1) | 1.0 (1.2) | 1.5 (1.5) | 1.3 (1.3) | 1.3 (1.3) | 1.3 ( 1.3) | 1.0 (1.2) | 0.9 (1.1) |
| TT-10U seconds | D110mg | 13.6 (1.1) | 38.8 (1.6) | 56.4 (1.2) | 52.9 (1.3) | 53.6 (1.3) | 55.2 ( 1.2) | 42.5 (1.6) | 22.5 (1.6) |
| | D150mg | 13.1 (1.1) | 59.0 (1.1) | 60.0 (1.0) | 60.0 (1.0) | 60.0 (1.0) | 60.0 ( 1.0) | 50.3 (1.4) | 25.0 (1.5) |
| | Combined | 13.3 (1.1) | 48.4 (1.5) | 58.3 (1.1) | 56.6 (1.2) | 56.8 (1.2) | 57.6 ( 1.1) | 46.5 (1.5) | 23.8 (1.5) |
| | UFH | 14.6 (1.5) | 14.6 (1.5) | 60.0 (1.0) | 60.0 (1.0) | 60.0 (1.0) | 60.0 ( 1.0) | 20.7 (2.0) | 15.2 (1.6) |
| F1+2 | D110mg | 203.6 (1.4) | 166.7 (1.3) | 217.7 (1.5) | 212.7 (1.7) | 211.3 (3.4) | 278.7 ( 1.7) | 196.1 (1.5) | 214.9 (1.8) |
| | D150mg | 209.8 (1.4) | 152.7 (1.4) | 174.5 (1.3) | 245.3 (1.6) | 248.5 (1.4) | 263.2 ( 1.7) | 191.8 (1.5) | 269.3 (1.8) |
| | Combined | 207.0 (1.7) | 159.1 (1.4) | 193.5 (1.4) | 229.7 (1.6) | 229.6 (2.4) | 270.6 ( 1.7) | 193.8 (1.5) | 242.8 (1.8) |
| | UFH | 190.2 (1.6) | 190.2 (1.6) | 138.1 (1.4) | 160.5 (1.5) | 147.3 (1.5) | 179.0 ( 2.1) | 242.1 (2.1) | 246.8 (1.5) |
| TAT | D110mg | 3.7 (2.0) | 4.8 (2.3) | 6.0 (2.7) | 7.9 (2.1) | 11.6 (2.4) | 10.4 ( 2.0) | 5.5 (2.2) | 6.4 (2.5) |
| | D150mg | 2.9 (1.9) | 3.7 (2.2) | 4.6 (2.4) | 6.6 (2.2) | 6.2 (2.1) | 7.1 ( 2.6) | 4.0 (2.7) | 7.7 (3.0) |
| | Combined | 3.2 (1.9) | 4.2 (2.2) | 5.2 (2.5) | 7.2 (2.2) | 8.4 (2.4) | 8.5 ( 2.3) | 4.6 (2.5) | 7.1 (2.7) |
| | UFH | 3.9 (2.0) | 4.1 (2.1) | 3.2 (1.7) | 4.4 (1.8) | 3.3 (1.8) | 4.5 ( 3.8) | 5.4 (2.5) | 6.8 (2.9) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Fibrin Ddimers | D110mg | 3.7 (1.2) | 3.5 (0.9) | 3.1 (1.2) | 3.0 (1.2) | 3.2 (1.2) | 3.1 ( 1.2) | 3.2 (1.2) | 3.8 (1.2) |
| | D150mg | 3.6 (1.1) | 3.6 (1.1) | 3.4 (0.6) | 2.88 (1.3) | 3.0 (1.2) | 3.1 ( 1.2) | 3.1 (1.2) | 3.6 (1.2) |
| | Combined | 3.7 (1.2) | 3.5 (0.7) | 2.9 (1.3) | 3.0 (1.2) | 3.1 (1.2) | 3.1 ( 1.2) | 3.2 (1.2) | 3.7 (1.2) |
| | UFH | 2.5 (1.8) | 2.8 (1.0) | 2.1 (2.1) | 2.2 (2.0) | 2.4 (1.9) | 2.4 ( 2.0) | 2.5 (2.0) | 2.8 (2.0) |
| | D110mg | 0.08 (0.05) | 0.08 (0.13) | 0.07 (0.06) | 0.06 (0.07) | 0.06 (0.04) | 0.11 ( 0.20) | 0.06 (0.05) | 0.09 (0.06) |
| | D150mg | 0.20 (0.50) | 0.09 (0.06) | 0.07 (0.05) | 0.08 (0.05) | 0.08 (0.05) | 0.08 ( 0.05) | 0.08 (0.05) | 0.09 (0.05) |
| | Combined | 0.14 (0.37) | 0.09 (0.10) | 0.07 (0.05) | 0.07 (0.06) | 0.07 (0.06) | 0.09 ( 0.14) | 0.07 (0.05) | 0.09 (0.05) |
| | UFH | 0.14 (0.10) | 0.14 (0.10) | 0.09 (0.05) | 0.11 (0.08) | 0.11 (0.06) | 0.11 ( 0.05) | 0.09 (0.07) | 0.29 (0.47) |

D110mg denotes dabigatran 110mg
D150mg denotes dabigatran 150mg
Combined denotes dabigatran 110mg or 150mg
UFH denotes unfractionated heparin
ND denotes not done
F1+2 denotes prothrombin fragments 1+2
TAT denotes Thrombin antithrombin III complexes
* First measurement at the time of the PCI providing 'optimal' study medication.
** At 60' following start of the PCI procedure.

## SUPPLEMENTARY APPENDIX

### Patient selection:

*inclusion criteria*

Patients were eligible for the D-fine study if they were:

1. between 18 and 85 years of age, both included
2. due to undergo an elective (non urgent) PCI on one or multiple lesions in the native coronary vessel(s) via a femoral approach
3. if they provide informed consent.

*Exclusion criteria*

Patients were excluded from the D-fine study if:

1. They were not a candidate for PCI or due to lesion specific conditions:
   a. Left main disease
   b. Chronic Total Occlusions
   c. Bifurcation lesions, with hemodynamic important side branch*
   d. Three vessel disease requiring treatment of more than 2 lesions (no staging is allowed)
2. Had to underwent PCI for restenosis.**
3. Hemodynamic instability.
4. Severe hypertension not adequately controlled by antihypertensive therapy at the screening visit (Blood Pressure > 180/110mmHg).
5. Significant mitral or aortic valves disease.
6. Increased bleeding risk:
   a. Ischemic stroke within the last year or history of any previous hemorrhagic stroke, or
   b. intracranial aneurysm
   c. Recent (< 1 month) trauma or major surgery (including bypass surgery) in the last 3 Months
   d. Symptomatic or endoscopically documented ulcer disease in the previous 30 days
   e. Active or recent (< 3 months) major, minor TIMI definition-bleeding
   f. Impaired hemostasis: Thrombocytopenia ( platelet count <100*109) or active bleeding disorder
   g. Anticoagulant (heparin, coumarin) use; international normalized ratio >1.5
   h. Use of oral non steroidal inflammatory drugs (NSAID) within 12 hrs prior to PCI

i. Past or present bleeding disorder (including congenital bleeding disorders such as von Willebrand's disease or hemophillia; acquired bleeding disorders; and unexplained clinically significant bleeding disorders)
j. Thrombolytic therapy within 24 hours preceding randomization

7. Severe renal impairment (e.g. known creatinine clearance < 30 mL/min (GFR – assessed by the Modification of Diet in Renal Disease (MDRD) study equation) or clinical markers of severe renal impairment) [R02-2429] [R02-2529]
8. Known liver disease (e.g. known high concentrations of liver enzymes (more than twice the ULN))
9. Pre-menopausal (last menstruation < 1 year prior to screening) sexually active women who: are pregnant or nursing or are not surgically sterile or are of child bearing potential and not practicing an acceptable method of birth control, (acceptable methods include intrauterine devices (IUD), oral, implantable or injectable contraceptives, double barrier or vasectomised partner). A pregnancy test indicating pregnancy in a woman of childbearing potential at screening.
10. Treatment with other investigational drugs or devices within 30 days before enrolment or
11. Planned use of investigational drugs or devices during the study
12. Use of quinidine
13. Known allergy, hypersensitivity or contraindication to clopidogrel, aspirin.
14. Inability to give informed consent or high likelihood of being unavailable for follow-up
    a. Inability or unwillingness to perform 7-14 day follow up
    b. Patients considered unreliable by the investigator concerning the requirements for follow up during the study and/or compliance with study drug administration or has any condition which in the opinion of the investigator, would not allow safe participation in the study (e.g. drug addiction, alcohol abuse).

*PROTOCOL AMENDMENT 17/11/2009:*

- Simple bifurcation lesions (Medina class: 1/0/0, 0/1/0, 1/0/1 and angle between the distal main vessel and the side branch >70°), with a minimal diameter of the side branch of >2.0mm by visual estimate. (In all cases of side branch stenting the operator is required to attempt a "kissing balloon" dilatation at the end of the procedure).

** PCI for diffuse restenosis (focal in-stent restenosis can be treated in this study)

**Supplementary table-1:** Procedural characteristics*

| | Dabigatran 110mg (n:22) | Dabigatran 150mg (n:21) | Dabigatran 110or 150mg (n: 43) | Heparin (n:10) |
|---|---|---|---|---|
| Lesions treated, mean (SD) | 1.2 (0.4) | 1.4 (0.5) | 1.3 (0.5) | 1.3 (0.5) |
| Target vessel, N(%) | | | | |
| LAD | 8 (42.1) | 9 (42.9) | 17 (42.5) | 4 (40.0) |
| CFX | 6 (31.6) | 9 (42.9) | 15 (37.5) | 1 (10.0) |
| RCA | 6 (31.6) | 6 (28.6) | 12 (30.0) | 6 (60.0) |
| 2-vessel PCI, N (%) | 2 (10.5) | 5 (23.8) | 7 (17.5) | 2 (20.0) |
| Number of stents used, N (%) | | | | |
| 0 | 1 (5.3) | 3 (14.3) | 4 (10.0) | 1 (10.0) |
| 1 | 13 (68.4) | 9 (42.9) | 22 (55.0) | 4 (40.0) |
| 2 | 1 (5.3) | 2 (9.5) | 3 (7.5) | 5 (50.0) |
| >2 | 4 (21.1) | 7 (33.3) | 11 (27.5) | 0 (0.0) |
| Total stent length [mm] (gMean) | 21.7 | 29.2 | 25.5 | 27.4 |
| Procedure time [min] (Mean) | 36.7 | 56.9 | 46.8 | 46.1 |

*As reported by the investigator

LAD denotes left anterior descendens coronary artery, CFX: circumflex coronary artery, RCA: right coronary artery

**Supplementary table-2:** The need of rescue medication and/or clinical signs of catheter ralated thrombosis during the PCI procedure.

| | Dabigatran 110mg N (%) | Dabigatran 150mg N (%) | Dabigatran 110 or 150mg N (%) | Heparin N (%) |
|---|---|---|---|---|
| Total number of patients in analysis set | 19 (100) | 21 (100) | 40 (100) | 10 (100) |
| Bailout AC therapy and/or catheter related thrombosis during the procedure* | 2 (11) | 3 (14) | 5 (13) | 1 (10) |
| Odds ratio (95% CI) vs heparin | 1.00 (0.08, 12.76) | 1.50 (0.13, 16.82) | 1.25 (0.13, 12.25) | |
| Bail out antithrombotic therapy | | | | |
| UFH | 0 | 3 (14) | 3 (8) | 0 |
| GPIIb/IIIa inhibitor | 1 (5) | 2 10) | 3 (8) | 1 (10) |
| Abrupt vessel closure, new thrombus with reduced flow, or no-reflow | 2 (11) | 1 (5) | 3 8) | 0) |
| Myocardial infarction | | | | |
| Periprocedural | 2 (11) | 3 (14) | 5 (13) | 0 |
| Procedural | 1 (5) | 3 (14) | 4 (11) | 0 |

*Until removal of the guiding catheter and the patient left the catheterization laboratory

AC denotes anticoagulation

UFH denotes unfractionated heparin

GPIIb/IIIa inhibitor = abciximab

**Supplementary table-3:** Patient narratives.

| | Study group | Event Type | Case scenario |
|---|---|---|---|
| 1 | UFH | RE-LY minor bleeding | 69 years old female patient. Access site bleeding, no drop in haemoglobin. No transfusion required. No additional treatment required. The patient has recovered. |
| 2 | UFH | Flow limiting thrombus | 63 years old female patient. Target vessel was a severe in-stent restenosis in segment 2. During the PCI phase a flow reducing thrombus was seen at the first contrast injection, before any wire insertion. The patient experienced no chest pain and no ST-T changes were seen. Cardiac enzymes: CK and CK-MB were not elevated. cTn peak 0.05 ug/l (URL:<0.03 ug/L). The event has been treated with thrombus aspiration and rescue medication: GPIIb/IIIa inhibitor. The patient has recovered. |
| 3 | Dabigatran 110mg | Flow limiting thrombus ***and*** procedural myocardial infarction | 69 years old female patient. During PCI phase a thrombus with reduced flow in segment 2 was seen. The patient experienced chest pain with on the monitor ST elevations. CK peak was 145 U/l (URL:<170U/l) and cTn peak was 0.11 ug/l (URL:<0.03 ug/L). The event was treated with rescue medication: UFH and GPIIb/IIIa inhibitor. The patient has recovered. |
| 4 | Dabigatran 150mg | Flow limiting thrombus ***and*** procedural myocardial infarction | 69 years old male patient. The patient was treated by PCI and stenting for a lesion (segment 13) in the CFX coronary artery. Following the index study procedure an IVUS examination towards the LAD was performed. During the IVUS procedure a large thrombus appeared in the LAD, the left main and proximal CFX coronary artery (procedural stent thrombosis). The patient experienced chest pain with ST segment elevations on the ECG. There was an increase in cardiac biomarkers: CK peak 428 IU/L (URL:<200U/L), CKMBpeak 81.5 U/l (<24 U/L) and cTn peak 1.57 ug/l (URL:<0.03 ug/L). The event was treated with rescue medication: UFH and GPIIb/IIIa inhibitor An additional stent was deployed in segment 6. The patient has recovered. |
| 5 | Dabigatran 110mg | Periprocedural myocardial infarction ***and*** rescue therapy. | 63 years old male patient. Clinical signs and symptoms consistent with myocardial ischemia *after* leaving the catheterisation suite but within 12 hours post PCI. There was an increase in cardiac biomarkers: CKpeak 999IU/L (URL:<200U/L), CKMBpeak: 93 ug/L (<7.6ug/L) and cTn peak 2.13 ug/l (URL:<0.03 ug/L). The event has was treated with rescue medication: GPIIb/IIIa inhibitor; atropine and nitroglycerin. The patient has recovered. |
| 6 | Dabigatran 150mg | Procedural myocardial infarction | 64 years old male patient. During the PCI phase the patient experienced no chest pain but showed abnormalities on the ECG. The PCI target segment was 15 mm in segment 6. Cardiac enzymes increased: cTn peak 0.23 ug/l (URL:<0.03 ugram/L), CK peak 215 U/l (URL:<200U/L ) and CK MB peak 12 U/l (<24 U/L). No rescue medication was given. The patient has recovered. |
| 7 | Dabigatran 150mg | Procedural myocardial infarction | 62 years old male patient. Index procedure complicated with spiral dissection. The patient experienced chest pain with on the ECG Q-waves and ST-elevation. There was an increase in cardiac biomarkers: CK peak 1339IU/l (URL:<200U/L ) and CK-MB peak 144U/l (<24 U/L) and CTn peak 2.76ug/l (URL:<0.03 ug/L);. The event was treated with rescue medication: UFH and GPIIb/IIIa inhibitor; and multiple additional stents. The DSMB/CEC judged the lesions were complex and not suitable for the trial. The patient has recovered. |

cTn denotes cardiac troponin
UFH denotes unfractionated heparin
IVUS denotes intravascular ultrasound

# CHAPTER 2.5

## For the PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia study (PRODIGY) Investigators. Six Versus Twenty-four Month Dual Antiplatelet Therapy After Coronary Stenting: A Randomized Multicenter Trial

Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, Castriota F, Colombo F, Tebaldi M, Fucà G, Kubbajeh M, Cangiano E, Minarelli M, Scalone A, Cavazza C, Frangione A, Borghesi M, Marchesini J, Parrinello G, Ferrari R; Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) Investigators.

*Circulation*. 2012, **125**:2015-26. [**original research paper**]

# Short- Versus Long-Term Duration of Dual-Antiplatelet Therapy After Coronary Stenting

## A Randomized Multicenter Trial

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***Background***—The optimal duration of dual-antiplatelet therapy and the risk-benefit ratio for long-term dual-antiplatelet therapy after coronary stenting remain poorly defined. We evaluated the impact of up to 6 versus 24 months of dual-antiplatelet therapy in a broad all-comers patient population receiving a balanced proportion of Food and Drug Administration–approved drug-eluting or bare-metal stents.

***Methods and Results***—We randomly assigned 2013 patients to receive bare-metal, zotarolimus-eluting, paclitaxel-eluting, or everolimus-eluting stent implantation. At 30 days, patients in each stent group were randomly allocated to receive up to 6 or 24 months of clopidogrel therapy in addition to aspirin. The primary end point was a composite of death of any cause, myocardial infarction, or cerebrovascular accident. The cumulative risk of the primary outcome at 2 years was 10.1% with 24-month dual-antiplatelet therapy compared with 10.0% with 6-month dual-antiplatelet therapy (hazard ratio, 0.98; 95% confidence interval, 0.74–1.29; $P=0.91$). The individual risks of death, myocardial infarction, cerebrovascular accident, or stent thrombosis did not differ between the study groups; however, there was a consistently greater risk of hemorrhage in the 24-month clopidogrel group according to all prespecified bleeding definitions, including the recently proposed Bleeding Academic Research Consortium classification.

***Conclusions***—A regimen of 24 months of clopidogrel therapy in patients who had received a balanced mixture of drug-eluting or bare-metal stents was not significantly more effective than a 6-month clopidogrel regimen in reducing the composite of death due to any cause, myocardial infarction, or cerebrovascular accident.

***Clinical Trial Registration***—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00611286.

**(*Circulation*. 2012;125:2015-2026.)**

**Key Words:** antiplatelet therapy ■ aspirin ■ clopidogrel ■ percutaneous coronary intervention ■ dual antiplatelet therapy

Nine to 12 months of clopidogrel therapy after bare-metal stenting has been shown to reduce the composite of death, myocardial infarction, or stroke by nearly 30% in patients with non–ST-segment–elevation acute coronary syndrome compared with 1-month duration of treatment.[1,2] The design of these studies, however, was such that only patients who received preprocedural clopidogrel continued to receive it long-term.[1,2] Therefore, the actual effect of long-term clopidogrel may have been biased by the positive influence of upstream initiation of treatment in these patients. Because of prior experience with patients affected by non–ST-segment–elevation acute coronary syndromes, as well as patients undergoing coronary stenting, long-term therapy with clopidogrel is also

Received October 2, 2011; accepted February 27, 2012.

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**The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.111.071589/-/DC1.**

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***Circulation* is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.111.071589**

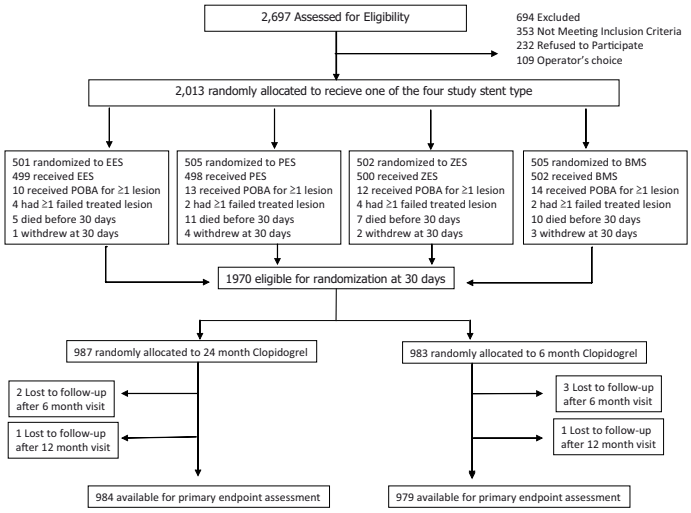


**Figure 1.** Study profile. BMS indicates bare-metal stent; DAPT, dual-antiplatelet therapy; EES, everolimus-eluting stent; POBA, plain balloon angioplasty; PES, paclitaxel-eluting stent; and ZES, zotarolimus-eluting stent.

recommended for patients with ST-segment elevation myocardial infarction.[3,4]

**Editorial see p 1967**
**Clinical Perspective on p 2026**

Clopidogrel therapy should be prolonged for at least 12 months or for 6 to 12 months after drug-eluting stent (DES) implantation, according to the American College of Cardiology/American Heart Association[5] and European Society of Cardiology[6] guidelines, respectively, based on concerns that delayed vessel healing may be responsible for late (>30 days) or very late (>1 year) stent thrombosis. Yet randomized data supporting this recommendation are limited,[7] and findings of observational studies have been inconsistent.[8–11] Therefore, the optimal duration of dual-antiplatelet therapy and the risk-benefit ratio for long-term dual-antiplatelet therapy after percutaneous coronary intervention remain uncertain.

The purpose of the present trial was to assess the effect of using dual-antiplatelet therapy for 6 versus 24 months on long-term clinical outcomes after coronary intervention in a broad all-comers patient population receiving a balanced proportion of Food and Drug Administration–approved DES or bare-metal stents (BMS).

## Methods

### Study Design and Population

The Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) is a 4-by-2 randomized, multicenter, open-label clinical trial designed to evaluate the efficacy and safety of prolonging the duration of clopidogrel therapy for up to 24 months in all-comer patients receiving a balanced mixture of stents with varying anti-intimal hyperplasia potency and belonging to both first- and second-generation DES.[12] Patients undergoing elective, urgent, or emergent coronary angioplasty with intended stent implantation at 3 referral Italian sites were randomly assigned in a 1:1:1:1 fashion to 1 of 4 stent types, including an everolimus-eluting stent, paclitaxel-eluting stent, zotarolimus-eluting Endeavor Sprint stent, or third-generation thin-strut BMS. At 30 days, patients in each stent group were randomized in a balanced fashion to either 6 or 24 months of dual-antiplatelet treatment (Figure 1). In the 6-month dual-antiplatelet therapy group, clopidogrel discontinuation at any time after 30 days was allowed in patients who were randomized to a BMS if coronary intervention was indicated by the presence of stable coronary artery disease. This was driven by the lack of data showing the value of clopidogrel in addition to aspirin beyond 30 days in this patient population. The inclusion of a BMS group allowed us to prespecify the interaction testing between stent type and duration of therapy.

Individuals eligible for enrolment were patients ≥18 years of age with chronic stable coronary artery disease or acute coronary syndromes, including non–ST-elevation and ST-elevation myocardial infarction. They were eligible if they had at least 1 lesion with a diameter stenosis of ≥50% that was suitable for coronary stent implantation in a vessel with a reference vessel diameter of ≥2.25 mm. Selection criteria were broad, reflecting routine clinical practice. We set no limit for the number of treated lesions, vessels, or lesion length, and we excluded no patients on the basis of comorbid disorders or age, apart from the following prespecified criteria: Known allergy to acetylsalicylic acid or clopidogrel; planned surgery within 24 months of percutaneous coronary intervention unless the dual-antiplatelet therapy could be maintained throughout the perisurgical period; history of bleeding diathesis; major surgery within 15 days; active bleeding or previous stroke in the past 6 months; concomitant or foreseeable need for oral anticoagulation therapy; pregnancy; life expectancy <24 months; participation in another trial; and inability to provide informed consent.

The ethics committees of the 3 participating centers independently approved the protocol, and all participants gave written informed consent.

## Randomization Procedures

The treating physician performed allocation of study treatment immediately after eligibility criteria were met and subsequently at 30±5 days after intervention via sealed envelopes. Both randomization procedures were achieved with a computer-generated random sequence that was produced in the coordinating center with random block sizes of 4, 8, and 12. Treatment allocation was not masked.

### *Stent Randomization*

A randomization scheme to stent type based on a 1:1:1:1 ratio to everolimus-eluting, paclitaxel-eluting, zotarolimus-eluting Endeavor Sprint, or BMS (any thin-strut, uncoated-stent type approved by the regulatory agency) was stratified by the center, the presence of ongoing ST-segment–elevation myocardial infarction, diabetes mellitus, or the need for intervention on at least 1 in-stent restenotic lesion. Patients were then treated with aspirin and clopidogrel for the first 30 days after intervention. In the case of intercurrent or staged revascularization procedures that required stent implantation, the study protocol mandated the use of a study stent as per the original randomization scheme.

### *Clopidogrel Randomization*

Random allocation to 1 of the 2 antiplatelet treatment strategies occurred at 30±5 days based on a random scheme that was stratified by the same covariates implemented in the balancing randomization at the time of the index procedure, plus randomized stent group.

## Treatment Protocol and Follow-Up Procedures

All patients received aspirin (160 to 325 mg orally or 500 mg IV as a loading dose and then 80 to 160 mg orally indefinitely) and clopidogrel (300 or 600 mg orally as a loading dose) and then 75 mg/d for the treatment duration according to the randomization scheme as follows: For either 6 months in the 6-month dual-antiplatelet group (in patients randomized to BMS and presenting with stable coronary artery disease, a shorter [but not <30 day] duration of dual-antiplatelet treatment was allowed, to comply with available evidence) or 24 months in the 24-month dual-antiplatelet arm irrespective of the previously implanted stent type or indication for the coronary procedure.

Anticoagulation during coronary intervention was accomplished through administration of either unfractionated heparin or bivalirudin. All interventions were performed according to current standard guidelines, and the final interventional strategy, including administration of glycoprotein IIb/IIIa antagonists, predilation or postdilation, or use of intravascular imaging techniques, was left entirely to the discretion of the operator, except for the stent utilization. Angiographic success was defined as residual stenosis <30% by visual analysis in the presence of TIMI (Thrombolysis In Myocardial Infarction) 3 grade flow.

## Follow-Up

All randomized patients who were not lost to follow-up, irrespective of their compliance with the assigned treatment schedule, returned for study visits at 30 days, and then every 6 months up to 2 years. During follow-up visits, patients were examined and assessed for adverse events, and 12-lead ECG recordings were obtained. At all follow-up time points, patients were questioned about their compliance with the study medication. Any interruptions or termination, as well as the reasons for this, were documented. To ensure a high adherence rate to the assigned study treatment, a dedicated study nurse per site telephonically contacted each patient on a monthly basis.

## Study End Points

The primary objective of the present study was to assess whether 24-month dual-antiplatelet treatment consisting of clopidogrel and aspirin after coronary stenting, evaluated from the time of randomization up to 2 years, was associated with a lower cumulative incidence of death of any cause, nonfatal myocardial infarction, or cerebrovascular accident compared with 6-month clopidogrel and aspirin duration. Because the therapy did not differ between the 2 groups in the first month after stenting, the time frame of interest for the primary end point was from 30 days (ie, after the primary end point randomization) to 24 months.

Secondary end points included each component of the primary end point, cardiovascular death, the incidence of stent thrombosis defined on the basis of the Academic Research Consortium criteria,[13] and bleeding outcomes. The key safety end point was the rate of bleeding according to TIMI criteria and the BleedScore.[14] The study protocol was then amended in March 2010 to incorporate the recently developed Bleeding Academic Research Consortium (BARC) criteria,[15] with the key safety end point being a composite of type 5, 3, or 2 bleeding.

Prespecified analysis of the primary and secondary end points was performed according to age, sex, presence of diabetes mellitus, type of stent implanted (BMS versus DES), clinical presentation, complexity, number of treated lesions, and renal function. All deaths were considered to be of cardiovascular causes unless an unequivocal noncardiovascular cause could be established. The diagnosis of acute myocardial infarction was based on the universal definition of myocardial infarction.[16] Stroke, as detected by the occurrence of a new neurological deficit, was confirmed by a neurologist and on imaging, whereas the occurrence of a transient ischemic attack required hospitalization and clinical confirmation by a neurologist.

All study end points and bleeding events were confirmed on the basis of documentation collected at each hospital and were centrally adjudicated by the clinical events committee, whose members were unaware of patients' treatment-group assignments. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Statistical Analysis

Assuming an event rate of 8.0% at 2 years for the primary end point of death of any cause, nonfatal myocardial infarction, or cerebrovascular accident among patients who were assigned to 6-month clopidogrel duration, we estimated that at least 1700 patients (850 in each group) would need to be enrolled to detect a 40% reduction in the relative risk of the primary end point in the 24-month clopidogrel group compared with 6-month duration of clopidogrel therapy, with statistical power of ≥80% at a 2-sided significance level of 0.05. The assumed rate for the primary end point and the assumed reduction in relative risk were based on historical data.[9,10,12] No interaction was expected between stent type (DES versus BMS) and assigned treatment. The planned sample size was then increased up to 2000 to allow for fatalities occurring within the first 30 days, noncompliance, and loss to follow-up.

Categorical variables were expressed as frequency (percentage), whereas continuous variables were expressed as median (interquartile range). Baseline continuous variables were compared between randomized groups with the Wilcoxon rank sum test, whereas for baseline binary variables, the Fisher exact test was used.

Estimation of the cumulative major adverse cardiovascular event rate was performed by the Kaplan-Meier method, and events were compared by the log-rank test. Hazard ratios with 95% confidence intervals (CIs) were calculated for long-term clopidogrel versus short-term clopidogrel (ie, values >1 indicated increased hazard in the long-term group) with a proportional hazards model. The proportionality assumptions were checked by visual estimation after we plotted the log cumulative hazard versus (log) time at follow-up after the index procedure and by applying a test for nonproportional hazards using Schoenfeld residuals as described previously,[17] which failed to reject the null hypothesis that event rate was affected by time ($P=0.87$). We performed a Cox regression analysis with interaction testing to determine whether the effect of duration of dual-antiplatelet therapy on the primary efficacy end point at 2 years was consistent across important prespecified subgroups. Interaction tests were performed with likelihood ratio tests of the null hypothesis that the interaction coefficient was zero. A 2-sided probability value <0.05 was considered significant. All analyses, performed on the basis of the intention-to-treat principle, were performed with STATA, version 11.1 (Stata Corp, College Station, TX).

**Table 1. Baseline Characteristics of Patients**

| Characteristic | 24-Month Clopidogrel (n=987) | 6-Month Clopidogrel (n=983) | *P* |
|---|---|---|---|
| Age, y | | | |
| Mean±SD | 67.8±11 | 67.9±11 | |
| Median | 69 | 69 | 0.85 |
| Interquartile range | 61–76 | 60–77 | |
| Range | 29–94 | 31–99 | |
| Male sex, n (%) | 764 (77.4) | 747 (76.0) | 0.46 |
| Body mass index, kg/m$^2$ | | | |
| Median | 26.6 | 26.7 | 0.68 |
| Interquartile range | 24.6–29.4 | 24.8–29.3 | |
| Diabetes, n (%) | 244 (24.7) | 233 (23.7) | 0.87 |
| Insulin dependent, n (%) | 59 (6.0) | 55 (5.6) | |
| Hypertension, n (%) | 721 (73.0) | 693 (70.4) | 0.22 |
| Hyperlipidemia, n (%) | 553 (56.0) | 525 (53.4) | 0.25 |
| Current cigarette use, n (%) | 222 (22.5) | 247 (25.1) | 0.28 |
| Creatinine clearance, mL/min | | | |
| Median | 74.4 | 75.4 | 0.53 |
| Interquartile range | 56.5–99.2 | 57.1–94.8 | |
| Prior myocardial infarction, n (%) | 270 (27.3) | 258 (26.2) | 0.67 |
| Prior percutaneous coronary intervention, n (%) | 184 (18.6) | 174 (17.7) | 0.65 |
| Prior coronary bypass surgery n (%) | 110 (11.1) | 105 (10.7) | 0.79 |
| Prior stroke or transient ischemic attack, n (%) | 37 (3.7) | 39 (4.0) | 0.81 |
| Left ventricular ejection fraction | | | |
| Median | 55.0 | 50.0 | 0.25 |
| Interquartile range | 45–60 | 43.3–60 | |
| Clinical presentation, n (%) | | | |
| Stable angina pectoris | 257 (26.0) | 250 (25.4) | 0.75 |
| Acute coronary syndrome | 732 (74.2) | 733 (74.6) | |
| Non–ST-elevation acute coronary syndrome | 411 (41.6) | 406 (41.3) | 0.88 |
| Unstable angina | 183 (18.5) | 182 (18.5) | 0.99 |
| Non–ST-elevation MI | 226 (22.9) | 224 (22.8) | 0.95 |
| ST-segment-elevation MI | 321 (32.5) | 327 (33.3) | 0.73 |
| Angiographic features, n (%) | | | |
| Single-vessel disease | 344 (34.9) | 334 (34.0) | |
| Double-vessel disease | 351 (35.6) | 350 (35.6) | 0.89 |
| Triple-vessel disease | 292 (29.6) | 299 (30.4) | |

MI indicates myocardial infarction.

**Table 2. Procedural Results**

| Patients | 24-Month Clopidogrel (n=987) | 6-Month Clopidogrel (n=983) | *P* |
|---|---|---|---|
| No. of treated lesions | 1500 | 1546 | |
| Mean±SD | 1.52±0.86 | 1.57±0.94 | |
| Median | 1 | 1 | 0.37 |
| Interquartile range | 1–2 | 1–2 | |
| Range | 1–7 | 1–7 | |
| ≥2 Treated lesions, n (%) | 365 (37) | 371 (37.7) | 0.73 |
| ≥3 Treated lesions, n (%) | 108 (10.9) | 115 (11.7) | 0.57 |
| ≥4 Treated lesions, n (%) | 38 (3.9) | 44 (4.5) | 0.49 |
| Multivessel intervention, n (%) | 253 (25.6) | 273 (27.8) | 0.28 |
| LAD treated, n (%) | 518 (52.5) | 518 (52.7) | 0.92 |
| CFX treated, n (%) | 321 (32.5) | 318 (32.4) | 0.93 |
| RCA treated, n (%) | 346 (35.1) | 363 (36.9) | 0.39 |
| LMCA treated, n (%) | 55 (5.6) | 56 (5.7) | 0.90 |
| SVG treated, n (%) | 23 (2.3) | 17 (1.7) | 0.34 |
| At least 1 complex (type B2 or C) lesion, n (%)* | 642 (65.1) | 664 (67.6) | 0.24 |
| Total ACC/AHA score*† | | | 0.19 |
| Median | 3 | 3 | |
| Interquartile range | 2–4 | 2–5 | |
| At least 1 restenotic lesion, n (%) | 45 (4.6) | 48 (4.9) | 0.75 |
| Implanted stent type, n (%) | | | 0.99 |
| Bare-metal stent | 246 (24.9) | 246 (25.0) | |
| Everolimus-eluting stent | 248 (25.1) | 245 (24.9) | |
| Paclitaxel-eluting stent | 245 (24.8) | 245 (24.9) | |
| Everolimus-eluting stent | 248 (25.1) | 247 (25.1) | |
| No. of stents implanted | | | 0.27 |
| Mean±SD | 1.82±1.23 | 1.90±1.25 | |
| Median | 2 | 2 | |
| Interquartile range | 1–2 | 1–2 | |
| Range | 1–10 | 1–11 | |
| Length of stent, mm | | | 0.43 |
| Median | 30 | 30 | |
| Interquartile range | 20–48 | 20–48 | |
| Range | 8–303 | 8–250 | |
| Mean stent diameter, mm | | | 0.43 |
| Median | 3 | 3 | |
| Interquartile range | 2.65–3.33 | 2.66–3.25 | |

LAD indicates left anterior descending artery; CFX, circumflex artery; RCA, right coronary artery; LMCA, left main coronary artery; SVG, saphenous vein graft; and ACC/AHA, American College of Cardiology/American Heart Association.

*Calculated in 952 patients in the 24-month clopidogrel arm and in 943 patients in the 6-month clopidogrel arm who presented with ≥1 de novo lesion; ACC/AHA score was missing in 3 patients.

†As described previously,[18] type A stenoses were coded 1 point, type B1 stenoses 2 points, type B2 stenoses 3 points, and type C stenoses 4 points.

## Results

From December 2006 to December 2008, a total of 2789 patients underwent screening, and 2013 were ultimately recruited into the study and randomized to receive 1 of the 4 stent types (Figure 1). Thirty-three patients (1.6%) died within 30 days, and 10 patients withdrew consent; therefore, 1970 patients were randomly allocated at 1 month to undergo 24-month versus 6-month clopidogrel therapy. The 2 groups were well balanced with regard to baseline and angiographic characteristics (Tables 1 and 2).

The median age was 69 years; roughly one fourth of the patient population had a history of diabetes mellitus or prior myocardial infarction. Nearly two thirds of the patients presented with acute coronary syndromes, including acute ST-segment–elevation myocardial infarction in 30% of the

**Table 3. Use of Medications During Trial**

| | 24-Month Clopidogrel | 6-Month Clopidogrel | *P* |
|---|---|---|---|
| Drug therapy at 30 d, n (%) | | | |
| No. evaluated | 987 | 983 | |
| Aspirin | 987 (100) | 983 (100) | >0.99 |
| Clopidogrel | 987 (100) | 983 (100) | >0.99 |
| Aspirin and clopidogrel | 987 (100) | 983 (100) | >0.99 |
| ACE inhibitors | 789 (80.0) | 743 (75.6) | 0.25 |
| Angiotensin II receptor antagonist | 69 (7.0) | 86 (8.7) | 0.18 |
| β-blockers | 828 (84.6) | 810 (83.6) | 0.55 |
| Statins | 898 (91.0) | 905 (92.1) | 0.85 |
| Proton pump inhibitors | 375 (38.0) | 363 (36.9) | 0.62 |
| Drug therapy at 6 mo, n (%) | | | |
| No evaluated, total (DES/BMS) | 966 (725/241) | 963 (723/240) | |
| Aspirin | 960 (99.4) | 954 (99.1) | 0.43 |
| Clopidogrel | 960 (99.4) | 805 (83.6) | <0.0001 |
| DES patients | 721 (99.5) | 711 (98.3) | 0.09 |
| BMS patients | 239 (99.2) | 94 (39.2) | <0.0001 |
| Aspirin and clopidogrel | 954 (98.8) | 800 (83.1) | <0.0001 |
| ACE inhibitors | 754 (78.0) | 743 (77.2) | 0.87 |
| Angiotensin II receptor antagonist | 94 (9.7) | 89 (9.2) | 0.74 |
| β-blockers | 811 (84.0) | 802 (83.3) | 0.91 |
| Statins | 876 (90.7) | 866 (89.9) | 0.90 |
| Proton pump inhibitors | 369 (38.2) | 298 (30.9) | 0.019 |
| Drug therapy at 12 mo, n (%) | | | |
| No. evaluated, total (DES/BMS) | 948 (712/236) | 942 (710/232) | |
| Aspirin | 939 (99.0) | 926 (98.3) | 0.15 |
| Clopidogrel | 932 (98.3) | 33 (3.5) | <0.0001 |
| DES patients | 699 (98.2) | 25 (3.5) | <0.0001 |
| BMS patients | 233 (98.7) | 8 (3.5) | <0.0001 |
| Aspirin and clopidogrel | 923 (97.4) | 32 (3.4) | <0.0001 |
| ACE inhibitors | 743 (78.4) | 739 (78.5) | 0.99 |
| Angiotensin II receptor antagonist | 102 (10.8) | 102 (10.8) | 0.96 |
| β-blockers | 770 (81.2) | 772 (82.0) | 0.90 |
| Statins | 845 (89.1) | 834 (88.5) | 0.92 |
| Proton pump inhibitors | 358 (37.8) | 294 (31.2) | 0.036 |
| Drug therapy at 18 mo, n (%) | | | |
| No. evaluated, total (DES/BMS) | 933 (699/234) | 932 (701/231) | |
| Aspirin | 921 (98.7) | 913 (98.0) | 0.21 |
| Clopidogrel | 904 (96.9) | 8 (0.9) | <0.0001 |
| DES patients | 673 (96.3) | 6 (0.9) | <0.0001 |
| BMS patients | 231 (98.7) | 2 (0.9) | <0.0001 |
| Aspirin and clopidogrel | 895 (95.9) | 6 (0.6) | <0.0001 |
| ACE inhibitors | 717 (76.8) | 712 (76.4) | 0.93 |
| Angiotensin II receptor antagonist | 104 (11.1) | 118 (12.7) | 0.37 |
| β-blockers | 757 (81.1) | 755 (81.0) | 0.98 |
| Statins | 828 (88.7) | 821 (88.1) | 0.91 |
| Proton pump inhibitors | 352 (37.7) | 301 (32.3) | 0.088 |
| Drug therapy at 24 mo, n (%) | | | |
| No. evaluated, total (DES/BMS) | 920 (690/230) | 920 (693/227) | |
| Aspirin | 905 (98.4) | 897 (97.5) | 0.19 |
| Clopidogrel | 880 (95.7) | 5 (0.5) | <0.0001 |
| DES patients | 654 (94.8) | 5 (0.7) | <0.0001 |
| BMS patients | 226 (98.3) | 0 | <0.0001 |
| Aspirin and clopidogrel | 871 (94.7) | 3 (0.3) | <0.0001 |
| ACE inhibitors | 707 (76.8) | 708 (77.0) | 0.97 |
| Angiotensin II receptor antagonist | 112 (12.2) | 119 (12.9) | 0.65 |
| β-blockers | 750 (81.5) | 749 (81.4) | 0.99 |
| Statins | 818 (88.9) | 811 (88.2) | 0.91 |
| Proton pump inhibitors | 344 (37.4) | 302 (32.8) | 0.16 |

ACE indicates angiotensin-converting enzyme; DES, drug-eluting stent; and BMS, bare-metal stent.

cases, and more than half of the patients had multivessel disease. At least 1 complex lesion, defined according to the American College of Cardiology/American Heart Association scale,[18] was treated in >65% of the patients, and everolimus-eluting, paclitaxel-eluting, or zotarolimus-eluting stents or BMS were implanted in one fourth of the patients, as per the randomization scheme.

## Follow-Up and Clinical Outcomes

Overall, there were 118 patients (12%) in the short-term arm who discontinued clopidogrel after the first month versus 2 (0.2%) in the 24-month clopidogrel group. All of these patients received BMS at the time of intervention as per randomization. Among the patients allocated to the DES groups, clopidogrel was discontinued for various reasons before 6 months in 5 and 7 patients in the long- and short-term clopidogrel groups, respectively.

During the follow-up period, adherence to the assigned study treatment progressively increased from 6 to 12 months in both groups, and it was ≈97% at 12 months and ≈95% at 24 months in the 24-month clopidogrel group and >95% at both 12 and 24 months in the 6-month clopidogrel group (Table 3). Clinical follow-up at 2 years with respect to the primary and secondary end points was complete for 99.7% of patients in the long-term clopidogrel group and for 99.6% of those in the short-term clopidogrel group.

During the follow-up period, 130 patients died, 73 of cardiovascular causes. A total of 80 patients had an acute myocardial infarction, 35 had a cerebrovascular accident (of which 14 were confirmed as having intracranial hemorrhage), and 12 had definite stent thrombosis. Overall, there were 181 bleeding events according to the Bleeding Academic Research Consortium classification, of which 107 were included in the key safety end point and 14 were reported to be fatal.

The Kaplan-Meier estimate of the event rate for the primary end point (death of any cause, myocardial infarction, or cerebrovascular accident) at 2 years was 10.1% in the 24-month clopidogrel group compared with 10.0% in the 6-month clopidogrel group (hazard ratio, 0.98; 95% CI,

**Table 4. Outcome Rates at 24 Months According to Treatment Group***

| | 24-Month Clopidogrel (n=987) | 6-Month Clopidogrel (n=983) | Hazard Ratio (95% CI) | *P* |
|---|---|---|---|---|
| Primary efficacy end point, n (%) | | | | |
| Death of any cause, myocardial infarction, or cerebrovascular accident | 100 (10.1) | 98 (10.0) | 0.98 (0.74–1.29) | 0.91 |
| Secondary efficacy end points, n (%) | | | | |
| Death of any cause or myocardial infarction | 88 (8.9) | 94 (9.6) | 1.07 (0.80–1.43) | 0.62 |
| Death of any cause or cerebrovascular accident | 77 (7.8) | 70 (7.1) | 0.91 (0.66–1.26) | 0.57 |
| Death of any cause | 65 (6.6) | 65 (6.6) | 1.00 (0.72–1.40) | 0.98 |
| Death of cardiovascular cause | 36 (3.7) | 37 (3.8) | 1.03 (0.66–1.61) | 0.89 |
| Myocardial infarction | 39 (4.0) | 41 (4.2) | 1.06 (0.69–1.63) | 0.80 |
| Cerebrovascular accident | 21 (2.1) | 14 (1.4) | 0.60 (0.29–1.23) | 0.17 |
| Confirmed intracranial hemorrhage | 10 (1.0) | 4 (0.4) | 0.40 (0.13–1.28) | 0.12 |
| Definite stent thrombosis | | | | |
| Late | 8 (0.8) | 4 (0.4) | 0.67 (0.19–2.37) | 0.53 |
| Very late | 0 | 3 (0.3) | 1.51 (0.25–9.00) | 0.65 |
| Cumulative | 8 (0.8) | 7 (0.7) | 0.88 (0.32–2.42) | 0.80 |
| Definite or probable stent thrombosis | | | | |
| Late | 10 (1.0) | 9 (0.9) | 0.90 (0.37–2.22) | 0.82 |
| Very late | 3 (0.3) | 6 (0.6) | 2.00 (0.50–8.06) | 0.32 |
| Cumulative | 13 (1.3) | 15 (1.5) | 1.15 (0.55–2.41) | 0.70 |
| Definite, probable, or possible stent thrombosis | | | | |
| Late | 26 (2.6) | 28 (2.9) | 1.07 (0.64–1.83) | 0.78 |
| Very late | 12 (1.3) | 18 (1.9) | 1.50 (0.73–3.12) | 0.27 |
| Cumulative | 38 (3.9) | 46 (4.7) | 1.21 (0.79–1.86) | 0.38 |
| Safety end points, n (%) | | | | |
| BARC classification* | | | | |
| Type 5 | 9 (0.9) | 5 (0.5) | 0.56 (0.19–1.66) | 0.29 |
| Type 5A | 3 (0.3) | 0 | | |
| Type 5B | 6 (0.6) | 5 (0.5) | | |
| Type 4 | 0 | 2 (0.2) | | 0.47 |
| Type 3 | 25 (2.5) | 14 (1.4) | 0.56 (0.29–1.07) | 0.075 |
| Type 3A | 16 (1.6) | 11 (1.1) | | |
| Type 3B | 5 (0.5) | 3 (0.3) | | |
| Type 3C | 4 (0.4) | 0 | | |
| Type 2 | 39 (4.0) | 15 (1.5) | 0.38 (0.21–0.69) | 0.0016 |
| Type 1 | 11 (1.1) | 8 (0.8) | 0.72 (0.11–1.47) | 0.65 |
| Key safety end point (type 5, 3, or 2) | 73 (7.4) | 34 (3.5) | 0.46 (0.31–0.69) | 0.00018 |
| Type 5 or 3 | 34 (3.4) | 19 (1.9) | 0.56 (0.32–0.98) | 0.037 |
| Type 3 or 2 | 64 (6.5) | 29 (3.0) | 0.45 (0.29–0.69) | 0.00033 |
| TIMI classification | | | | |
| Major | 16 (1.6) | 6 (0.6) | 0.38 (0.15–0.97) | 0.041 |
| Minor | 11 (1.1) | 9 (0.9) | 0.82 (0.34–1.94) | 0.66 |
| Major or minor | 27 (2.7) | 15 (1.5) | 0.55 (0.30–1.04) | 0.063 |
| BleedScore | | | | |
| Total score | | | | |
| Median | 0 | 0 | | <0.0001 |
| Interquartile range | 0–1 | 0–0 | | |

(*Continued*)

**Table 4. Continued**

| | 24-Month Clopidogrel (n=987) | 6-Month Clopidogrel (n=983) | Hazard Ratio (95% CI) | *P* |
|---|---|---|---|---|
| Range | 0–18 | 0–18 | | |
| 0 | 729 (73.9) | 845 (86.0) | | <0.0001 |
| 1 | 47 (4.8) | 20 (2.0) | | |
| 2 | 27 (2.7) | 11 (1.1) | | |
| 3 | 104 (10.5) | 65 (6.6) | | |
| 4 | 13 (1.3) | 4 (0.4) | | |
| ≥5 | 67 (6.8) | 38 (3.9) | | |
| Red blood cell transfusion | 26 (2.6) | 13 (1.3) | 0.50 (0.26–0.98) | 0.041 |

CI indicates confidence interval; BARC, Bleeding Academic Research Consortium; and TIMI, Thrombolysis In Myocardial Infarction.

For the total number of events for each type of end point, first events only were counted. Cumulative rates of events were based on Kaplan-Meier estimates.

*Type 5 refers to fatal bleeding. Type 4 refers to coronary artery bypass–related bleeds. Type 3 bleeds are divided into 3A (overt bleeding plus hemoglobin drop of 3 to <5 g/dL or any transfusion with overt bleeding), 3B (overt bleeding plus hemoglobin drop ≥5 g/dL or cardiac tamponade or bleeding requiring surgical intervention for control, excluding dental/nasal/skin/hemorrhoid, or bleeding requiring intravenous inotropes), or 3C (intracranial hemorrhage or intraocular bleed compromising vision). Type 2 bleeds are any overt, actionable sign of hemorrhage that does not fit the criteria for types 3, 4, or 5 but does meet at least 1 of the following criteria: (1) Requires nonsurgical/medical intervention by a healthcare professional; (2) leads to hospitalization or increased level of care; or (3) prompts evaluation. Type I refers to bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional.

0.74–1.29; $P=0.91$; Table 4; Figure 2A). There was no significant difference between the 2 treatment groups regarding the risk of individual secondary end points (death of any cause, death of cardiovascular causes, myocardial infarction, stroke, or stent thrombosis; Table 4; Figures 2B–2F).

Among the patients assigned to receive long-term dual-antiplatelet therapy compared with those assigned to receive short-term clopidogrel plus aspirin, there was a roughly 2-fold greater risk of type 5, 3, or 2 (hazard ratio, 2.17; 95% CI, from 1.44–3.22; $P=0.00018$; Table 4; Figure 1F) and type 5 or 3 bleeding events (hazard ratio, 1.78; 95% CI, from 1.02–3.13; $P=0.037$) according to the Bleeding Academic Research Consortium classification (Table 4).

The risks of TIMI-defined major bleeding and red blood cell transfusion were also increased in the 24-month clopidogrel group (Table 4). Consistent findings were also obtained by application of the BleedScore (Table 4).

### Subgroup and Landmark Analysis

As shown in Figure 3, treatment assignment and the ischemic composite end point at 2 years proved to be consistent across the 9 prespecified subgroups. A signal of heterogeneity was noted in younger patients and individuals presenting with stable coronary artery disease, in whom there was a trend toward a lower ischemic composite end point at 2 years in the 6-month dual-antiplatelet therapy group; however, interaction tests did not reach formal significance. The effect of study treatment also proved to be consistent across recruitment sites ($P=0.85$ for interaction; online-only Data Supplement Figure I).

A total of 1924 patients reached the 6-month follow-up, of whom 963 were allocated to the 24-month dual-antiplatelet therapy group and 961 to the short-term clopidogrel duration arm; the incidence of the primary composite end point from 6 to 24 months was 7.2% (69 patients) in the long-term and 6.5% (62 patients) in the short-term clopidogrel therapy group (hazard ratio, 0.89; 95% CI, from 0.64–1.25; $P=0.53$; Figure 4A). Among 1443 patients who were randomly allocated to DES at the time of angioplasty, death of any cause, myocardial infarction, or cerebrovascular accident from the landmark time point of 6 up to 24 months occurred in 49 patients (6.8%) in the 24-month group and in 43 (6.0%) in the 6-month group (hazard ratio, 0.87; 95% CI, from 0.58–1.31; $P=0.51$; Figure 4B). Finally, in this subset of DES-treated patients, all-cause mortality (4.4% versus 4.0%; $P=0.81$), the composite of all-cause death or MI (6.0% versus 5.7%; $P=0.92$), and the rate of definite stent thrombosis (0.42% versus 0.56%; $P>0.99$) did not differ from 6 months onward in the 24-month versus the 6-month treatment groups.

## Discussion

The present multicenter trial recruited a largely unselected patient population predominantly presenting with unstable coronary artery disease. Patients received implantation of a balanced proportion among 4 different stents, including 3 Food and Drug Administration–approved DES. We found no significant benefit associated with clopidogrel continuation (use of clopidogrel plus aspirin) compared with clopidogrel discontinuation (use of aspirin alone) after 6 months in reducing the incidence of death of any cause, myocardial infarction, or cerebrovascular accident at 2 years. On the other hand, 2-year clopidogrel therapy resulted in a significant increase in the number of actionable bleeding episodes,[19] which included events that required medical or surgical treatment, red blood cell transfusion, and life-threatening events.

Two randomized controlled studies have shown that 9 to 12 months of dual-antiplatelet therapy reduces the composite ischemic end point of death, myocardial infarction, or stroke compared with a 1-month regimen after BMS implantation.[1,2,12] However, 1-year results of these studies were

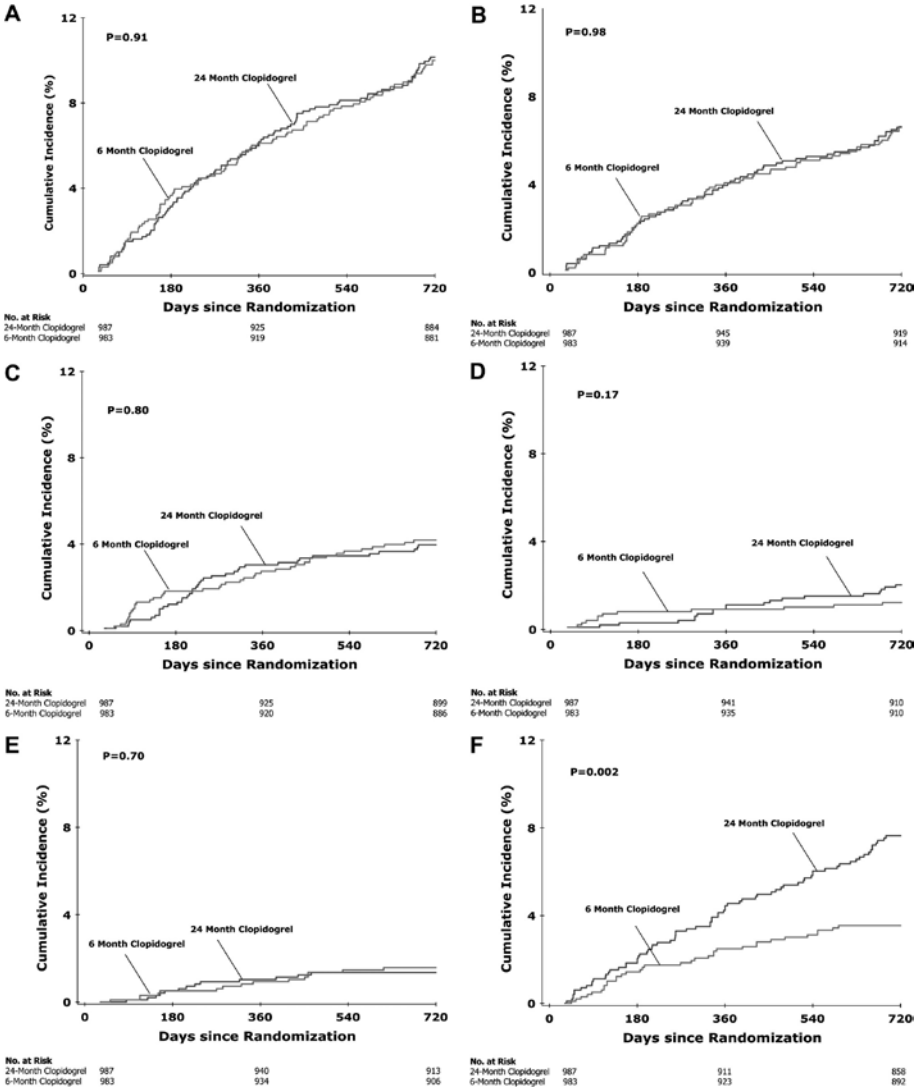


**Figure 2.** Cumulative incidence of the primary end point and selected secondary end points, according to treatment group. Cumulative incidence curves are shown for the primary end point of death of any cause, myocardial infarction, or cerebrovascular accident (**A**), death of any cause (**B**), myocardial infarction (**C**), any cerebrovascular accident (**D**), definite or probable stent thrombosis (**E**), and cumulative type 5, 3, or 2 bleeding events according to the Bleeding Academic Research Consortium classification (**F**). Probability values were calculated with log-rank test.

potentially biased by the difference in the pretreatment regimen between the 2 groups and were conducted more than a decade ago. Therefore, it remains unclear to what extent they remain relevant to current practice.

In the absence of randomized data, 2 independent observational registries[9,10] have largely influenced the current recommendation to prolong clopidogrel therapy for at least 12 months or for 6 to 12 months after DES implantation,

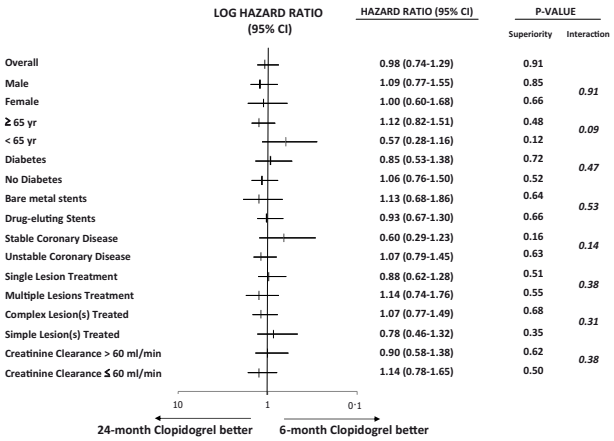


**Figure 3.** Subgroup analyses of the primary end point. Subgroup analyses are shown with hazard ratios and 95% confidence intervals (CI) for the primary end point of death of any cause, myocardial infarction, or cerebrovascular accident among subgroups of patients randomly assigned to either the 6- or 24-month clopidogrel therapy. The probability value for interaction represents the likelihood of interaction between the variable and the relative treatment effect.

despite the fact that their findings were not confirmed by many others.[8,11,20] The Basel Stent Cost-Effectiveness Trial–Late Thrombotic Events (BASKET-LATE; Current Controlled Trials No. ISRCTN75663024)[10] reported a >70% increase in death or myocardial infarction in DES recipients who discontinued clopidogrel at 6 months compared with patients who were treated with BMS. Similarly, a 50% increase in rates of death of any cause or myocardial infarction was observed in the Duke Heart Center registry in patients treated with DES who discontinued clopidogrel at 6 months compared with those who continued the treatment for 24 months.[9]

Therefore, we designed the present study to prospectively validate or refute previous observational data that would lead one to assume that prolonged and interrupted use of dual-antiplatelet therapy beyond 6 months is critical to achievement of an acceptable safety profile for DES while retaining its higher efficacy on reintervention compared with BMS.[21] Because the benefit of long-term clopidogrel therapy may extend beyond the type of coronary stent type implanted,[1,2] patients treated with BMS were also included in the present study.

The present patient population was minimally selected upfront and prospectively recruited at the time of intervention. As a consequence, the event rate and final study power were adequate, and the results of the present study can be interpreted with confidence.

At variance with previous[7] or ongoing[22–24] studies in which only event-free patients were or will be randomized to stop or continue clopidogrel therapy at 12 or 6 months, in the present

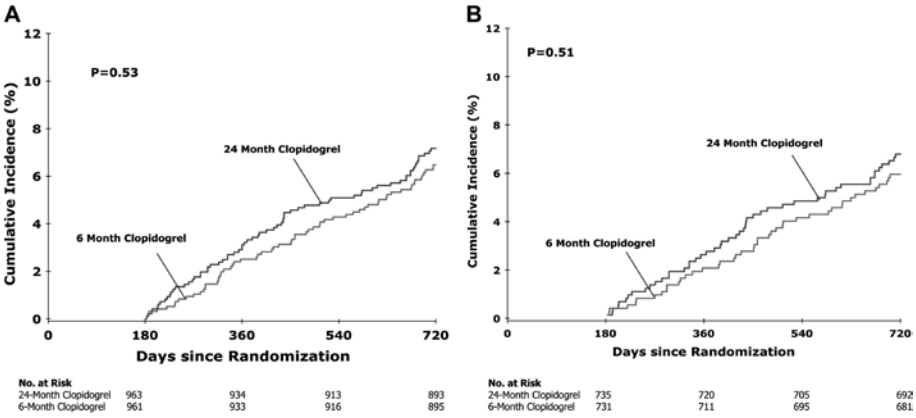


**Figure 4.** Landmark analyses. Cumulative rates of composite of death, myocardial infarction, or cerebrovascular accident in all recruited patients (**A**) or in patients who were randomly allocated to the drug-eluting stent groups (**B**) using the 6-month landmark analysis.

trial, patients were randomized at 1 month to continue dual-antiplatelet therapy for an additional 5 or 23 months, regardless of previous nonfatal ischemic or bleeding events. This was to avoid the selection of low-risk patients and to enable the provision of unique intention-to-treat data. Considerations regarding the ability to preserve long-term therapy with clopidogrel should influence the stent-type selection process.[3,6] Studies that randomize different durations of antiplatelet therapy as closely as possible to angioplasty may therefore be better suited to inform the decision-making process regarding DES versus BMS.

In this setting, the results of the present study are consistent with those reported previously by Park and colleagues,[7] who showed that the use of dual-antiplatelet therapy for a period of >12 months in patients who had received DES was not significantly more effective than aspirin monotherapy in reducing the rate of myocardial infarction or death of cardiac causes. In that study, ischemic and bleeding events were low, which negatively affected the power of the study and which may have been the consequence of selecting and randomizing event-free patients at 12 months.[7] Contrary to the findings of Park and colleagues,[7] bleeding events and transfusions were found to be higher in the 24-month clopidogrel group in the present study. The difference between the findings by Park et al[7] and our findings concerning bleeding may simply reflect the small number of hemorrhagic events reported in their study.

Stent thrombosis rates did not differ between the 2 groups, yet possible stent thrombosis events were numerically slightly higher in the 6-month dual-antiplatelet therapy group, especially from 12 months onward, when the difference in adherence to the 2 different treatment strategies was highest. Whether this minor difference is a play of chance or a true finding remains to be established.

On the other hand, cerebrovascular accidents trended in the opposite direction and were numerically increased in the 24-month dual-antiplatelet therapy group, which is again in keeping with previous observations.[7] Moreover, bleeding events, including life-threatening and fatal episodes, were numerically consistently higher in the group with 24 months of dual-antiplatelet therapy.

On subgroup analysis, a tendency toward more composite ischemic events in the 24-month dual-antiplatelet group was noted in some low-risk patients, ie, younger patients or individuals who presented with stable coronary artery disease. This observation is supported at least in part by previous evidence[25] and deserves further exploration.

Several limitations of the present study should be considered. The sample size of the present study was meant to confirm or refute the hypothesis that 24-month clopidogrel therapy would result in a ≥40% reduction in patient-oriented ischemic events compared with 6-month clopidogrel duration. Therefore, the present study cannot rule out the possibility that prolonging clopidogrel beyond 6 months would result in a lower than expected benefit or in a reduction in device-oriented end points such as stent thrombosis.

The open-label design may have introduced a potential for bias. We minimized this potential with the requirement that an independent committee that was unaware of the treatment assignments adjudicate all ischemic and hemorrhagic events. Moreover, no placebo therapy was administered to replace clopidogrel after 6 months in the short-term clopidogrel group.

It may be perceived that the inclusion of one fourth of the patients who were treated with BMS in the present study may have diluted the potential benefit of 24 months of dual-antiplatelet therapy in patients treated exclusively with DES implantation. However, the subgroup analysis provided reassuring data, because the point estimate for patients treated exclusively with DES slightly favored the 6-month duration of treatment with respect to the primary end point of the study, and no interaction was noted between stent type and duration of dual-antiplatelet therapy.

In the present study, we allowed BMS-treated patients with stable symptoms to stop treatment with clopidogrel after 1 month if they were allocated to the short-term group. This was justified by the lack of evidence supporting >1 month of treatment in this patient population. Because therapy was expected to start to differ between the 2 groups after 30 days (and actually did so in roughly 50% of the BMS group), the time frame of interest for the primary end point analysis was from 30 days onward. However, it can be argued that the use of clopidogrel did not differ in the vast majority of patients for the first 6 months and that the inclusion of events during the first 6 months, which would dilute the events that were possibly related to clopidogrel, may have biased the long-term clopidogrel group toward the null. Our landmark analysis focusing on events that occurred after 6 months in the whole population or in DES-only treated patients provides reassurance that the null finding of the present study may not be related to the study design but rather to a true biological observation.

In conclusion, the present study shows that the extended use of dual-antiplatelet therapy, for up to 24 months, was not significantly more effective than a 6-month duration of clopidogrel followed by aspirin monotherapy in reducing the risk of death of any cause, myocardial infarction, or cerebrovascular accident among all-comer patients recruited at the time of the index intervention. On the other hand, long-term duration of dual-antiplatelet therapy was associated with higher bleeding events and blood transfusion.

## Appendix

### Investigators Participating in the Study

*Executive Committee:* M. Valgimigli (principal investigator), G. Campo, G. Percoco, and R. Ferrari. *Data and Safety Monitoring Board:* N. Avigni and R. Mazzucco. *Clinical Events Committee:* P. Vranckx (chair), Belgium; S. Curello, Italy; G. Guardigli, Italy. *Data Management and Monitoring:* Medical Trial Analysis, Switzerland and Eustrategy Research Coordination, Italy (M. Monti, S. Gambetti, and L. Bristot). *Statistical Committee:* G. Parrinello (chair), University of Brescia.

### Clinical Sites

*Azienda Ospedaliero Universitaria di Ferrara, Italy:* M. Valgimigli, G. Campo, M. Tebaldi, C. Tumscitz, C. Cavazza, E. Cangiano, M. Minarelli, C. Arcozzi, A. Scalone, M. Borghesi, J. Marchesini, and M. Monti. *Valle Oppio Hospital:* G.F. Percoco, M. Kubbajeh, and A. Frangione. *Villa Maria Cecilia Hospital:* A. Cremonesi, F. Castriota,

F. Colombo, K. Oshoala, C. Garattoni, and P. Sbarzaglia. *Cento Hospital:* G. Fucà.

## Sources of Funding

The present study is an investigator-driven clinical trial. The conduct of this study did not receive any direct or indirect external funding but was entirely supported by the University of Ferrara, which employed dedicated personnel for data monitoring, data management, events adjudication, and independent statistical analysis.

## Disclosures

Dr Valgimigli has received honoraria for lectures/advisory board and research grants from Merck, Iroko, Eli Lilly, Medtronic and Terumo; honoraria for advisory board and lectures from The Medicines Company, Eli Lilly Co; Daiichi Sankyo, Inc., St Jude and Abbott Vascular; lectures from Cordis, CID and Terumo.

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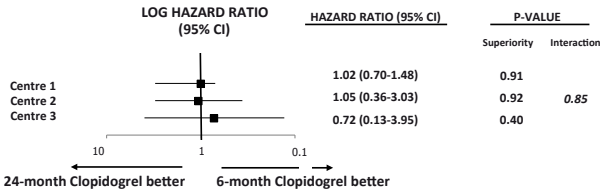
## CLINICAL PERSPECTIVE

This study focusing on 2013 patients undergoing coronary stent implantation who received bare-metal, zotarolimus-eluting, paclitaxel-eluting, or everolimus-eluting stent implantation and were subsequently allocated to up to 6 months versus 24 months of clopidogrel therapy in addition to aspirin failed to show the anticipated superiority of long-term duration of dual-antiplatelet therapy in terms of a lower composite ischemic end point of overall death, myocardial infarction, or cerebrovascular accidents. The cumulative risk of the primary outcome at 2 years was 10.1% with 24-month dual-antiplatelet therapy compared with 10.0% with 6-month dual-antiplatelet therapy (hazard ratio, 0.98; 95% confidence interval, 0.74–1.29; $P=0.91$). The individual risks of death, myocardial infarction, cerebrovascular accident, or stent thrombosis did not differ between the study groups; however, there was a consistently greater risk of hemorrhage in the 24-month clopidogrel group according to all prespecified bleeding definitions, including the recently proposed Bleeding Academic Research Consortium classification. Two Korean studies have also previously reported a lack of benefit of either 12 or 24 months of clopidogrel therapy over 6 or 12 months of therapy, respectively. Therefore, altogether, the available evidence does not support the concept that the longer the duration of clopidogrel therapy after drug-eluting stent implantation, the better the outcomes. On the contrary, this study identifies the potential for harm with respect to major bleeding associated with prolonged use of dual-antiplatelet therapy.

# SUPPLEMENTAL MATERIAL

Supplemental Figure 1




**Supplemental Figure 1 Legend:** heterogeneity of primary endpoint across recruiting sites.
Log hazard ratio for the primary endpoint of the study consisting of overall death, myocardial infarction or cerebrovascular accident across the three recruiting sites. The effects of study treatment is shown to be consistent with no signal of heterogeneity across study sites.

# CHAPTER 2.6

## Tailoring treatment with Tirofiban in patients showing resistance to aspirin and/ or resistance to Clopidogrel (3T/2R)

Valgimigli M, Campo G, de Cesare N, Meliga E, Vranckx P, Furgieri A, Angiolillo DJ, Sabatè M, Hamon M, Repetto A, Colangelo S, Brugaletta S, Parrinello G, Percoco G, Ferrari R; Tailoring Treatment With Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel (3T/2R) Investigators.

*Circulation*. 2009;**119**:3215-22.[**original research paper**]

# Intensifying Platelet Inhibition With Tirofiban in Poor Responders to Aspirin, Clopidogrel, or Both Agents Undergoing Elective Coronary Intervention

## Results From the Double-Blind, Prospective, Randomized Tailoring Treatment With Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel Study

Marco Valgimigli, MD, PhD, FESC; Gianluca Campo, MD; Nicoletta de Cesare, MD; Emanuele Meliga, MD; Pascal Vranckx, MD; Alessandro Furgieri, MD; Dominick J. Angiolillo, MD, PhD; Manel Sabatè, MD, PhD; Martial Hamon, MD; Alessandra Repetto, MD; Salvatore Colangelo, MD; Salvatore Brugaletta, MD; Giovanni Parrinello, PhD; Gianfranco Percoco, MD; Roberto Ferrari, MD, PhD, FESC; for the Tailoring Treatment With Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel (3T/2R) Investigators

***Background***—Inhibition of platelet aggregation after aspirin or clopidogrel intake varies greatly among patients, and previous studies have suggested that poor response to oral antiplatelet agents may increase the risk of thrombotic events, especially after coronary angioplasty. Whether this reflects suboptimal platelet inhibition per se, which might benefit from more potent antiplatelet agents such as tirofiban, is unknown.

***Methods and Results***—We screened 1277 patients to enroll 93 aspirin, 147 clopidogrel, and 23 dual poor responders, based on a point-of-care assay, who underwent elective coronary angioplasty at 10 European sites for stable or low-risk unstable coronary artery disease. Patients were randomly assigned in a double-blind manner to receive either tirofiban (n=132) or placebo (n=131) on top of standard aspirin and clopidogrel therapy. The primary end point, consisting of troponin I/T elevation at least 3 times the upper limit of normal, was attained in 20.4% (n=27) in the tirofiban group compared with 35.1% (n=46) in the placebo group (relative risk, 0.58; 95% confidence interval, 0.39 to 0.88; $P=0.009$). The rate of major adverse cardiovascular events within 30 days in the tirofiban group also was reduced (3.8% versus 10.7%; $P=0.031$). The overall incidence of bleeding was low, likely explained by a substantial use of the transradial approach, and did not differ between the 2 groups.

***Conclusions***—In low-risk patients according to clinical presentation who had poor responsiveness to standard oral platelet inhibitors via a point-of-care assay, intensified platelet inhibition with tirofiban lowers the incidence of myocardial infarction after elective coronary intervention. (***Circulation*****. 2009;119:3215-3222.)**

**Key Words:** angioplasty ■ aspirin ■ clinical trials ■ clopidogrel ■ glycoproteins

Current treatment strategies for patients with coronary artery disease ignore the individual response to antiplatelet agent(s) and likewise fail to identify therapeutic targets for platelet reactivity necessary to titrate the intensity of treatment. This largely contrasts with the existing practice for many other cardiovascular medications, including antihypertensive[1] and lipid-lowering agents[2] or even various antithrombotic drugs,[3,4] in which the response or lack thereof drives subsequent treatment decisions.

Received November 2, 2008; accepted April 30, 2009.

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Clinical trial registration information—URL: http://clinicaltrials.gov. Unique identifier: NCT00398463.

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***Circulation*** **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.108.833236**

## Clinical Perspective on p 3222

Inhibition of platelet aggregation after aspirin or clopidogrel intake varies greatly among patients.[5–11] Poor response to oral antiplatelet agents has been shown to increase the risk of thrombotic events, including myocardial infarction (MI), 1.8- to 10-fold, particularly after coronary angioplasty.[12–20] Whether this reflects suboptimal platelet inhibition per se, which might benefit from alternative/more potent antiplatelet agents, is unknown.[5,6,9] Studies aimed at improving outcomes while intensifying platelet inhibition in these patients are critical to establishing a causal relationship between poor response to a standard antiplatelet regimen and worse outcome.[21] We hypothesized that intensifying platelet inhibition with tailored infusion of tirofiban, a platelet glycoprotein IIb/IIIa inhibitor, in patients who are identified as poor responders to aspirin, clopidogrel, or both of these agents on the basis of a point-of-care assay may reduce the incidence of MI after elective coronary angioplasty compared with standard care.

## Methods

### Patients

We prospectively enrolled patients at 10 sites in Italy, Belgium, France, and Spain to participate in the Tailoring Treatment With Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel (3T/2R) study. The study protocol was approved by the ethics committee at each institution and was conducted according to the principles of the Declaration of Helsinki. All patients provided written informed consent before enrollment.

The design of the study has previously been detailed.[22] Briefly, all patients >18 years of age scheduled for coronary angiography, percutaneous coronary intervention (PCI), or both who presented with stable or troponin-negative non–ST-segment elevation acute coronary syndrome were eligible for screening. The exclusion criteria included any evidence of myocardial damage as witnessed by a rise of cardiac specific injury markers and ongoing MI, defined as the presence of ST-segment elevation at ECG or new or presumably new left bundle-branch block.

### Screening Procedure

Response to aspirin and clopidogrel was assessed by means of the VerifyNow Aspirin and $P2Y_{12}$ assays, respectively (Accumetrics Inc, San Diego, Calif), according to the manufacturer's instructions.[22] Patients were eligible for aspirin response evaluation if they were taking aspirin orally at doses of at least 80 mg/d for ≥5 days or received intravenous 500 mg aspirin ≥15 minutes before and did not receive clopidogrel or ticlopidine in the previous 7 days. Aspirin nonresponsiveness was defined as aspirin reaction units >550.[23] Patients meeting aspirin poor responsiveness criteria qualified for randomization before PCI only when clopidogrel screening requirements (as detailed below) were met. Screening for clopidogrel response was undertaken in patients at steady state for aspirin provided at least 1 of the following 2 requirements was fulfilled: the patient received a 600- or 300-mg loading dose ≥2 or 6 hours before, respectively, or the patient received a 75-mg maintenance clopidogrel dose for ≥7 consecutive days. Poor clopidogrel responsiveness was defined as <40% platelet inhibition.[24] Intravenous aspirin at the time of coronary angioplasty in patients at steady state for the treatment was allowed by the protocol and left to the discretion of the treating physician.

### Randomization

An independent study nurse at each site performed assignments of study treatments via a procedure using sealed envelopes. In preselected blocks of 6, patients were stratified according to the presence of stable or unstable coronary artery disease and poor responsiveness to aspirin, clopidogrel, or both. Patients showing poor response to both antiplatelet agents followed the aspirin poor responders randomization scheme. In patients randomly allocated to receive tirofiban, 50 mL of drug was diluted in 200 mL of 0.9% NaCl (1:5) solution, whereas in patients allocated to receive placebo, 50 mL of 0.9% NaCl was injected in 200 mL of 0.9% NaCl solution by an unblinded research study nurse. This procedure allowed the investigators and medical and nursing staff to remain blinded to assignment of study treatment. Bailout use of tirofiban was allowed by the protocol, which did not result in unblinding of treatment assignments. Tirofiban or 0.9% NaCl solution was started by the unblinded study nurse in patients allocated to placebo or tirofiban, respectively, if the treating physician called for bailout use of study treatment.

### Study Medications and Interventions

Tirofiban was given as a bolus of 25 $\mu g \cdot kg^{-1} \cdot 3\ min^{-1}$, followed by an infusion of 0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 14 to 24 hours based on previous experience.[22,25] Periprocedural administration of either unfractionated heparin or bivalirudin was allowed in all patients regardless of their receiving tirofiban or placebo. However, each site was required to prespecify 1 agent and then use it exclusively in both arms. Heparin was titrated as follows: Patients assigned to tirofiban received 50 to 70 U/kg heparin (≈7000 IU), whereas patients assigned to placebo received an initial bolus of 100 U/kg (maximum, 10 000 IU). Bivalirudin was administered as an intravenous bolus of 0.75 mg/kg, followed by an infusion of 1.75 $mg \cdot kg^{-1} \cdot h^{-1}$. Arterial sheath removal with an arteriotomy closure device was allowed immediately after intervention or with external compression when activated clotting time was <180 seconds. In cases when a radial access site was obtained, the sheath had to be removed immediately after angioplasty.

### Study End Points and Definitions

The primary end point was the rate of periprocedural MI defined as an elevation of troponin I/T ratio ≥3 times the upper limit of normal (ULN) within 48 hours after completion of the PCI according to the recent universal definition of MI.[26]

Key secondary end points included assessment of any myocardial injury according to an elevation within 30 days of serum creatine kinase-MB (CK-MB) mass >1, 3, or 5 times the ULN; the rate of any elevation of troponin I or T above the ULN; the rate of major adverse cardiovascular events defined as the composite of death, MI, or urgent target vessel revascularization within 30 days; and the incidence of stent thrombosis. CK-MB and troponin I or T were measured before and 6, 12, and 18 or 24 hours after intervention. Bleedings were collected according to the criteria of the Thrombolysis in Myocardial Infarction trials. An independent clinical events committee adjudicated all serious adverse events based on the review of the original source documents.

### Statistical Analysis

The sample size of at least 240 patients was based on an anticipated reduction in event rate from 45% in the standard care/placebo group to 25% in the tirofiban group with an estimated power of 90% at a 2-sided $\alpha$ level of 0.05. Categorical variables are expressed as frequency (percentage); continuous variables are expressed as median (interquartile range). Continuous variables were compared between randomized groups by use of the Wilcoxon rank-sum test; for binary variables, Fisher exact test was used. Risk ratios and 95% confidence intervals (CIs) were calculated for the primary end-point outcomes and for several prespecified subgroups as an exploratory analysis.

The Breslow-Day statistic test was used to assess the homogeneous association of risk ratios between treatment and study primary end point across prespecified subgroups, including age; sex; presence of diabetes mellitus; poor responsiveness to aspirin, clopidogrel, or both; indication to PCI; and number and complexity of treated lesions.

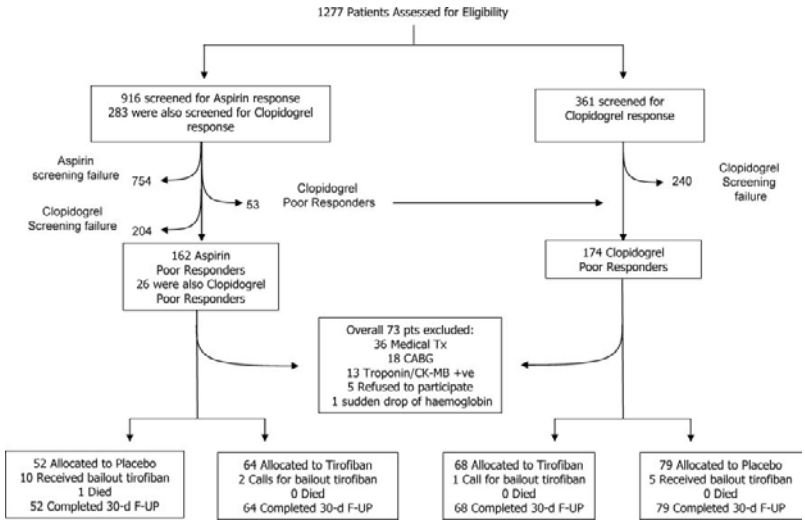


**Figure 1.** Study profile. Tx indicates treatment; +ve, positive; CABG, coronary artery bypass grafting; and F-UP, follow-up.

Estimation of the cumulative major adverse cardiovascular event rate was done with the Kaplan-Meier method, and events over time were compared by use of the log-rank test. A 2-sided value of $P<0.05$ was considered significant. All analyses, carried out on the intention-to-treat principle, were performed with STATA, version 9.2 (Stata Corp, College Station, Tex).

The corresponding author had full access to the data in the study and had final responsibility for the decision to submit for publication. All authors have read and agree to the manuscript as written.

## Results

Between February 2006 and June 2008, 1277 patients were screened; of these, 136 (14.8%) showed poor response to aspirin, 174 (27%) were clopidogrel poor responders, and 26 (9.2%) met the criteria for poor responsiveness to both drugs (Figure 1). Of these, 54 patients did not undergo PCI after coronary angiogram, 14 failed to meet inclusion criteria, and 5 refused to participate; thus, 263 patients were finally enrolled in the study. Baseline characteristics and the type of intervention performed for the study population are shown in Tables 1 and 2. The median age was 69 years; 67% had either silent or stable angina; 73% had multivessel disease; slightly >40% and <40% had a history of MI and PCI, respectively; 25% had diabetes mellitus; and almost 60% of the target lesions were type B2 or C. Anticoagulation was established with infusion of bivalirudin in 4 patients only who received concomitant transradial intervention. Intervention was performed in multiple lesions in 40% of the tirofiban group and 34% of the placebo group ($P=0.55$). Thirty-day follow-up was complete in all patients.

### Efficacy Analysis

Periprocedural MI, according to the primary end-point definition, occurred in 27 (20.4%) and 46 (35.1%) patients in the tirofiban and placebo groups, respectively (relative risk, 0.58; 95% CI, 0.39 to 0.88; $P=0.0089$; Figure 2). Figure 3 shows the incidence of periprocedural MI according to multiples of the upper limit of reference value for either troponin I or T and CK-MB. One Q-wave MI (0.8%) occurred in the placebo arm compared with none in the tirofiban arm ($P=0.99$). The efficacy of tirofiban was consistent among multiple prespecified subgroups, including both aspirin and clopidogrel poor responders (Figure 4). Bailout tirofiban was called for in 3 patients in the tirofiban group and 11 in the placebo arm ($P=0.053$).

At 30 days, there was 1 fatal event (0.8%) in the placebo arm resulting from massive pulmonary embolism and 2 cases of nonfatal MI: 1 after a staged percutaneous intervention and 1 episode of definite stent thrombosis that required urgent reintervention. In the tirofiban group, no patient died and 1 patient developed a periprocedural MI after a staged percutaneous intervention performed under standard care consisting of treatment with aspirin and clopidogrel. The cumulative incidence of major adverse cardiovascular events, based on CK-MB elevation >3 times the ULN in at least 2 consecutive samples per the definition of periprocedural MI, also was reduced in the tirofiban group (10.7% versus 3.8%; $P=0.031$).

### Safety Analysis

No major bleeding occurred. Two patients in the tirofiban group (1.5%) and 1 in the placebo group (0.8%; $P=0.99$) experienced minor bleeding that did not require transfusion. One patient in each group developed mild thrombocytopenia.

## Discussion

The main findings of this study can be summarized as follows: Triple antiplatelet therapy, including a tailored

**Table 1. Baseline Patient Characteristics and Medications During the Trial**

| Characteristic | Tirofiban (n=132) | Placebo (n=131) | *P* |
|---|---|---|---|
| Age, y | | | 0.84 |
| Mean±SD | 68.3±10 | 68±9.4 | |
| Median | 68.6 | 69.2 | |
| Interquartile range | 61.8–75.3 | 61–74.6 | |
| Male, n (%) | 98 (74.2) | 95 (72.5) | 0.78 |
| Body mass index, kg/m$^2$ | | | 0.89 |
| Median | 27.6 | 27 | |
| Interquartile range | 25.18–29.7 | 24.8–29.4 | |
| Diabetes mellitus, n (%) | 32 (24.4) | 37 (28.0) | 0.57 |
| Insulin dependent | 8 (6.1) | 9 (6.8) | 0.99 |
| Hypertension, n (%) | 88 (66.7) | 100 (76.3) | 0.10 |
| Hyperlipidemia, n (%) | 68 (51.5) | 73 (55.7) | 0.53 |
| Current cigarette use, n (%) | 20 (15.5) | 20 (15.4) | 0.99 |
| Creatinine clearance, mL/min | | | 0.77 |
| Median | 75.6 | 74.5 | |
| Interquartile range | 60.1–92.2 | 57.9–99.3 | |
| Prior MI, n (%) | 63 (47.7) | 50 (38.2) | 0.13 |
| Prior PCI, n (%) | 52 (38.9) | 51 (38.9) | 0.99 |
| Prior coronary bypass surgery, n (%) | 9 (6.8) | 8 (6.1) | 0.99 |
| Prior stroke or transient ischemic attack, n (%) | 6 (4.5) | 8 (6.1) | 0.78 |
| Left ventricular ejection fraction, % | | | 0.98 |
| Median | 56.5 | 58 | |
| Interquartile range | 50–60 | 50–60 | |
| Clinical presentation, n (%) | | | |
| Silent ischemia | 31 (23.4) | 36 (27.5) | 0.48 |
| Stable angina | 55 (41.7) | 55 (42) | 0.99 |
| Unstable angina | 46 (34.8) | 40 (30.5) | 0.51 |
| Angiographic features, n (%) | | | |
| Single-vessel disease | 35 (26.5) | 37 (28.2) | 0.78 |
| Double-vessel disease | 41 (31.0) | 38 (29.0) | 0.79 |
| Triple-vessel disease | 56 (42.4) | 56 (42.7) | 0.99 |
| Drug therapy at admission, n (%) | | | |
| NSAIDs in the previous 7 d | 5 (4.2) | 3 (2.3) | 0.48 |
| CCSs in the previous 7 d | 4 (3.4) | 6 (4.6) | 0.75 |
| Aspirin | 126 (94.5) | 122 (93.1) | 0.44 |
| Clopidogrel | 41 (31.1) | 40 (30.5) | 0.99 |
| ACE inhibitors | 77 (58.3) | 77 (589.8) | 0.99 |
| $\beta$-Blockers | 82 (62.1) | 82 (62.6) | 0.99 |
| Statins | 87 (65.9) | 80 (61.1) | 0.44 |
| Background antiplatelet therapy at the time of intervention, n (%) | | | |
| Oral aspirin ≥80 mg/d for ≥5 d | 118 (89.4) | 120 (91.6) | 0.96 |
| Intravenous 500 mg aspirin | 18 (13.6) | 20 (15.3) | 0.86 |
| Clopidogrel 75 mg/d for ≥7 h | 44 (33.3) | 46 (35.1) | 0.90 |
| Clopidogrel 300 mg for >6 h | 37 (28) | 38 (29) | 0.99 |
| Clopidogrel 600 mg for >2 h | 51 (38.6) | 47 (35.9) | 0.81 |

NSAIDs indicates nonsteroidal antiinflammatory drugs; CCSs, corticosteroids; and ACE, angiotensin-converting enzyme.

**Table 2. Procedural Results**

| | Tirofiban (n=132 Patients, n=193 Lesions) | Placebo (n=131 Patients, n=188 Lesions) | *P* |
|---|---|---|---|
| Patients | | | 0.96 |
| Treated lesions, n | | | |
| Median | 1 | 1 | |
| Interquartile range | 1–2 | 1–2 | |
| Multivessel intervention, n (%) | 32 (24.2) | 25 (19.1) | 0.37 |
| Stents implanted, n | | | 0.97 |
| Median | 1 | 1 | |
| Interquartile range | 1–2 | 1–2 | |
| Range | 0–5 | 0–5 | |
| Length of stent, mm | | | |
| Median | 27 | 27 | 0.59 |
| Interquartile range | 18–42 | 15–40 | |
| Use of unfractionated heparin (IU), n (%) | 130 (98) | 129 (98) | 0.99 |
| Dose of unfractionated heparin (IU) | | | |
| Median | 5500 | 7500 | <0.0001 |
| Interquartile range | 5000–6500 | 7000–7500 | |
| Activated clotting time, s | | | |
| Median | 220 | 231 | <0.01 |
| Interquartile range | 192–267 | 226–296 | |
| Use of bivalirudin, n (%) | 2 (1.5) | 2 (1.5) | 0.99 |
| Transradial intervention, n (%) | 61 (46) | 62 (47) | 0.99 |
| Lesions | | | |
| Location of treated lesion, n (%) | | | |
| Left main coronary artery | 5 (2.6) | 3 (1.6) | 0.72 |
| Left anterior descending coronary artery | 79 (40.9) | 64 (34.0) | 0.17 |
| Left circumflex coronary artery | 42 (21.8) | 47 (25.0) | 0.47 |
| Right coronary artery | 70 (37.2) | 64 (37.2) | 0.40 |
| Bypass vein graft | 4 (2.1) | 1 (0.5) | 0.37 |
| Complex (type B2 or C) lesions, n (%) | 110 (58.2) | 103 (55.6) | 0.86 |
| Thrombus present, n (%) | 11 (5.7) | 8 (4.3) | 0.64 |
| Total occlusion, n (%) | 11 (5.8) | 19 (9.8) | 0.18 |
| Bifurcation, n (%) | 48 (24.9) | 34 (18.1) | 0.13 |
| Restenotic lesion, n (%) | 15 (7.8) | 18 (9.6) | 0.58 |
| Type of intervention, n (%) | | | |
| Stenting | 177 (91.7) | 176 (93.6) | 0.82 |
| Balloon angioplasty | 16 (8.3) | 12 (6.4) | 0.78 |

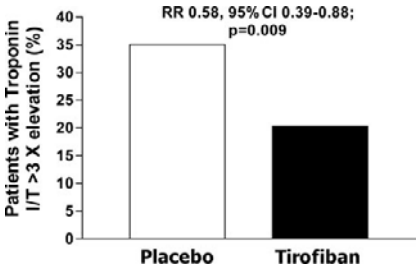


**Figure 2.** Rates of periprocedural MI according to the primary end-point definition. RR indicates relative risk.

infusion of tirofiban in patients who responded poorly to aspirin, clopidogrel, or both, resulted in a >40% reduction in the incidence of periprocedural MI compared with standard care. This treatment effect was consistent across all exploratory definitions of periprocedural MI, with proportional reductions in ischemic events ranging from 37% to ≥70% based on an elevation of CK-MB ratio >5 times the ULN in at least 1 or 2 consecutive blood sample, respectively. These results suggest that the incremental risk for worse outcomes conveyed by poor response to aspirin, clopidogrel, or both[7,9] may be significantly mitigated in the PCI setting by tailored intensification of platelet inhibition.

Notably, the rate of bleeding, which has recently emerged as an independent mortality predictor, was low and did not differ in the 2 study groups, nor did the incidence of thrombocytopenia, and no patient required transfusion of blood products during hospitalization. Whether patients who respond poorly to aspirin, clopidogrel, or both, who likely present with higher residual platelet reactivity after treatment, are intrinsically at lower risk for bleeding complications is currently unknown and worth further investigation.[27] Alternatively, the extensive use of transradial intervention and the implementation of the well-validated Thrombolysis in Myocardial Infarction classification explain the overall low bleeding rate observed in our study.

The early benefit, in terms of periprocedural MI, was largely maintained at 30 days, with the cumulative incidence of major adverse cardiovascular events reduced from 21.2% in the tailored tirofiban group to 36.6% in the placebo group based on the primary end-point definition of periprocedural MI and from 10.7% to 3.8%, respectively, when the periprocedural MI rate was defined according ≥3 times the ULN for CK-MB elevation in ≥2 consecutive samples. In exploratory analysis, the effect of tailored tirofiban infusion was consistent across all subgroups, including both aspirin and clopidogrel poor responders. Thus, data are provided for the first time showing that implementing alterative treatment strategies in this patient population may result in an improved outcome compared with standard care.

Our focus on stable and low-risk unstable coronary artery disease patients undergoing PCI with evidence of poor response to aspirin, clopidogrel, or both is based on the following: First, in this setting, the untailored use of a glycoprotein IIb/IIIa inhibitor failed to reduce the incidence of ischemic events when administered on top of dual antiplatelet therapy with aspirin and clopidogrel.[28,29] Second, poor response to aspirin and clopidogrel may frequently be associated,[30,31] and both carry an independent risk for periprocedural MI after elective PCI performed under standard care.[20,32] Consistently, the periprocedural event rate observed in the placebo arm of our study was substantially

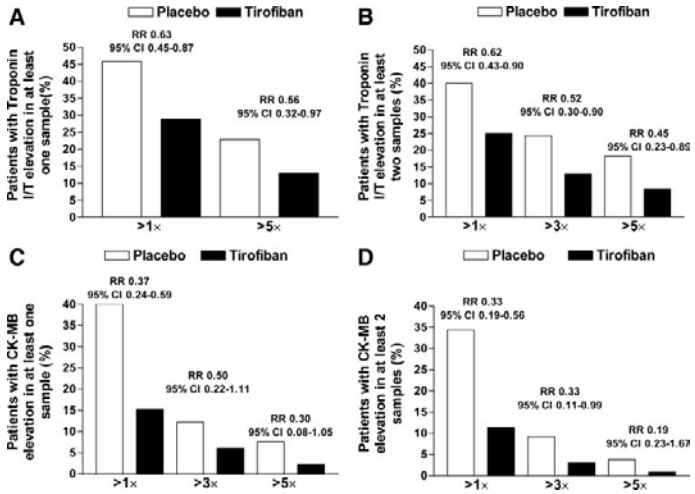


**Figure 3.** Rates of periprocedural myocardial damage according to multiples of the upper limit of reference value in at least 1 (A and C) or 2 (B and D) consecutive sample(s) for either troponin I or T (A and B) and CK-MB (C and D). RR indicates relative risk.

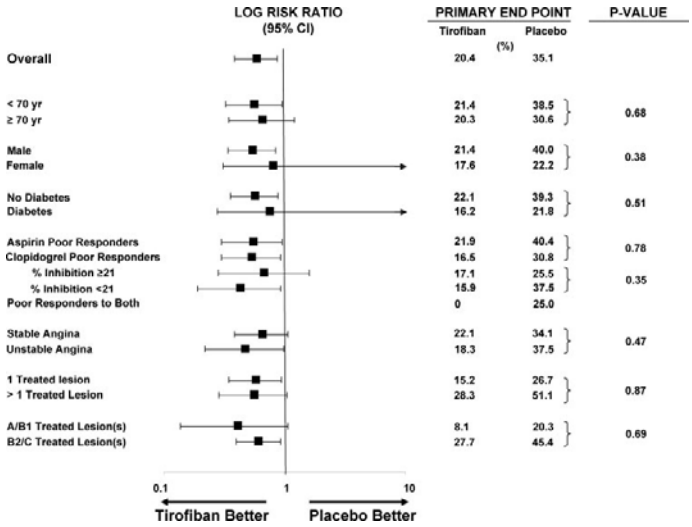


**Figure 4.** Logarithmic (log) risk ratios and rates of the primary end point according to selected subgroups of patients. *P* values denote interaction between study treatment and tested subgroups.

higher than that previously reported in unselected patients undergoing elective PCI.[28,29] This observation is in keeping with previous findings[12–14,17,20] and confirms the notion that poor response to standard oral antiplatelet agents identifies a high-risk patient population whose outcomes remains suboptimal when treated under standard care.

Adjusting clopidogrel loading doses according to a vasodilator-stimulated phosphoprotein phosphorylation index has been suggested to reduce the rate of major adverse cardiovascular events in poor responders to standard clopidogrel loading dose regimen.[33] However, despite repeated loading doses (up to 2400 mg) over days, clopidogrel did not yield adequate platelet inhibition in all patients. In addition, vasodilator-stimulated phosphoprotein phosphorylation assessment requires the use of flow cytometric assay, which introduces logistic and economic concerns and, like light transmittance aggregometry, cannot be considered a bedside tool. This highlights the need for more user-friendly platelet function assays and alternative antithrombotic agents such as glycoprotein IIb/IIIa inhibitors as used in our study, which more promptly achieve enhanced platelet inhibition.[34] We used the VerifyNow system in our study because of evidence that it correlates to measurements with standard light transmittance aggregometry.[35] Further driving this decision were previous studies in which poor response to either aspirin[20] or clopidogrel,[32,36] as detected by this point-of-care assay, independently predicted worse outcomes after coronary intervention.

Our protocol defined clopidogrel poor responder patients with <40% platelet inhibition. Notably, in clopidogrel poor responders presenting with platelet inhibition above a median value (21%), the incidence of the primary end point was low, and the proportional event rate reduction by treatment with tirofiban was in the range of 30%, which did not reach statistical significance. Conversely, both the absolute event rate in the placebo arm and the relative risk reduction driven by treatment were almost doubled in those with platelet inhibition below the median value. This may suggest, in keeping with recent studies,[6,12,36,37] that those patients showing minimal platelet inhibition after clopidogrel intake, who are at even greater risk for worse cardiovascular outcomes, may derive the greatest benefit from a tailored intensification of platelet inhibition. CIs remain wide in our exploratory analyses of subgroups, as reflected by a lack of statistical interaction between response to clopidogrel and treatment effect. Thus, confirmation from larger data sets as to which threshold for response to clopidogrel should trigger a tailored intensified antiplatelet strategy remains warranted. It is currently debated whether the relative change in platelet inhibition after treatment or absolute posttreatment platelet reactivity is better for use in identifying patients who may benefit from a tailored intensification of platelet inhibition. We arbitrary decided to use the former in our study. Interestingly, the percentage of platelet inhibition by clopidogrel and absolute platelet reactivity units by the VerifyNow system were highly inversely correlated in our patient population undergoing screening for response to clopidogrel ($r=-0.86$; $P<0.001$), with 20% inhibition corresponding to platelet reactivity units in the range of 210 in regression analysis (data not shown).

Several limitations of our study deserve attention. To minimize the potential for bias, the protocol mandated double-blind administration of study drug, which was obtained through the assistance of an unblinded independent study nurse at each site. Ideally, no care providers should be

aware of the randomization scheme, but this would require dedicated manufacturing of drug and placebo.

We would like to acknowledge that, unlike for clopidogrel, molecular mechanisms subtending hyporesponsiveness to aspirin are only poorly understood and are likely far more complex than failure of the drug to "hit the target."[9] Moreover, it remains unclear whether aspirin poor responsiveness and clopidogrel poor responsiveness are equally associated with higher atherothrombotic risks.

Our study was designed as a proof-of-concept study and as such was powered to assess the effect of treatment on PCI-related myocardial necrosis. Although the rate of major adverse cardiovascular events was significantly reduced at 30 days in the tirofiban arm, this reduction almost exclusively reflected the different rate of periprocedural MI because the event rate, which was not related to the intervention itself, was extremely low up to 30 days. Moreover, by implementing random allocation of tirofiban versus placebo in the study, we focused on short-term outcome after intervention. Studies investigating alternative maintenance treatment strategies in poor responders to standard regimen of clopidogrel are underway and will complement our findings. Although there is no consensus on the most appropriate definition of aspirin and clopidogrel poor responsiveness,[6,21] in the present study, we used cutoff values previously reported in the scientific literature.[24] Data from other studies[36] and this study suggest, however, that a higher threshold to define clopidogrel poor responsiveness may be desirable in future investigations. In clopidogrel-naïve patients, longer duration of clopidogrel pretreatment after a 300- or 600-mg loading dose may decrease the rate of drug poor responsiveness and consequently diminish the need for an additional intravenous antiplatelet agent at the time of PCI.

Ideally, the effect of intensified platelet inhibition versus placebo in patients who failed to meet the poor responsiveness criteria for aspirin, clopidogrel, or both may have complemented our findings by showing no or marginal benefit on ischemic end points. This may have further corroborated the importance of on-treatment high residual platelet activity as a key player in ischemic events. The inclusion of patients at steady state for the treatment or who received clopidogrel at different loading regimens also may be perceived as a study limitation. Importantly, subgroup analysis did not disclose any heterogeneity of results based on different pretreatment modalities.

## Conclusions

We showed that the intensification of platelet inhibition through the infusion of tirofiban in poor responders to aspirin, clopidogrel, or both who undergo elective PCI decreased the rate of periprocedural MI and resulted in a lower rate of major adverse cardiovascular events at 30 days. Our study provides proof of concept for a new treatment strategy in patients with coronary artery disease that, by assessing response to standard antiplatelet agents by a point-of-care assay, modulates the intensity of treatment accordingly.

## Sources of Funding

This study was partially supported by a research grant from Merck, USA, and Iroko, USA, which had no role in the study design; collection, analysis, and interpretation of data; writing of the report; and the decision to submit the paper for publication.

## Disclosures

Dr Valgimigli has received honoraria for lectures from or served on advisory boards for Merck/Iroko, The Medicines Co, Eli Lilly Co, and Daiichi Sankyo Inc and has received research grants from Merck/Iroko and Eli Lilly. Dr Angiolillo has received honoraria for lectures from or served on advisory boards for Bristol Myers Squibb, Sanofi-Aventis, Eli Lilly Co, The Medicines Co, Portola, Novartis, and Daiichi Sankyo Inc. Dr Hamon has received honoraria for lectures from The Medicines Co, GSK, Nycomed, and Merck.

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## CLINICAL PERSPECTIVE

Previous studies have shown that individual response to aspirin or clopidogrel intake may vary significantly among patients, and those who respond less have been reported to be at higher risk for worse cardiovascular outcomes, especially if treated with percutaneous coronary intervention. It is unknown whether this worse cardiovascular outcome directly reflects suboptimal platelet inhibition per se, which might benefit from more potent antiplatelet agents. Alternatively, this may simply represent a "marker" of worse prognosis without clear therapeutic implications. In this study, we have shown that intensifying platelet inhibition through the use of tirofiban, a potent intravenous antiplatelet agent, in patients undergoing percutaneous coronary intervention who have previously been selected to be poor responders to aspirin, clopidogrel, or both agents leads to lower incidence of periprocedural myocardial infarction compared with standard care consisting of aspirin and clopidogrel. Thus, data are provided for the first time showing that implementing alterative treatment strategies in this patient population may result in an improved outcome compared with standard care. Our results may suggest a causal relationship between suboptimal platelet inhibition and worse outcomes in this selected patient population.

# APPENDIX 2.1

## Standardized Bleeding Definitions for Cardiovascular Clinical Trials: A Consensus Report from the Bleeding Academic Research Consortium (BARC)

Mehran R, Rao SR, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik J, Cutlip D, Krucoff M, Ohman EM, Steg PG and White H,

*Circulation* 2011;**123**:2736-47. [**technical report, only provided as a reference** ]

# Standardized Bleeding Definitions for Cardiovascular Clinical Trials

## A Consensus Report From the Bleeding Academic Research Consortium

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Advances in antithrombotic therapy, along with an early invasive strategy, have reduced the incidence of recurrent ischemic events and death in patients with acute coronary syndromes (ACS; unstable angina, non–ST-segment–elevation myocardial infarction [MI], and ST-segment–elevation MI).[1–4] However, the combination of multiple pharmacotherapies, including aspirin, platelet $P2Y_{12}$ inhibitors, heparin plus glycoprotein IIb/IIIa inhibitors, direct thrombin inhibitors, and the increasing use of invasive procedures, has also been associated with an increased risk of bleeding.

**Editorial see p 2664**

Bleeding complications have been associated with an increased risk of subsequent adverse outcomes, including MI, stroke, stent thrombosis, and death, in patients with ACS and in those undergoing percutaneous coronary intervention (PCI),[5–10] as well as in the long-term antithrombotic setting.[11,12] Thus, balancing the anti-ischemic benefits against the bleeding risk of antithrombotic agents and interventions is of paramount importance in assessing new therapies and in managing patients. Prior randomized trials comparing antithrombotic agents suggest that a reduction in bleeding events is associated with improved survival.[13,14]

Because prevention of major bleeding may represent an important step in improving outcomes by balancing safety and efficacy in the contemporary treatment of ACS, bleeding events have been systematically identified as a crucial end point for the assessment of the safety of drugs during the course of randomized clinical trials, and are an important aspect of the evaluation of new devices and interventional therapies.[15] Unlike ischemic clinical events (eg, cardiac death, MI, stent thrombosis), for which there is now general consensus on end-point definitions,[16,17] there is substantial heterogeneity among the many bleeding definitions currently in use. Lack of standardization makes it difficult to optimally organize key clinical trial processes such as adjudication, and even more difficult to interpret relative safety comparisons of different antithrombotic agents across studies, or even within a given trial, because results may vary according to the definition(s) used for bleeding. Finally, as reflected by the various terms used to describe bleeding (serious, severe, catastrophic, major, life-threatening, etc), the heterogeneity of definitions may undermine the ability of clinical trials to meaningfully define the balance of safety and efficacy in vascular interventions.

In response to the need to develop, disseminate, and ultimately adopt standardized bleeding end-point definitions for patients receiving antithrombotic therapy, the Bleeding Academic Research Consortium (BARC) convened in February 2010 at the US Food and Drug Administration (FDA) headquarters in White Oak, MD. Modeled after the 2006 Academic Research Consortium, which standardized key ischemic end-point definitions in studies aimed at evaluating coronary stents,[17] the BARC effort brought together representatives from academic research organizations, the FDA, the National Institutes of Health, and pharmaceutical and cardiovascular device manufacturers and independent physician thought leaders in the field of cardiovascular disease to develop consensus bleeding definitions that would be useful

The BARC represents a collaboration of independent academic research organizations (Cardialysis, Rotterdam, the Netherlands; Cardiovascular Research Foundation, New York City, NY; Duke Clinical Research Institute, Durham, NC; TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA; Harvard Clinical Research Institute, Boston, MA; Green Lane Coordinating Centre, Auckland, New Zealand; Cleveland Clinic Coordinating Center for Clinical Research, Cleveland, OH; and PERFUSE, Boston, MA), professional societies (European Society of Cardiology, and Society of Cardiac Angiography and Intervention), federal agencies (the US FDA, National Institutes of Health), and independent expert scientists and consultants (Appendix).

Guest Editor for this article was Frans J. Van de Werf, MD, PhD.

**The online-only Data Supplement is available with this article at http://circ.ahajournals.org/cgi/content/full/123/23/2736/DC1.**

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(*Circulation*. 2011;123:2736-2747.)



*Circulation* is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.110.009449

**Table 1. Impact of Major Bleeding on Mortality in Registries and Randomized Trials of Patients With Acute Coronary Syndromes or Undergoing Percutaneous Coronary Interventions**

| | | | | | Outcomes in Patients With Major or Severe Bleeding vs No Bleeding | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Early Deaths (In Hospital or at 30 d) | | Deaths up to 1 y | |
| Study | Setting, Design | Primary Definition* | Patients | Patients With Bleeding, n (%) | Death Rates, % | Adjusted Risk Ratio for Death (95% CI) | Death Rates, % | Adjusted Risk Ratio for Death (95% CI) |
| Kinnaird et al,[7] 2003 | PCI, registry | TIMI | 10 974 | 588 (5.4) | 7.5 vs 0.6 | 3.5 (1.9–6.7) | 17.2 vs 5.5 | Not significant† |
| GRACE,[10] 2003 | ACS, registry | GRACE | 24 045 | 933 (3.9) | 18.6 vs 5.1 | 1.6 (1.2–2.3) | . . . | . . . |
| GRACE,[21] 2007 | ACS, registry | GRACE | 40 087 | 1140 (2.8) | 20.9 vs 5.6 | 1.9 (1.6–2.2) | 7.9 vs 5.2 | 0.8 (0.6–1.0) |
| REPLACE-2,[25] 2007 | PCI, RCT | REPLACE-2/ ISAR-REACT 3 | 6001 | 195 (3.2) | 5.1 vs 0.2 | . . . | 8.7 vs 1.9 | 2.7 (1.4–4.9) |
| Rao et al,[6] 2005 | NSTE-ACS, meta-analysis of RCTs | GUSTO | 26 452 | 107 (0.4) | 25.7 vs 2.9 | 10.6 (8.3–13.6) | 35.1 vs 4.2 | 7.5 (6.1–9.3) |
| Eikelboom et al,[5] 2006 | NSTE-ACS, meta-analysis of RCTs/registry | CURE | 34 146 | 783 (2.3) | 12.8 vs 2.5 | 9.8 (7.5–12.7) | 4.6 vs 2.9‡ | 1.9 (1.3–2.8) |
| ACUITY,[9] 2007 | NSTE-ACS, RCT | ACUITY | 13 819 | 644 (4.7) | 7.3 vs 1.2 | 7.6 (4.7–12.2) | . . . | 3.5 (2.7–4.4) |
| Ndrepepa et al,[15] 2008 | PCI, meta-analysis of RCTs | TIMI | 5384 | 215 (4.0; n=59 major/n=156 minor) | . . . | . . . | 12.2 vs 3.3 | 4.1 (2.1–8.3) |
| EVENT,[26] 2009 | PCI, registry | TIMI | 5961 | (3.0 overall: 0.7 major, 2.3 minor) | . . . | . . . | 15.6 vs 2.4 | 3.8 (2.5–5.9) |
| OASIS-5,[27] 2009 | NSTE-ACS, RCT | ESSENCE | 20 078 | 990 (4.9): major, 423 (2.1) minor | 8.4 vs 2.7 | 3.5 (2.6–4.6) | 14.3 vs 5.4 | 3.1 (2.6–3.8) |
| Amlani et al,[28] 2010 | STEMI, registry | Protocol defined | 1389 | 152 (10.9) | 19.7 vs 8.2 | 2.8 (1.8–4.3) | . . . | . . . |
| ISAR-REACT 3,[29] 2010 | PCI, RCT | REPLACE-2/ ISAR-REACT 3 | 4570 | 555 (12.1) 174 major/381 minor | . . . | . . . | 5.2 vs 1.3 | 4.1 (2.6–6.5) |

CI indicates confidence interval; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; ACS, acute coronary syndrome; GRACE, Global Registry of Acute Coronary Events; RCT, randomized controlled trial; REPLACE-2, Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events; ISAR-REACT 3, Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment; NSTE, non–ST-elevation; GUSTO, Global Use of Strategies to Open Occluded Arteries; CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Events; ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy; EVENT, Evaluation of Drug Eluting Stents and Ischemic Events; and OASIS-5, Organization for the Assessment of Strategies for Ischemic Syndromes.

*For Definitions, please see Table 2.

†Data not provided.

‡Events between 30 days and 6 months.

for cardiovascular clinical trials. Application of these definitions is recommended for both clinical trials and registries.

## Importance of Bleeding as an End Point

Hemorrhagic complications occur with a frequency of 1% to 10% during treatment for ACS and after PCI.[18–20] This wide variability in the measured incidence is due to several factors, including differences in patient characteristics, concomitant therapies, timing of event reporting, and definitions across data sets. Regardless of the definition used, several studies have demonstrated that bleeding is associated with an increased risk for short- and long-term adverse outcomes, including death,[18,20] nonfatal MI,[6] stroke,[5] and stent thrombosis.[9] The exact mechanisms underlying this relationship are not known, but may include the cessation of evidence-based therapies, including antiplatelet agents, $\beta$-blockers, and/or statin therapies, in patients who suffer bleeding complications,[21,22] the direct effects of blood transfusion used to treat bleeding,[20,23] or greater prevalence of comorbidities in patients who bleed,[21] as well as a deleterious role of anemia.[24]

The relationship between bleeding and morbidity and mortality is underscored by studies demonstrating that bleeding reduction strategies are associated with improved survival in patients with ACS and those undergoing PCI. The data summarized in Table 1 emphasize the importance of bleeding as a common, clinically relevant safety event. To optimize both the end point and its role in clinical trial designs, a consistent approach to collecting bleeding data and adjudicating events is critical.[30] Toward this end, a thoughtful, broadly based consensus definition of what constitutes a bleeding event, similar to what has been done with MI and stent thrombosis, is the objective of BARC efforts.[17]

## Bleeding Academic Research Consortium Composition and Goals

An informal collaboration among academic research organizations from the United States and Europe, joined by representatives from the FDA and device manufacturers, led to a consensus document to standardize clinical end points for coronary stent trials.[17] This Academic Research Consortium developed a rapid, scholarly, and clinically relevant process resulting in a portfolio of clinical end-point definitions that

were endorsed by the FDA and broadly incorporated into clinical trial end points.[31,32] The Academic Research Consortium process was a demonstration of effective collaboration among the academic community, FDA, and industry to respond to safety concerns over drug-eluting stents and to improve the conduct of clinical research. This initiative has since been expanded to other clinical domains, including percutaneous valves and peripheral arterial disease, and the effort to establish standardized bleeding definitions presented in this consensus document. These standardized definitions are intended to allow the clinical community to determine the relative safety of different antithrombotic strategies, to provide the industry with a framework in which to evaluate the safety of emerging antithrombotic therapies, and potentially to enhance the regulatory review of new anticoagulant and antiplatelet drugs.

## Heterogeneity of Bleeding Definitions Across Trials

Several definitions of bleeding have been used in published clinical trials and registries.[33–35] Table 2 highlights the lack of uniformity in bleeding definitions among recent ACS and PCI clinical trials. Current bleeding definitions consist of both laboratory parameters, such as decreases in hemoglobin and hematocrit scores, and clinical events, including the need for transfusion or surgery, cardiac tamponade, hematomas, and various degrees of bleeding. Each definition incorporates a different combination of these data elements and then rank orders these combinations into severity categories, which vary widely between definitions.

The Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria have been in use for nearly 30 years, and have been reported in most cardiovascular trials. These criteria were developed during the early TIMI trials to define and classify major and minor hemorrhagic events in patients with ST-segment–elevation MI treated with a fibrinolytic drug. The original TIMI definition relies predominantly on laboratory data elements based on decreases in hemoglobin or hematocrit values after adjustment for the effect of blood transfusion.[36] Over time, the definitions have evolved to represent a broader range of bleeding categories and events while specifically defining each individual category.[37–42] The current updated TIMI definition is shown in Table 2.[42,43] Potential limitations of the criteria include that they were developed in the fibrinolytic era, and thus typically characterized severe acute events and difficulties with perception of the nomenclature (eg, many would consider TIMI minor bleeding to hold greater clinical significance than that connoted by the term minor). Common pitfalls that may occur when the TIMI definition is applied are recording hemoglobin drops without clinically overt signs as major bleeding events, as well as uncertainty on the timing of assessing hemoglobin values that may lead to inappropriate peaks and nadirs related to bleeding, therefore obscuring the timing of the bleeding in relation to the intervention. The TIMI criteria also characterize 3 different types of death in relation to bleeding: fatal bleeding, when a bleeding event directly leads to death within 7 days (eg, an intracranial hemorrhage that leads to herniation of the brain and death, hemopericardium that results in death, and a massive gastrointestinal hemorrhage that results in shock, hemodynamic collapse, and death); bleeding contributing to death (ie, a death in which a bleeding event was part of a causal chain of medical events that ultimately led to death within 30 days of the bleed, but bleeding did not directly and/or immediately relate to subject's death; an example is a bleed resulting in discontinuation of antiplatelet therapy followed by stent thrombosis and death); and death unrelated to a bleeding event (the death was unrelated to bleeding because either there was no clinically significant bleeding in the month before death or the bleeding event did not contribute to the subject's death).

The Global Use of Strategies to Open Occluded Arteries (GUSTO) definition of bleeding has also been implemented in a number of trials over the past 2 decades.[44] GUSTO bleeding criteria were initially used to identify significant bleeding in the setting of fibrinolytic therapy for ST-segment–elevation MI. Its various components combine to define bleeding on a graded scale of severity based on clinical acuity and impact. Notably, the GUSTO definition differs from several other definitions in that it does not require changes in hemoglobin, nor does it quantify the amount of blood transfused. Because the GUSTO bleeding criterion is clinically driven, the gradations of bleeding severity track well with risk of death/MI.[45] However, the GUSTO definition also has limitations. In addition to the fact that it was conceived during the fibrinolytic era, adjudication by a clinical events committee is often challenging, given lack of objective standardized criterion. Consequently, outcomes may not be consistent across geographic regions because thresholds for intervention and transfusion vary, depending on local patterns of clinical practice, imaging use, blood banking, etc. Thus, applying this definition requires unique attention to thorough adjudication processes to ensure that outcomes are consistently captured and to statistical analyses to ensure against regional outlier effects.

More recently, bleeding definitions in ACS and PCI trials have combined both laboratory and clinical parameters in an attempt to leverage the strengths and overcome the limitations of the TIMI and GUSTO definitions. Several trials have incorporated a combination of elements from both the TIMI and GUSTO definition,[46,47] have modified these elements,[13,49–53] or have added new parameters.[48,52–54] The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE), Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY), Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS), Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized Evaluation (STEEPLE), and Platelet Inhibition and Patient Outcomes (PLATO) trials, among others, have used different definitions for major/severe and minor bleeding (Table 2). The ACUITY[48] and Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI)[52] bleeding definitions are identical and were developed by adapting the components of TIMI major and GUSTO severe/moderate bleeding that are relevant to patients undergoing PCI.

**Table 2. Heterogeneity in Bleeding Definitions Used in Acute Coronary Syndrome Trials**

| Trial | Bleeding Definition |
|---|---|
| TIMI[6,37,38] | Non-CABG related bleeding |
| | Major |
| | Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI) |
| | Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL |
| | Fatal bleeding (bleeding that directly results in death within 7 d) |
| | Minor |
| | Clinically overt (including imaging), resulting in hemoglobin drop of 3 to <5 g/dL |
| | Requiring medical attention |
| | Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above |
| | Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug) |
| | Leading to or prolonging hospitalization |
| | Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging) |
| | Minimal |
| | Any overt bleeding event that does not meet the criteria above |
| | Bleeding in the setting of CABG |
| | Fatal bleeding (bleeding that directly results in death) |
| | Perioperative intracranial bleeding |
| | Reoperation after closure of the sternotomy incision for the purpose of controlling bleeding |
| | Transfusion of ≥5 U PRBCs or whole blood within a 48-h period; cell saver transfusion will not be counted in calculations of blood products. |
| | Chest tube output >2 L within a 24-h period |
| GUSTO[24] | Severe or life-threatening |
| | Intracerebral hemorrhage |
| | Resulting in substantial hemodynamic compromise requiring treatment |
| | Moderate |
| | Requiring blood transfusion but not resulting in hemodynamic compromise |
| | Mild |
| | Bleeding that does not meet above criteria |
| CURE[5] | Major bleeding |
| | Life-threatening (fatal, intracranial, requiring surgical intervention, results in substantial hypotension requiring the use of intravenous inotropic agents) |
| | Hemoglobin decrease ≥5 g/dL or required ≥4 U of blood |
| | Other major bleeding |
| | Transfusion of 2–3 U, intraocular |
| | Minor |
| | Led to discontinuation of study drug |
| ACUITY,[28] HORIZONS[32] | Major |
| | Intracranial or intraocular hemorrhage |
| | Access-site hemorrhage requiring intervention |
| | ≥5-cm hematoma |
| | Retroperitoneal |
| | Reduction in hemoglobin concentration of ≥4 g/dL without an overt source of bleeding |
| | Reduction in hemoglobin concentration of ≥3 g/dL with an overt source of bleeding |
| | Reoperation for bleeding |
| | Use of any blood product transfusion |
| CURRENT-OASIS 7[33] | Severe |
| | Requiring transfusion ≥4 U of PRBCs or equivalent whole blood |
| | Resulting in hemoglobin drop ≥5 g/dL |
| | Leading to hypotension that requires inotropes |
| | Requiring surgery |
| | Symptomatic intracranial hemorrhage |
| | Fatal |

(*Continued*)

**Table 2. Continued**

| Trial | Bleeding Definition |
|---|---|
| | Other major |
| | Requiring transfusion of 2 to 3 U |
| | Significantly disabling, intraocular bleeding leading to significant loss of vision |
| | Minor |
| | Other bleeding that leads to modification of drug regimen |
| | Other |
| | Bleeding not meeting criteria for major or minor |
| STEEPLE[31] | Major bleeding |
| | Fatal bleeding |
| | Retroperitoneal, intracranial, or intraocular bleeding |
| | Bleeding that causes hemodynamic compromise requiring specific treatment |
| | Bleeding that requires intervention (surgical or endoscopic) or decompression of a closed space to stop or control the event |
| | Clinically overt bleeding, requiring any transfusion of ≥1 U PRBC or whole blood |
| | Clinically overt bleeding, causing a decrease in hemoglobin of ≥3 g/dL (or, if hemoglobin level is not available, a decrease in hematocrit of ≥10%) |
| | Minor |
| | Gross hematuria not associated with trauma (eg, from instrumentation) |
| | Epistaxis that is prolonged, is repeated, or requires plugging or intervention |
| | Gastrointestinal hemorrhage |
| | Hemoptysis |
| | Subconjunctival hemorrhage |
| | Hematoma >5 cm or leading to prolonged or new hospitalization |
| | Clinically overt bleeding, causing a decrease in hemoglobin of 2 to 3 g/dL |
| | Uncontrolled bleeding requiring protamine sulfate administration |
| PLATO[34] | Major life-threatening |
| | Fatal |
| | Intracranial |
| | Intrapericardial with cardiac tamponade |
| | Resulting in hypovolemic shock or severe hypotension that requires pressors or surgery |
| | Clinically overt or apparent bleeding associated with decrease in hemoglobin >5 g/dL |
| | Requiring transfusion of ≥4 U whole blood or PRBCs |
| | Other major |
| | Significantly disabling (eg, intraocular with permanent vision loss) |
| | Associated drop in hemoglobin of 3 to 5 g/dL |
| | Requiring transfusion of 2 to 3 U whole blood or PRBCs |
| | Any major |
| | Any one of the above criteria |
| | Minor |
| | Requiring medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing) |
| | Minimal |
| | All others (eg, bruising, bleeding gums, oozing from injection sites) not requiring intervention or treatment |
| GRACE[10,21] | Major |
| | Requiring a transfusion of ≥2 U PRBCs |
| | Resulting in a decrease in hematocrit of ≥10% |
| | Occurring intracerebrally |
| | Resulting in stroke or death |
| REPLACE-2/ ISAR-REACT 3[25] | Major |
| | Intracranial, intraocular, or retroperitoneal |
| | Overt blood loss with hemoglobin decrease >3 g/dl |
| | Any hemoglobin decrease >4 g/dL |
| | Transfusion of ≥2 U blood products |

(*Continued*)

**Table 2. Continued**

| Trial | Bleeding Definition |
|---|---|
| | Minor |
| | Overt bleeding not meeting criteria for major bleeding |
| ESSENCE[27] | Major |
| | Clinically overt bleeding that was fatal (bleeding reported to cause death) |
| | Symptomatic intracranial hemorrhage |
| | Retroperitoneal hemorrhage |
| | Intraocular hemorrhage leading to significant vision loss |
| | Decrease in hemoglobin of at least 3.0 g/dL (with each blood transfusion unit counting for 1.0 g/dL hemoglobin) |
| | Bleeding requiring transfusion of $\geq$2 U RBCs or equivalent of whole blood |
| | Minor |
| | All other clinically significant bleeding not meeting the definition for major bleeding and that led to interruption of the study drug for at least 24 h, surgical intervention, or transfusion of $\leq$1 U blood |
| Amlani et al[28] | Major |
| | Hemoglobin drop $\geq$5 g/dL |
| | Intracranial hemorrhage |
| | Bleeding requiring surgery |
| | Blood transfusion of at least 2 U |

TIMI indicates Thrombolysis in Myocardial Infarction; CABG, coronary artery bypass graft; MRI, magnetic resonance imaging; PRBC, packed red blood cell; GUSTO, Global Use of Strategies to Open Occluded Arteries; CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Events; ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy; HORIZONS, Harmonizing Outcomes With Revascularization and Stents; CURRENT-OASIS 7, Clopidogrel optimal loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions; STEEPLE, Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized Evaluation; PLATO, Platelet Inhibition and Patient Outcomes; GRACE, Global Registry of Acute Coronary Events; REPLACE-2, Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events; ISAR-REACT, Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment; and ESSENCE, Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events.

## Challenges to Creating a Universal Bleeding Definition

There are several challenges in creating a universal bleeding definition.[55] It is crucial to first consider the purpose. A comprehensive bleeding classification is required that captures information about the cause (procedural or nonprocedural), site (intraocular, intracranial, visceral, peritoneal, access site, etc), and severity (quantified by impact on laboratory data and clinical status) of bleeding. Such a classification should correlate closely with prognosis and should be able to direct specific diagnostic and treatment protocols. Moreover, the different bleeding categories and the classification system should be carefully considered, whether descriptive such as major or life-threatening or objective using numeric or alphanumeric score. Ideally, a standardized definition should be able to address all these issues. In addition, the definition should be practical and easy to use; ie, it should be based on data that can be readily collected by sites, monitored, and adjudicated.

A key challenge is to maintain an appropriate balance between sensitivity and specificity of criteria to optimize the ability to detect dose response or to discern small variations between therapies while arriving at clinically meaningful conclusions. As noted in the coronary effort,[17] it is generally recognized that no universal definition can be crafted that is perfectly accurate (sensitive and specific) or that is perfect for all applications. The value of a consensus definition that is used consistently across clinical trials is not dependent on perfection.

Nomenclature presents another challenge. Depending on context, the meanings of terms change; if a nuisance bleed encourages a patient to stop taking beneficial medications, it can still have major importance in other senses. Moreover, the site of bleeding affects its relationship with mortality. For example, non–access-site bleeds may have a more significant impact on the likelihood of death/MI than access-site bleeding.[55a] The duration of follow-up also matters, and there may be unmeasured factors. The definitions also change over time. It is not yet known which components of a bleeding definition are predictors of mortality; large groin hematomas, for example, appear less detrimental than TIMI major bleeding or ACUITY major bleeding with or without transfusion.[56] Furthermore, adjudication of bleeding events is a process that does not solely revolve around a definition. Bleeding rates depend on several factors, including how aggressively investigators seek to ascertain information, how definitions are written, and how the definitions are applied. These aspects can complicate the interpretation of safety results from clinical trials, a fact underscored by the complexity of current treatment guidelines.[1,2,57] Short of a comprehensive analysis of very large databases of prospectively acquired detailed bleeding data linking various definitions to subsequent clinical outcomes, which is still lacking, the optimal universal bleeding definition can be arrived at only through expert consensus because the expert consensus process allows weighing and balancing multiple options.

## Special Considerations for Coronary Artery Bypass Graft–Related Bleeding Definition

Bleeding after cardiac surgery is a serious complication, and excessive blood loss frequently results in transfusion of allogeneic blood, blood products, or surgical re-exploration.

Most studies have traditionally not considered coronary artery bypass graft (CABG)–related bleeding, but because up to 12% of ACS patients may undergo CABG[58] during the index hospitalization, the BARC group felt that it was important to include CABG-related bleeding in the BARC consensus document. Because CABG surgery is one of the rare instances of surgery performed under full anticoagulation and because transfusion is inherent to cardiopulmonary bypass, it is difficult to define a threshold for bleeding in CABG that would separate the amount of bleeding expected during routine surgery from the unusual or unexpected. It is even more difficult to determine the thresholds for CABG bleeding that are related to a change in prognosis. Mean postoperative chest tube output during the first 24 hours after standard CABG is estimated to be 400±200 mL and up to 1200 mL in patients treated with dual antiplatelet therapy including clopidogrel.[59–62] Bleeding is similar with off-pump CABG and on-pump CABG.[63] Five percent to 7% of patients lose >2 L of blood within the first 24 hours after surgery,[64] and up to 5% require reintervention for bleeding after sternotomy closure.[65]

Both surgical re-exploration and red blood cell transfusion are associated in a dose-dependent and often durable manner with prolonged intensive care and hospital stays and reduced survival rates.[66,67] There are international differences in the threshold for transfusions and probably also for rates of reoperation for bleeding associated with the use of scorecards.[68]

In a pooled analysis of the ACUITY and HORIZONS-AMI trials, CABG-related major ACUITY-graded bleeding in a time-adjusted baseline covariate-adjusted Cox model of 1600 patients did not independently predict subsequent 12-month mortality (hazard ratio, 1.21; 95% confidence interval, 0.81 to 1.80; $P=0.34$).[69]

Rather than developing a specific set of data elements distinct from other types of BARC bleeding (Table 3), BARC was guided with the following principles in developing the definition for BARC type 4 (CABG-related) bleeding. First, BARC CABG-related bleeding definitions must include the same criteria for fatal bleeding, intracranial hemorrhage, need for intervention to control bleeding, and number of transfusions as BARC non–CABG-related bleeding. Second, specific criteria for the amount of chest tube drainage need to be included. Third, if bleeding does not meet the severity criteria for at least a BARC type 3 event, it will not be counted as an event. Fourth, specific time intervals will need to apply for CABG-related events: up to 48 hours for transfusions and intracranial bleeding and within a 24 hour period for excessive chest tube drainage. It is appropriate that there will be no time window for the occurrence of fatal bleeding. It is important to note that the temporal relationship of the bleeding event to the CABG surgery is the primary factor that differentiates type 4 bleeding from type 3 bleeding. Therefore, if a bleeding event occurs during the specified time frame in relation to a CABG procedure but does not meet type 4 severity markers, it will not be adjudicated as a bleeding event. It is also noteworthy to include that only allogenic transfusions are considered transfusions for CABG-related bleeds.

**Table 3. Bleeding Academic Research Consortium Definition for Bleeding**

| |
|---|
| Type 0: no bleeding |
| Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional |
| Type 2: any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation |
| Type 3 |
| Type 3a |
| Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed) |
| Any transfusion with overt bleeding |
| Type 3b |
| Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed) |
| Cardiac tamponade |
| Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) |
| Bleeding requiring intravenous vasoactive agents |
| Type 3c |
| Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal) |
| Subcategories confirmed by autopsy or imaging or lumbar puncture |
| Intraocular bleed compromising vision |
| Type 4: CABG-related bleeding |
| Perioperative intracranial bleeding within 48 h |
| Reoperation after closure of sternotomy for the purpose of controlling bleeding |
| Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period† |
| Chest tube output ≥2L within a 24-h period |
| Type 5: fatal bleeding |
| Type 5a |
| Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious |
| Type 5b |
| Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation |

CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (ie, within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

*Corrected for transfusion (1 U packed red blood cells or 1 U whole blood=1 g/dL hemoglobin).

†Cell saver products are not counted.

Because CABG-related bleeding is so common, it may overwhelm the incidence of non-CABG bleeding, especially in drug trials. Thus, comparing the effects of treatments on total bleeding rates may not be significantly different between the treatments, even though non-CABG bleeding rates may be significantly different.[70] It is important to report total, CABG-related, and non–CABG-related bleeding separately. In addition, BARC acknowledges that there is a need to know when to stop drugs with a propensity to cause bleeding with CABG (and with other types of surgery). Further research is required to better define the risk associated with CABG bleeding and the effect of components of the definition, particularly transfusions of (different) blood products on subsequent mortality.

In developing a universal bleeding definition, BARC was driven by the following criteria: (1) The definitions should apply in a broad clinical context, and hence will be applicable to cardiovascular clinical trials and/or registries in which bleeding is used as an end point; (2) although CABG-related bleeding may potentially relate to either technical issues or drug effects, BARC acknowledges a need to report CABG-related, non–CABG-related, and total bleeding rates separately and the effects of treatment; and (3) bleeding should be reported in a hierarchical manner characterizing severity with a graded numeric system nomenclature, not with subjective or descriptive terms such as minor or nuisance. Importantly, after a consensus report is proposed, it should result in an end-point definition that will be embraced by the clinical research community, by pharmaceutical and device manufacturers, by regulatory agencies, and ultimately in clinical practice. Finally, the definition should be validated against data sets from several trials.

## Proposed Bleeding Definition

- Type 0: no evidence of bleeding.
- Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional. Examples include, but are not limited to, bruising, hematoma, nosebleeds, or hemorrhoidal bleeding for which the patient does not seek medical attention. Type 1 bleeding may include episodes that lead to discontinuation of medications by the patient because of bleeding without visiting a healthcare provider.
- Type 2: any clinically overt sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that is actionable but does not meet criteria for type 3, type 4 (CABG-related), or type 5 (fatal bleeding) BARC bleeding. The bleeding must require diagnostic studies, hospitalization, or treatment by a healthcare professional. In particular, the bleeding must meet at least one of the following criteria: First, it requires intervention, defined as a healthcare professional–guided medical treatment or percutaneous intervention to stop or treat bleeding, including temporarily or permanently discontinuing a medication or study drug. Examples include, but are not limited to, coiling, compression, use of reversal agents (eg, vitamin K, protamine), local injections to reduce oozing, or a temporary/permanent cessation of antiplatelet, antithrombin, or fibrinolytic therapy. Second, the bleeding leads to hospitalization or an increased level of care, defined as leading to or prolonging hospitalization or transfer to a hospital unit capable of providing a higher level of care. Or third, the bleeding prompts evaluation, defined as leading to an unscheduled visit to a healthcare professional resulting in diagnostic testing (laboratory or imaging). Examples include, but are not limited to, hematocrit testing, hemoccult testing, endoscopy, colonoscopy, computed tomography scanning, or urinalysis. A visit or phone call to a healthcare professional during which neither testing nor treatment is undertaken does not constitute type 2 bleeding.
- Type 3: clinical, laboratory, and/or imaging evidence of bleeding with specific healthcare provider responses, as listed below:
  - Bleeding Academic Research Consortium type 3a bleeding
    - Any transfusion with overt bleeding
    - Overt bleeding plus hemoglobin drop ≥3 to <5 g/dL (provided hemoglobin drop is related to bleeding). Hemoglobin drop should be corrected for intracurrent transfusion in which 1 U packed red blood cells or 1 U whole blood would be expected to increase hemoglobin by 1 g/dL.
  - Bleeding Academic Research Consortium type 3b bleeding
    - Overt bleeding plus hemoglobin drop ≥5 g/dL (provided hemoglobin drop is related to bleed). Hemoglobin drop should be corrected for intracurrent transfusion in which 1 U packed red blood cells or 1 U whole blood would be expected to increase hemoglobin by 1 g/dL.
    - Cardiac tamponade
    - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
    - Bleeding requiring intravenous vasoactive drugs
  - Bleeding Academic Research Consortium type 3c bleeding
    - Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal); subcategories confirmed by autopsy, imaging, or lumbar puncture
    - Intraocular bleed compromising vision
  - Type 4: Coronary Artery Bypass Graft–related bleeding
    - Perioperative intracranial bleeding within 48 hours
    - Reoperation after closure of sternotomy for the purpose of controlling bleeding
    - Transfusion of ≥5 U whole blood or packed red blood cells within a 48-hour period (only allogenic transfusions are considered transfusions for CABG-related bleeds)
    - Chest tube output ≥2 L within a 24-hour period
    - Notes: If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as

not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (ie, within a 48-hour time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

— Type 5: Fatal bleeding

Fatal bleeding is bleeding that directly causes death with no other explainable cause. BARC fatal bleeding is categorized as either definite or probable as follows:

- Probable fatal bleeding (type 5a) is bleeding that is clinically suspicious as the cause of death, but the bleeding is not directly observed and there is no autopsy or confirmatory imaging.
- Definite fatal bleeding (type 5b) is bleeding that is directly observed (by either clinical specimen [blood, emesis, stool, etc] or imaging) or confirmed on autopsy.
- The site of fatal bleeding is specified as intracranial, gastrointestinal, retroperitoneal, pulmonary, pericardial, genitourinary, or other.
- Bleeding Academic Research Consortium fatal bleeding is meant to capture deaths that are directly due to bleeding with no other cause. The time interval from the bleeding event to the death should be considered with respect to likely causality, but there is no specific time limit proposed. Bleeding that is contributory but not directly causal to death is not classified as fatal bleeding but may be categorized as other forms of bleeding. Bleeding that leads to cessation of antithrombotic or other therapies may be contributory but again would not be classified as fatal bleeding. Bleeding associated with trauma or with surgery may be fatal, depending on whether it was determined to be directly causal or not.
- Examples of potential scenarios consistent with BARC fatal bleeding include the following: (1) A patient who receives a fibrinolytic agent for a small inferior MI loses consciousness and dies; autopsy shows an intracranial hemorrhage with mass effect: definite fatal bleed, intracranial; (2) a patient who receives a fibrinolytic agent for a large anterior MI loses consciousness and develops cardiac arrest; clinical examination immediately earlier showed a dilated left pupil: probable fatal bleed, intracranial; (3) a post-PCI patient on dual antiplatelet therapy who has a witnessed large gastrointestinal bleed becomes hypotensive and dies: definite fatal bleed, gastrointestinal; and (4) a patient develops a gastrointestinal bleed that is successfully cauterized; 3 days later, the gastroenterologist stops dual antiplatelet therapy and the patient has a fatal MI: not a fatal bleed.

## Bleeding End-Point Reporting

Bleeding Academic Research Consortium recommends defining the timing of events according to the clinical trial and according to the particular pharmacotherapy or intervention being studied, but at least at 7 days, 30 days, and/or at the end of the trial.

## Conclusions

Herein we have proposed a new objective, hierarchically graded, consensus classification for bleeding. After a review of the data and prior definitions, this new BARC categorization was reached by consensus of several groups with experience in considering end points in cardiovascular clinical trials and registries. Validation of these proposed consensus definitions is still needed. We strongly urge trialists and sponsors to begin reporting bleeding events according to BARC definitions in all research efforts from this point forward, even if in conjunction with other definitions. The universality of the definition will overcome the inherent limitations of a consensus-based effort and will allow comprehensive and consistent reporting of bleeding in future clinical investigations.

## Appendix

### Bleeding Academic Research Consortium Participants

***Academic Research Organizations***

Cardialysis, Rotterdam, the Netherlands: Pascal Vranckx, MD. Cardiovascular Research Foundation, New York, NY: Adriano Caixeta, MD, PhD; Roxana Mehran, MD; Eugenia Nikolsky, MD, PhD. Cleveland Clinic Coordinating Center for Clinical Research, Cleveland, OH: Venu Menon, MD. Duke Clinical Research Institute, Durham, NC: E. Magnus Ohman, MD; Sunil Rao, MD. Green Lane Coordinating Center, Auckland, New Zealand: Harvey White, MB ChB, DSc. TIMI Study Group, Boston, MA: Deepak L. Bhatt, MD, MPH; Stephen D. Wiviott, MD. Pharmacological/Percutaneous Endoluminal Revascularization for Unstable Syndromes and Its Evaluation (PERFUSE), Boston, MA: C. Michael Gibson, MD.

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## Acknowledgments

We wish to thank Maria Alu for manuscript preparation, editorial services, and logistical management of the BARC meetings and communications.

## Sources of Funding

Grants were provided to the Cardiovascular Research Foundation to cover the costs of travel, lodging, and meeting expenses for academic attendees to the meeting in Silver Spring, MD, by Abbott Vascular, AstraZeneca, Boston Scientific Corp, Bristol-Myers Squibb/Sanofi-Aventis, Daiichi Sankyo, The Medicines Company, Medtronic, and Regado Biosciences.

## Disclosures

Dr Bhatt has received research grants from AstraZeneca, Bristol-Myers Squibb, Eisai, Sanofi-Aventis, and The Medicines Company. Dr Eikelboom has received research grants from BIHR and The Heart and Stroke Foundation of Canada, as well as honoraria for lectures and/or consultancies from Bristol-Myers Squibb, Sanofi-Aventis, AstraZeneca, and Boehringer-Ingelheim. Dr Gibson has received honoraria for lectures and/or consultancies from Bayer Corp, Johnson & Johnson Corp, Medicure, Portola Pharmaceuticals, Sanofi-Aventis Pharmaceuticals, Schering Plough Corp, The Medicines Company, Daiichi Sankyo, and Eli Lilly. Dr Mehran has received a research grant from the Bristol Myers Squibb/Sanofi-Aventis pharmaceutical partnership, and has served on advisory boards for Abbott Vascular, Accumetrics, AstraZeneca, Cardiva, Cordis, Gilead, Guerbet, Ortho-McNeil, Regado Biosciences, and St. Jude Medical. Dr Nikolsky has served as a consultant for Medtronic Vascular. Dr Rao has received research grants from Cordis Corp, Novartis, Sanofi-Aventis, and Ikaria; has served on the Speaker's Bureau for The Medicines Company, BMS, Sanofi-Aventis, and Terumo Medical; has received honoraria from AstraZeneca, Daiichi-Sankyo/Eli Lilly, and BMS; and has served as a consultant or advisory board member for The Medicines Company, AstraZeneca, BMS, Terumo, and Daiichi-Sankyo/Eli Lilly. Dr Serebruany has received research grants from Bristol-Myers Squibb, Eli Lilly, and Novartis; has served on the speakers' bureau of Boehringer-Ingelheim and Sanofi-Aventis and as a consultant for Merck, Sanofi-Aventis, and Boehringer-Ingelheim; has received honoraria from AstraZeneca and Merck; and holds intellectual property with Eisai, Eli Lilly, and Pfizer. Dr Steg has received a research grant from Servier and honoraria for lectures and/or consultancies from AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, Eli Lilly, MSD/Schering Plough, Novartis, Otsuka, Roche, Sanofi-Aventis, Servier, The Medicines Company, Boehringer Ingelheim, and Medtronic. Dr Valgimigli has received research grants from Iroko, Eli Lilly, The Medicines Company, and Medtronic; has received honoraria from Cordis, Johnson & Johnson, Medtronic, Abbott, EISAI, Iroko, Merck, AstraZeneca, Chiesi, Terumo, Accumetrics, and The Medicines Company; and consults for Abbott, Eli Lilly, Choice Pharma, St. Jude, Chiesi, La Roche, CID, Iroko/Cardio, and AstraZeneca. Dr Wiviott has received honoraria for lectures or consultancies from Eli Lilly, Daiichi Sankyo, AstraZeneca, Sanofi-Aventis, Bristol-Myers Squibb, Pfizer, and ARENA and research grants from Eli Lilly/Daiichi Sankyo, Schering-Plough, and Merck. Dr Ohman receives research grant support from Daiichi-Sankyo, Datascope, and Eli Lilly, and has received consulting fees or honoraria from AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead, Liposcience, Merck, Sanofi-Aventis, The Medicines Company, Pozen, and WebMD. Dr White has received research grants from Sanofi-Aventis, Eli Lilly, The Medicines Company, The National Institutes of Health, Pfizer, Roche, Johnson and Johnson, Schering-Plough, MSD, AstraZeneca, GlaxoSmithKline, Daiichi Sankyo, and Bristol-Myers Squibb, and is a consultant for Regado Biosciences. The other authors report no conflicts.

The BARC meetings involved members of the Interventional Cardiology Devices Branch of the Office of Device Evaluation, Center for Devices and Radiological Health, US FDA. The opinions or assertions herein are the private views of the authors and are not to be construed as reflecting the views of the FDA.

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KEY WORDS: clinical trials ■ hemorrhage ■ outcome ■ pharmacology

## SUPPLEMENTAL MATERIAL

### Case example #1

A patient enrolled in a clinical trial of a new antithrombotic agent that is to be taken chronically for secondary prevention experiences epistaxis requiring an emergency room visit, nasal packing, and cessation of study drug. There is no associated hypotension and the patient does not require vasopressor support or transfusion. The associated hemoglobin decrease is 2 g/dl.

Meets criteria for Type 2 BARC bleeding, GUSTO mild bleeding, TIMI bleeding requiring medical attention, CURE minor bleeding, PLATO minor bleeding

### Case example #2

A patient hospitalized with acute coronary syndrome undergoes percutaneous coronary intervention. Post-procedure, the patient experiences a groin hematoma of 10 cm requiring aggressive manual compression. During the manual compression, she becomes hypotensive, likely due to a vagal reaction from compression of her femoral artery. During this period, she also receives one unit of packed red blood cells. She becomes clinically stable without the need for inotropic support or surgical intervention. There is no decrease in hemoglobin.

This event would require adjudication in order to distinguish hypotension that occurs as a result of brisk bleeding from hypotension that occurs from other causes (like a vagal reaction from manual compression of the femoral access site). This event meets criteria for BARC Type 3a bleeding (any transfusion). Without adjudication, the event would meet criteria for GUSTO severe bleeding (bleeding event with hypotension) and for TIMI Bleeding Requiring Medical Attention.

# APPENDIX 2.2

## BARC unified definition of bleeding. You can see if you look, but more if you look again...

Vranckx P, Valgimigli M.

*Circulation* 2012. [**Letter to the editor**]

We recognize the high value of the BARC-validation study reported by Dr. Ndrepepa et al. in this journal.(1) However, while important, their results should be interpreted within the context of the specific study limitations. As stressed in the accompanying editorial, the newly proposed BARC bleeding definitions heavily rely on adjudication. (2) The quality of event adjudication is dependent on the completeness, and detail in individual patient accounts, including protocol driven laboratory examinations. A potential underreporting of BARC-2 and BARC-1 bleeding events therefore, should be anticipated. This analysis focussed on in hospital bleeding only. How many were access site related? The significance of 'in-hospital' BARC 1 bleeding should be questioned. Moreover, most patients included in this analysis had an elective PCI for stable lesions. In this "low risk" patient population the lack of any discriminatory power of BARC≥2 towards one-year mortality over existing bleeding scales should not come as a surprise. We strongly believe that the "true" variation of the prognostic implication of BARC and its discriminatory power to predict a worst cardiovascular outcome comparable to other Bleeding scales will be revealed in prospective analysis.

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# PART 3

## PERFUSION.

## HEMOGLOBIN-BASED OXYGEN CARRIERS TO ANNIHILATE MYOCARDIAL ISCHEMIA DURING BRIEF CORONARY ARTERY OCCLUSION

# CHAPTER 3.1

## The multipurpose oxygen therapeutic. Technical Report

Dubé GP, Vranckx P.

HBOC-201: *EuroIntervention* 2008; **4**: 161-65. [**technical report**]

EuroIntervention

# HBOC-201: The multi-purpose oxygen therapeutic

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*Certain of the preclinical studies and clinical trials reviewed in this document were supported in part or in full by grants from Biopure Corporation.*

*Additional Note: Work described in this Technical Report was performed at various institutions (as noted in manuscript).*

## Product description

HBOC-201 (Haemoglobin glutamer-250 [bovine]; Hemopure®) is a polymerised, iso-oncotic, high-molecular weight, bovine haemoglobin-based oxygen carrier (HBOC) for intravenous infusion. HBOC-201 is manufactured by Biopure Corporation in Cambridge, Massachusetts, USA.

## History

The development of HBOC-201 has been driven by concerns over blood safety and military interest in a product having improved storage and emergency use flexibility. HBOC-201 has been approved for the treatment of acute surgical anaemia in South Africa since 2001. Of late, needs beyond surgical anaemia, trauma and haemorrhagic shock have evolved to include ischaemic rescue, applicable to cardiology and vascular surgery.

## Technical specifications

The manufacturing process involves: 1) purifying free haemoglobin (MW 65 kD) from bovine red cells by filtration and anion exchange chromatography, 2) polymerisation with glutaraldehyde, 3) fractionation to remove 65 kD haemoglobin, and 4) sterile packaging. The manufacturing process, approved by the FDA and European Medicine Evaluation Authority (EMEA), removes potential pathogens including bacteria, viruses, transmissible spongiform encephalopathy (TSE) and prions such as those believed to be responsible for Creutzfeldt-Jakob disease. Polymerisation with glutaraldehyde increases the molecular size (thereby increasing vascular retention) and stabilises the protein.

The finished solution is clear, deep purple and supplied in 250 ml units. The technical characteristics of HBOC-201 are summarised in Table 1. HBOC-201 has a circulatory half-life of 19 hours, (vs. approximately 0.5 hours for a similar amount of unmodified haemoglobin in animals). The $P_{50}$ (partial pressure of oxygen at which the Hb is 50% saturated) is approximately 40 mm Hg[1]

**Table 1. Characteristics of HBOC-201.**

| | |
|---|---|
| Average molecular weight | 250 kD[a] |
| MW > 500 kD | ≤ 15% |
| MW ≤ 65 kD | ≤ 2.5% |
| Relative size vs. a red blood cell | 1/100,000,000 X the volume of a RBC |
| Storage properties | Room temperature (2°C to 30°C) for 3 years[b] |
| Osmolality | 290 to 310 milliosmole/kg |
| Oncotic pressure | 25-27 mm Hg |
| Viscosity (37°C) | 2.2 centipoise at 13 g/dL, 37°C |
| Reconstitution | None required |
| Administration | i.v., via peripheral or central vein |
| pH | 7.6 to 7.9 |
| $P_{50}$ | 40 mm Hg ± 6 |
| n (Hill coefficient of cooperativity) | 1.0 |
| Hb concentration | 13±1 g/dL (300-350g Hg / 250 ml Unit) |
| Endotoxin concentration | < 0.02 endotoxin unit/ml |
| Phospholipid concentration | < 0.1 µg/ml |
| metHb content | < 5% |
| ml Oxygen per g Hb at maximal saturation | Approximately 1.26[c] |
| NaCl USP | 114 mmol/L |
| KCl USP | 4.0 mmol/L |
| $CaCl_2$-$2H_2O$ USP | 1.4 mmol/L |
| NaOH NF | 12.5 mmol/L |
| Sodium lactate | 27.1 mmol/L |
| N-acetyl-L-cysteine USP | 12.3 mmol/L |
| Carrier | Water for injection USP |

[a] kD: kiloDalton; [b] Data also supports stability at 40°C for 18 months; [c] Slightly less than human RBC Hb which binds 1.34 ml $O_2$/g Hb

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(Figure 1) and permits a greater percentage oxygen off-load than that of red blood cells (RBCs) , and other HBOCs characterised by lower $P_{50}$ values.[2] HBOC-201 has additional advantages over other oxygen therapeutics. Unlike HBOC products derived from human blood, HBOC-201 takes advantage of a plentiful supply of raw material (bovine haemoglobin). In addition, it has the highest haemoglobin concentration (13 g/dL) of any HBOC in clinical testing. This is a key advantage in maintaining oxygen delivery to ischaemic tissues with limited perfusion flow or in anaemia when early haemodilution with crystalloid or colloid solutions may complicate volume management. The smaller size of HBOC-201 polymers compared to a red cell and lower viscosity facilitate delivery of oxygen to remote tissues that may be poorly accessible by circulating erythrocytes. Unlike stored RBCs, which often carry the potential to elicit inflammatory responses and induce diminished host resistance[3], HBOC-201 is free of pro-inflammatory stimuli and possible infectious agents. Finally, HBOC-201 is compatible with all blood types, is the only HBOC demonstrated to be stable at 40°C and has the longest room-temperature shelf life (three years) of all HBOCs currently in development.

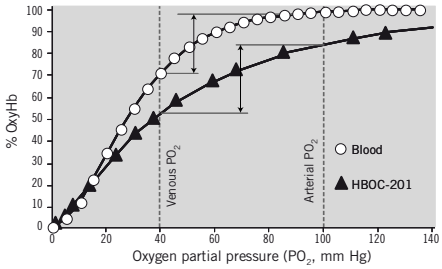


*Figure 1. Haemoglobin dissociation curves for Hemopure and RBCs. At an arterial $PO_2$ of 100 mm Hg, red cell haemoglobin is 98% saturated and Hemopure is 85% saturated. However, for a given decrease in $PO_2$ (from 100 mmHg to 40 mmHg in this example) as blood travels from the lungs to peripheral tissues, the fraction of total oxygen released by HBOC-201 is equal to or greater than that released by RBCs to target organs. Vertical arrows represent the percent oxygen extraction between arterial and venous $PO_2$ levels.*

## Clinical experience

### Summary of clinical experience

A total of 22 clinical trials evaluating the efficacy and safety of HBOC-201 have been completed with 826 subjects exposed to at least one dose of HBOC-201. Eighteen of the 22 studies were controlled, randomised trials. The clinical program was designed primarily to evaluate the extent to which HBOC-201 could replace red cell use or temporarily meet patient oxygen delivery needs in the setting of acute anaemia, an oxygen bridge™ for tissues until other definitive therapy was available. HEM-115, an elective surgery orthopaedic anaemia trial and the largest of the two phase III clinical trials, represents approximately 48% of all clinical trial subjects.

In four RBC-controlled studies, the median or mean number of allogeneic RBC units transfused was significantly lower for subjects randomised to HBOC-201 than in subjects randomised to RBCs. The mean ±SEM number of RBC units administered to HBOC-201 and RBC treatment groups, respectively, in HEM-115 were 1.4±0.1 and 3.1±0.1 ($p<0.001$).[4] For HBOC-201-treated patients who eventually received RBCs, there was a significant delay in the time to the first RBC infusion with 75% of the HBOC-201 patients requiring their first allogeneic RBC transfusion four days after their first HBOC-201 infusion.

HBOC-201 has also been evaluated in subjects with cardiovascular disease. In the phase II COR-0001 trial, HBOC-201 was infused intravenously into subjects with stable angina and non-ST-segment elevation acute coronary syndrome (ACS) scheduled for elective PCI.[5] Consistent with this drug's well-known vasoconstrictive properties, HBOC-201 elicited a transient, mild increase in mean blood pressure accompanied by a slight decrease in cardiac output, but had no effect on left ventricular stroke work index (LVSWI) or systemic oxygen consumption. Increases in blood pressure were readily addressed, when appropriate, by standard antihypertensive drugs.

Using a novel preparation and administration route, oxygenated HBOC-201 was infused into the coronary arteries of subjects characterised by silent ischaemia, stable angina or unstable angina (Braunwald class I-IIIB)[6] in a pilot phase II study (COR-0002) designed to determine if direct perfusion of the distal vessel with oxygenated HBOC-201 could mollify or avert ischaemia induced by total LAD coronary artery occlusion.[7] Patients first received either intracoronary HBOC-201 during a brief coronary occlusion (test treatment) or coronary occlusion in the absence of intracoronary infusion (control treatment). After completion of the first intervention and a 20-min recovery period, patients crossed over to the second intervention. Control coronary artery occlusions induced deterioration in both systolic and diastolic LV function and haemodynamic parameters and caused ST segment elevations (all $P< 0.05$ vs. baseline). In contrast, HBOC-201 infusion prevented these changes, and while arrhythmia and angina required premature termination of all control occlusions, this did not occur with HBOC-201 infusions.

### Expected physiological changes and side-effects

Clinical trials have identified adverse events (AEs) and side effects following treatment with HBOC-201. These effects include oliguria, increased blood pressure, nausea/vomiting, diarrhoea, abdominal pain and distension, dysphagia, flatulence, skin discoloration, scleral discolouration, decreases in pulse oximetry $O_2$ saturation and haematocrit measurements, transient increases in methaemoglobin and increases in hepatic and pancreatic enzymes. HBOC-201 is eliminated via the reticuloendothelial system which metabolises the breakdown products of protein and heme. The heme is metabolised into bilirubin or recycled into red cell production.

### Product safety

A full toxicology profile was completed for HBOC-201, including general toxicity (acute and repeat dose), cardiotoxicity, genotoxicity,

reproductive toxicity, immunotoxicity, and renal toxicity studies. Overall, the data suggest that HBOC-201 has an acceptable toxicity profile. Evaluation of HBOC-201 safety was performed on the results from 21 trials, including 797 subjects exposed to at least one dose of HBOC-201. The number of deaths (39, 2.7%) in the HBOC-201 group was not significantly different from mortality in the control groups (25, 2.1%).

Most incidents of increased blood pressure appear with greater frequency in the HBOC-201 groups than the comparators, are transient, mild and do not require treatment. Increases in blood pressure of sufficient amplitude to warrant treatment were captured as severe AEs (SAEs) and occurred with an incidence indistinguishable from that in control subjects.

Analysis of the potential for HBOC-201 to induce immunogenicity has been analysed in 473 HBOC-201 subjects and 418 controls across 14 clinical trials. The risk of immunogenicity was found to be exceedingly small (0.2% of subjects dosed with HBOC-201).

The serious adverse events occurring in the HEM-115 study have been analysed, including a search for their root causes.[4] In HEM-115, the SAE incidence (0.34 SAEs/patient) was slightly higher in patients randomised to HBOC-201 than in patients randomised to packed red blood cells (PRBCs) (0.25 SAEs/patient) (P=0.062). The severity of anaemia correlated with an increased occurrence of SAEs, independent of treatment arm (P<0.001). Moderate or high need patients were matched between treatment arms to effect a valid safety comparison. Of those patients randomised to HBOC-201, a subset (designated "HR") of the most severely anaemic were, per protocol, "crossed over" to receive PRBCs (Table 2). All other patients randomised to HBOC-201 (designated HH) were adequately treated with study drug alone. The HH subgroup, representing moderate need subjects, was matched to a subgroup of PRBC subjects who were adequately treated with ≤3 units PRBCs (R3–). The high-needs HR subgroup was compared to a corresponding high-needs PRBC subgroup (R3+), those that received >3 units.

The death rate and SAEs per patient were identical in groups HH and R3- (Table 3). Likewise, the death rate and SAEs per patient in groups HR and R3+ were similar. However, comparisons of the two levels of clinical need within each treatment arm indicates that SAEs/patient are 4.5 fold higher in HR than in HH (P<0.0001) (Table 3). Also, SAEs/patient are 3.4 fold higher in R3+ compared to R3- (P<0.0002). Patients randomised to treatment with HBOC-201 had lower total haemoglobin (THb) concentrations, with subjects in the HR group having the lowest THb of the need-based subgroups. Under-treatment (i.e., persistent anaemia, P=0.035), age (P=0.046) and pre-existing cardiac disease (P=0.004) were covariant predictors of cardiac SAEs. By comparison, randomisation to HBOC (P=0.603) had no value as a predictor of cardiac SAEs. Fluid mismanagement (volume overload) also contributed to the incidence of SAEs. These results indicate that patient care, and in particular, failure to adequately treat anaemia, rather than toxicity, explains the disproportionately high incidence of SAEs in patients randomised to HBOC-201.[8,9]

**Table 2. Characteristics in HH, HR, R3– and R3+ groups in HEM-115 study.**

| Parameters | HH | R3– | HR | R3+ |
|---|---|---|---|---|
| Number of patients (%) | 211 (60%) | 231 (68%) | 139 (40%) | 107 (32%) |
| Estimated blood loss (ml) | 537±35 | 525±31 | 1043±111 | 1140±117 |
| Hb levels at 1st administration (g/dL) | 9.1 | 9.0 | 8.6 | 8.6 |
| Total volume of non-study drug fluid (L) | | | | |
| Up to 3 days after surgery | 7.7±0.3 | 7.5±0.2 | 9.7±0.5 | 9.1±0.6 |
| HBOC (Unit) | 3.3±0.1 | – | 5.5±0.3 | – |
| PRBC (Unit) | – | 1.96±0.05 | 3.5±0.2 | 5.4±0.2 |
| Total haemoglobin (g) | 106 | 127 | 403 | 351 |

Characteristics were similar in the two pairs of matched subgroups, i.e., HH and R3– and HR and R3+, respectively, while the moderate- and high-need groups differed from each other substantially. The high-need groups (HR, R3+) had approximately twice the blood loss, a lower initial transfusion Hb concentration, received two litres more of non-study drug fluids, and were treated with approximately three times more haemoglobin than the moderate-need groups (HH, R3–). These differences highlight the fact that patient need/medical condition is a major covariate that must be taken into account in any meaningful comparison between patient populations.

**Table 3. Overall summary of serious adverse events.**

| Groups | N | Deaths | p-values[1] | SAE/pt | p-values |
|---|---|---|---|---|---|
| Overall comparison of treatment arms | | | | | |
| H | 350 | 0.03 | 0.450 | 0.34±0.04 | 0.016 |
| R | 338 | 0.02 | | 0.25±0.03 | |
| Paired comparison of treatment arms | | | | | |
| HBOC-201 | | | | | |
| HH | 211 | 0.01 | 0.056 | 0.14±0.03 | <0.0001 |
| HR | 139 | 0.05 | | 0.63±0.07 | |
| PRBC | | | | | |
| R3- | 231 | 0.01 | 0.386 | 0.14±0.03 | <0.0002 |
| R3+ | 107 | 0.03 | | 0.47±0.08 | |
| Paired comparisons: matching subgroups | | | | | |
| Moderate needs | | | | | |
| HH | 211 | 0.01 | 1.00 | 0.14±0.03 | 1.0 |
| R3- | 231 | 0.01 | | 0.14±0.03 | |
| High needs | | | | | |
| HR | 139 | 0.05 | 0.52 | 0.63±0.07 | 0.13 |
| R3+ | 107 | 0.03 | | 0.47±0.08 | |

[1] All p-values derived from t-test for continuous variables (SAEs/pt) and the two-tailed Fischer Exact test for dichotomous variables (SAEs).
H: HBOC-201; R: PRBC; HH: HBOC-201 only; HR: HBOC-201 plus PRBCs; R3–: ≤ 3 Units PRBCs; R3+ ≥ 3 units PRBCs; N: number of patients

## Indications for use

Elimination of the need to cross-match and a three-year shelf life at room temperature make HBOC-201 well-suited to a variety of field indications including civilian and military pre-hospital trauma with haemorrhagic shock. Extensive preclinical evaluation of HBOC-201 as a resuscitative fluid has demonstrated superior efficacy over crystalloid and colloid fluids in treating this indication.[10-12]

Encouraging results from several preclinical studies[11,13-15] warrant further exploration of the potential therapeutic effects of HBOC-201 in specific ischaemia-related pathologies including peripheral limb ischaemia, myocardial infarction (Figure 2) and stroke.

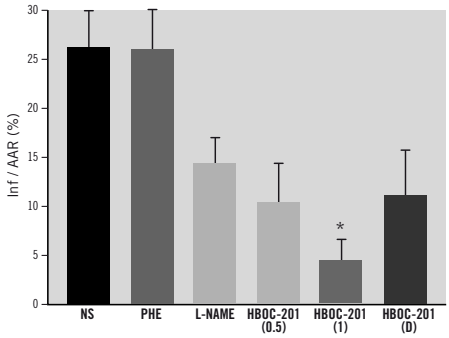


*Figure 2. Total infarct size after HBOC-201 infusion in a canine myocardial infarct model. Ischaemia was induced by occluding the LAD coronary artery to achieve an 85-90% flow reduction. After 15 min of ischaemia, each animal was randomised to the following intravenous therapies: HBOC-201 (0.5 g/kg, n=6), HBOC-201 (1 g/kg, n=6), normal saline (NS) (7 ml/kg, n=6), phenylephrine (PHE) to achieve an increase in MAP similar to that induced by HBOC-201 (n=6), L-NAME (0.1 ml/kg/min for 2 min, then at 0.3 ml/kg/min thereafter, n=6) or HBOC-201 (1 g/kg, n=5), delayed (D) until 60 min after the onset of ischaemia. The LV was paced at a rate 10% higher than the spontaneous heart rate beginning 15 min after induction of ischaemia. Ischaemia was maintained for a total of 195 min, at which point pacing was stopped, followed by reperfusion for 180 min. Staining for myocardial area at risk (AAR) and infarct area (Inf) was performed at the conclusion of reperfusion. Total infarct sizes expressed as Inf/AAR were significantly reduced after HBOC-201 (1 g/kg) compared with NS and PHE (*P < 0.05). From reference 15, modified with permission.*

Although known to induce small to modest increases in blood pressure, HBOC-201 vasoconstriction activity appears to be limited primarily to skeletal muscle vascular beds and the pulmonary circulation and does not involve the coronary, cerebral or splanchnic vasculature.[16] Consistent with these preclinical data, HBOC-201 had no effect on coronary blood flow or coronary artery tone in COR-0001 trial subjects.[5] The COR-0001 and COR-0002 clinical trials suggest that intravenous and intracoronary HBOC-201 is well-tolerated in patients with coronary artery disease. These results support the rationale for evaluating the efficacy of HBOC-201 against infarct development in ACS patients with ST segment elevation myocardial infarction (STEMI). HBOC-201 could be administered intravenously to a patient sustaining a myocardial infarction and/or via intracoronary infusion in the oxygenated state as an adjunct therapy to PCI, particularly when lesion access is difficult or when microvascular pathology contributes to low thrombolysis-in-myocardial-infarction (TIMI) coronary blood flow following successful treatment of a proximal coronary obstruction. The small particle size and low viscosity of HBOC-201 may bestow advantages to treatment of the low- or no-reflow patient over reperfusion with blood alone. An estimated 80,000 cases of post-revascularisation low (< 3) TIMI flow are realised annually in Europe.[17]

The efficacy of oxygenated HBOC-201 in preventing downstream ischaemia during coronary intervention and favourable optical transmission properties[18] are consistent with using HBOC-201 as an adjunct therapy with intravascular imaging modalities (Raman spectroscopy, laser speckle imaging, infrared microscopy) that require temporary displacement of blood from the target field. Intermittent or continuous arterial perfusion with oxygenated HBOC-201 may also effectively maintain the viability of organs undergoing surgical repair distal to an arterial cross-clamp or in maintaining donor organ viability during transport to a recipient. Relevant to these indications, enrolment is nearly complete in a 60-subject clinical trial designed to determine the safety and efficacy of HBOC-201 when infused prior to initiating cardiopulmonary bypass for patients undergoing coronary artery bypass surgery.

Cardiogenic shock is an indication for which HBOC-201 may be especially well suited. Cardiogenic shock develops in response to acute myocardial infarction, leading to low cardiac index, low blood pressure and vital organ underperfusion. Cardiogenic shock is further characterised by a proinflammatory response involving upregulation of iNOS and inappropriately high levels of nitric oxide (NO). Excessive NO expression exacerbates both weak cardiac function and low blood pressure. As a putative NO scavenger, HBOC-201 would oppose the NO contribution to cardiogenic shock and restore blood pressure while facilitating oxygen delivery to ischaemic myocardium and other organs.[19]

## Recommendations for management of patients receiving HBOC-201 (tips for use)

Although rare, increases in systolic blood pressure above 180 mmHg should be treated with standard antihypertensive drugs; successful treatment with nitroglycerin, nitroprusside and calcium channel blockers has been demonstrated. Because of plasma volume expansion, haematocrit is expected to decrease. Given the colloid properties of HBOC-201, attention to fluid management is necessary to avoid volume-related adverse events.

The data do not support the need for special monitoring of metHb in most patients treated with HBOC-201 unless also receiving one or more agents (e.g. benzocaine, lodocaine, prilocaine, dapsone, amyl nitrite, isobutyl nitrite, nitroglycerin, and primaquine) known to induce formation of methaemoglobinaemia. However, patients who receive higher doses of HBOC-201 and/or are intravascularly depleted prior to HBOC-201 infusion (e.g., trauma patients with massive bleeding) may have larger increases in metHb or may tolerate low metHb levels less well, and should have metHb levels monitored closely.

## Summary

Clinical and preclinical studies have revealed a diverse array of indications in which the effectiveness of HBOC-201 has been demonstrated or appears likely. Included among these are indications involving cardiac and peripheral ischaemia in which this oxygen therapeutic may prove to be an important tool in the armamentarium of the cardiologist and surgeon. Preclinical studies and clinical trials are under way to further delineate and optimise the role of HBOC-201 as an oxygen therapeutic in cardiovascular medicine.

## Acknowledgements

Source of funding: Certain preclinical studies and clinical trials reviewed in this document were supported in part or in full by grants from Biopure Corporation.

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# CHAPTER 3.2

## Hemodynamic Effects, Safety, and Tolerability of Hemoglobin-Based Oxygen Carrier-201 in Patients Undergoing PCI for CAD

Serruys PW, Vranckx P, Slagboom T, Regar E, Meliga1 E ,
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Symons J, for the COR-0001 trial investigators.

*EuroIntervention*.2008, **3**: 600-9. [**original research paper**]

EuroIntervention

# Haemodynamic effects, safety, and tolerability of haemoglobin-based oxygen carrier-201 in patients undergoing PCI for CAD

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*Financial Disclosure: The investigators have no conflict of interest related to the sponsor of this study or the study medication.*
*Funding/Support: This work was supported by a grant from The Biopure Corporation, Cambridge, MA, USA*

*This paper also includes accompanying moving images published at the following website: www.eurointervention.org*

**KEYWORDS**
*Coronary intervention, acute coronary syndromes, haemoglobin-based oxygen carrier*

## Abstract

**Aims:** Haemoglobin based oxygen carriers (HBOCs) are considered in the treatment of patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI). In light of their potential vasopressor and colloidal properties, their effect on coronary physiology, safety and tolerability needs to be established.

**Methods and results:** In this phase II pilot trial, 45 patients were randomly assigned, (1:1:1) to double blind treatment with a 30 minute intravenous (IV) infusion of either 15 or 30 g of HBOC-201, compared to an equivalent volume of non-oxygen carrier colloid control. Systemic, pulmonary, and coronary haemodynamics were studied during this infusion period. IV HBOC-201 administration produced an increase in systolic blood pressure (SBP), pulmonary capillary wedge pressure and calculated systemic vascular resistance (SVR) and a concomitant decrease in cardiac output (CO); there was a decrease in mixed venous saturation (SVO2) following IV HBOC-201. The left ventricular stroke work index (LVSWI) was not altered by HBOC-201 treatment. Of note, no coronary vasoconstriction was observed, nor were there significant changes in resting average peak velocity (APV), coronary-artery diameter, volumetric coronary blood flow, or coronary vascular resistance. The percentage of patients with adverse events did not differ between the HBOC-201 treated and control groups (76% vs. 63%, respectively, P=0.49). Seven serious adverse events (SAE) occurred in six patients in the treatment group and two in two patients in the control group. Only one SAE (hypertension) was judged HBOC-201 related. Patients in both the HBOC-201 and control group had a similar incidence of increased liver alanine transaminase (31% vs 31%, respectively, NS); 10% of the patients in the HBOC-201 group had increases greater than three times the upper limit of normal. Differential increases were noticed in some inflammatory markers (IL-6, CRP) 18-24 hours after infusion between the HBOC-201 arms and the control group.

**Conclusion:** No compromise in the coronary blood flow or LVSWI was observed despite HBOC-201's known vasoactive effects. One SAE was adjudicated as "drug related" and fully resolved. The clinical relevance of the differential rise in certain biochemical markers and the adverse effects of plasma haemoglobin in the context of ACS needs further investigation.

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## Introduction

Prompt reperfusion of ischaemic myocardium is the major focus of acute treatment of patients with ST-segment elevation myocardial infarction (STEMI). With (primary) PCI emerging as the new gold standard of ACS reperfusion therapy, new questions are arising about the best pharmaco-invasive strategy to limit the amount of myocardial damage occurring during the ischaemia and early reperfusion periods. Because of their ability to deliver oxygen, HBOCs have been considered for use in the treatment of ACS.

HBOC-201 is a cell-free polymerised bovine-haemoglobin solution in a balanced salt solution. HBOC-201 may act as a direct tissue oxygen donor and an "oxygen bridge" between RBCs and tissues[1,2], facilitating oxygen transport from erythrocytes through plasma to the endothelium and organs and eventually to post-stenotic areas where plasma oxygen transport can improve tissue oxygenation.[3] HBOC-201 can be stored at room temperature for a period of up to three years. In a dog myocardial ischaemia-reperfusion model, infusion of HBOC-201 prior to coronary artery occlusion reduced myocardial infarct size.[4,5] The current study is the first attempt at introducing HBOC-201 in the treatment of ACS and addresses safety issues in the controlled setting of elective PCI.

## Methods

### Study design

The COR-0001 trial was a randomised 3-arm (1:1:1), double-blind, placebo-controlled, dose-finding pilot (phase II) study designed to investigate the safety and tolerability of IV HBOC-201 versus an equivalent amount of artificial colloid in patients with stable angina and non-ST-segment elevation (NSTE) ACS scheduled for elective PCI.

The study had one control arm and two active treatment arms with HBOC-201 delivered at different doses. In one arm 230 ml HBOC-201, equivalent to 30 g bovine Hemoglobin (Hb) was infused over 30 minutes. In the second arm 115 ml of HBOC-201 was infused over 15 minutes, at the same infusion speed of the first arm; thus delivering 15 g of Hb, sequentially followed by a 115 ml infusion of Voluven-Fresenius (a colloidal volume expander chosen for its molecular weight, similar to that of the study drug). The control arm consisted of 230 ml Voluven-Fresenius infused over 30 minutes. Randomisation was stratified by clinical site, using permuted blocks of six patients.[6] Patients were allocated to a treatment by a central allocation telephone service. Patients, investigators and the members of the Data Safety Monitoring Board (DSMB) were blinded to the treatment allocation during the study period. For blinding purposes in the catheterisation laboratory a double dummy technique was used (see online-only Data Supplement for details). The study was performed under Medical Ethics Committee approval and in accordance with the Declaration of Helsinki.

### Patient population

The patients were enrolled in five centres in The Netherlands, Germany and Belgium selected for their expertise in cardiac physiology studies (Appendix 1, online-only Data Supplement).

Patients were eligible for the study if they had either unstable angina or NSTE ACS and had a severe stenosis in at least one coronary artery eligible for PCI. All patients had to provide written informed consent. Major exclusion criteria were: significant haemodynamic compromise requiring inotropic or vasopressor support, significantly altered left ventricular function (ejection fraction <35%), severe hypertension (>180/110 mmHg) not adequately controlled by antihypertensive therapy at time of study entry, renal impairment (serum creatinine >1.6 mg/dl) or contra-indications to the use of adenosine and/or standard drugs for coronary intervention and coronary artery disease. The patient weight at inclusion was limited to a maximum of 110 kg.

### Study procedures

The catheterisation laboratory procedure was divided into three consecutive phases: the baseline, the study drug infusion period (230 ml solution/30 minutes) and the index PCI procedure. Haemodynamic monitoring and control angiography were performed at baseline and at three consecutive time points (10', 20', 30') during the study drug infusion period. PCI, including adjunctive therapies, were performed according to standard institutional practices. No standard medications used in the management of patients with ischaemic heart disease were withheld by the study protocol, stopping rules on study drug infusion were predefined (online-only Data Supplement).

### Safety endpoints and assessments

The primary endpoint of the study was the in-hospital safety assessment including systemic and coronary haemodynamics, thrombotic events, untoward drug interaction effects, allergic reactions, drug-dye interactions, met-haemoglobin formation, serious adverse events, as well as biochemical markers of inflammation, myocardial necrosis, renal and hepatic function. The extent of deviation of blood values beyond the limits of normal was graded by the DSMB/CEC members. Calculated measurements of eGFR (estimated glomerular filtration rate) by the Cockroft-Gault equation were used for estimating and reporting renal dysfunction.[7] Additional analysis included a 30-day clinical follow-up, death (all-cause mortality), recurrent myocardial infarction, recurrent myocardial ischaemia and serious adverse events.

Patient symptoms and adverse events were evaluated by the study investigators using a graded severity index.[8] An independent Data Safety Monitoring Board/ Clinical Event Committee (DSMB/CEC) reviewed aggregate safety data (including blood values) to identify potential patient safety issues. Safety monitoring and adjudication of clinical events with respect to their clinical relevance was performed by this committee. The data as classified by the DSMB/CEC was used in the final safety analysis unless otherwise specified.

A doppler steerable guidewire (0.36 mm [0.014 in.] in diameter) (Flowire, Volcano Corporation, Rancho Cordova, CA, USA) was positioned in a reference coronary artery without any significant stenosis and was coupled to a real-time spectrum analyser and video cassette recorder. Coronary flow velocity and coronary flow reserve measurements were performed at baseline and after the study drug infusion period in the first 30 consecutive study patients.

To assess coronary flow reserve (the ratio of peak hyperaemic velocity to average peak velocity at base line), maximal hyperaemia was induced with peripheral IV infusion of adenosine (140 μg/kg/min).[9] Each measurement was duplicated to check for consistency. Coronary blood flow was calculated as follows: (the average peak velocity ÷ 2) x the cross-sectional area of the coronary artery, calculated as $\pi x$ (diameter of the artery ÷ 2)$^2$, which assumed a time-averaged parabolic velocity profile and a cylindrical coronary artery.[10] Coronary vascular resistance (in mmHg/ml/min) was calculated for the reference vessels as the mean arterial pressure divided by the coronary blood flow. The coronary vascular resistance index was calculated as the average peak velocity (APV) hyperaemic divided by the mean arterial pressure at rest.

Quantitative coronary angiographic assessments of the vessel segment comprising the flow wire as well as the coronary diameter at the tip of the Doppler wire, (between two side branches), were performed by an independent core laboratory (Cardialysis, Rotterdam, The Netherlands) with the use of edge-detection techniques.[11]

Systemic haemodynamic measurements included arterial blood pressure, recorded from a 7 Fr guiding catheter in the ascending aorta; pulmonary-artery and capillary wedge pressure (measured from the distal port of a 7 Fr Swan-Ganz catheter) and right atrial pressure (measured from the proximal port of the Swan-Ganz catheter). The heart rate and cardiac output, determined by thermodilution, were also recorded. Standard haemodynamic formulas were used to calculate systemic and pulmonary vascular resistance and their indexes.

### Statistical analysis

Continuous baseline characteristics were analysed with one way analysis of variance and categorical variables with the Fisher's Exact test. For individual variables, values during and after administration of the study drug were compared with base-line values by a mixed model analysis of variance on change from pre-infusion with the factors of time, treatment and time by treatment interaction. The different groups were compared by an analysis of covariance with treatment as a factor and the pre-infusion value as a covariate. Multiple comparisons between the treatment groups were performed with the Bonferroni correction. Differences were considered significant when P values were less than 0.05. All statistical analyses were performed with SAS version 8.

Cardialysis (Rotterdam, The Netherlands) was the core laboratory for angiographic and ECG analysis and the data management and coordinating centre. All listed authors (see appendix 1, online-only Data Supplement) participated in the study design, enrolment of patients, and/or data interpretation.

## Results

### Study population

A total of 47 patients were enrolled between December 2003 and March 2005. During this period, in November 2004, the Steering Committee temporarily suspended patient enrolment on the recommendation of the DSMB to permit a detailed analysis of a SAE described below. This SAE was adjudicated by the committee and individual review to be procedure and not drug related. The study was allowed to resume in January 2005. At this occasion the DSMB raised it's concern about the critical elevations in SBP following IV HBOC-201 encountered in some patients and a protocol amendment instructing SBP management was issued. Of the 47 patients randomised, one patient withdrew consent before any study drug infusion and one patient did not receive any study medication; both patients were excluded from analysis. The remaining 45 patients concluded the planned 30-day follow-up. Analysis was by intention to treat, including one patient in whom the 30 g dose was inadvertently infused instead of the 15 g dose.

As shown in Table 1, treatment groups were equally matched with respect to age, weight, anginal status and the overall cardiovascular risk profile at screening. There were five diabetic patients in the HBOC-201 group and none in the control group.

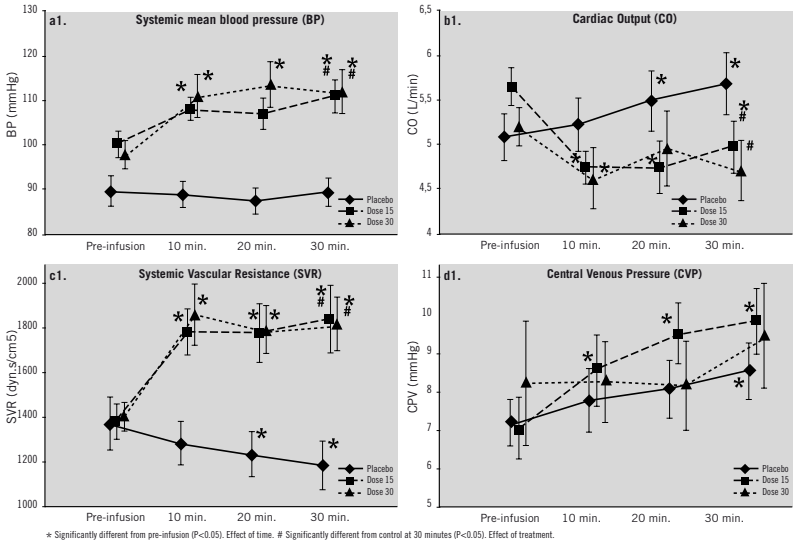
**Table 1. Baseline characteristics of the study population.**

| | Control (n=16) | 15 g HBOC-201 (n=17) | 30 g HBOC-201 (n=12) |
|---|---|---|---|
| Age, years | 60.6 ±7.5 | 56.8 ±10.3 | 62.8±6.5 |
| Male | 11 (69) | 12 (71) | 10 (83) |
| Weight | 80.2±12.4 | 84.1±12.4 | 81.3±13.4 |
| Stable angina | 3 (19) | 4 (24) | 6 (50) |
| Unstable angina | | | |
| Total | 13 (81) | 13 (76) | 6 (50) |
| Class IB | 3 (19) | 3 (18) | 0 |
| Class IIB | 8 (50) | 8 (47) | 6 (50) |
| Class IIIB | 2 (13) | 2 (12) | 0 |
| Previous non-Q-wave MI | 3 (19) | 0 | 2 (17) |
| Previous PCI | 3 (19) | 1 (6) | 2 (17) |
| Diabetes Melitus | 0 | 3 (18) | 2 (17) |
| Hypercholesterolaemia | 6 (38) | 4 (24) | 9 (75) |
| Cigarette smoker | 4 (25) | 4 (24) | 0 |
| Hypertension | 10 (63) | 9 (53) | 8 (67) |
| Diastolic blood pressure (mmHg) | 75.3±13.4 | 77.6±11.2 | 72.3±12.2 |
| Systolic blood pressure (mmHg) | 131.0±20.5 | 141.7 ±18.4 | 139±18.0 |

Data is represented as numbers with percentages or as mean values with standard deviations.

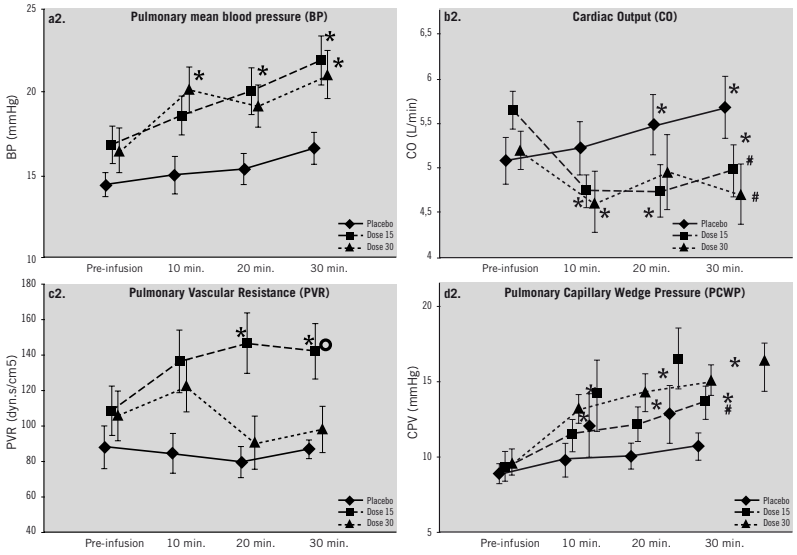
### Systemic hemodynamic effects

The most important haemodynamic effects of an IV infusion of HBOC-201 are summarised in Table 2. In both active treatment groups, there were significant increases in systemic arterial blood pressure (systolic, diastolic, or mean pressure) in conjunction with a significant reduction in cardiac index at 30 minutes after HBOC-201 infusion. The calculated systemic vascular resistance (SVR) (and pulmonary vascular resistance, PVR) was significantly increased in these patients. A dose relationship could not be established for these phenomena (Figure 1a-b-c-d). Critical elevations in SBP following IV HBOC-201 administration, for the purpose of this study defined as a SBP >180 mmHg, was seen in




⋆ Significantly different from pre-infusion (P<0.05). Effect of time. # Significantly different from control at 30 minutes (P<0.05). Effect of treatment.

*Figure 1.1 Relative change with respect to baseline values in systemic mean blood pressure (a), cardiac output (b), systemic vascular resistance (c) and central venous (right atrial) pressure (d). Effect of control or IV HBOC 15 g and 30 g on MBP (a1), SVR (b1), CO (c1) and CVD (d1).*




⋆ Significantly different from pre-infusion (P<0.05). Effect of time. # Significantly different from control at 30 minutes (P<0.05). Effect of treatment.
o Dose15 significantly different from Dose30 at 30 minutes (P<0.05). Effect of treatment.

*Figure 1.2 Relative change with respect to baseline values in pulmonary mean blood pressure (a), cardiac output (b), systemic vascular resistance (c) and pulmonary cardiac wedge pressure (d). Effect of control or IV HBOC 15 g and 30 g on PAP mean (1.2a), PVR (1.2b), CO (1.2c) and PCWP (1.2d). Measurements were made at baseline (pre-infusion) and at three different time-points during a 30 minute infusion period: 10', 20' and 30'=end of infusion. Values are shown as means ±SD for all patients.*

9/29 (31%) of the patients. Critical blood pressure elevations were reduced following the protocol amendment that instructed the use of appropriate antihypertensive treatment (IV nitroglycerin) when necessary; 7/20 (35%) patients before the amendment versus 2/9 (22%) patients post amendment. One patient was unresponsive to IV nitroglycerin and required nifedipine in order to control blood pressure. However, despite the reduction in absolute number of patients experiencing a clinically significant hypertensive episode, there was no difference between the amounts of nitroglycerin (NTG) used before and after the DSMB amendment instructing the use of NO donors to correct systolic blood pressure (a detailed description is provided in the online-only data supplement). At two hours post infusion (data not shown), any statistical difference in MAP remained between the active treatment groups and the control group. A significant decrease in heart rate was seen only in the HBOC-201 15 g group.

In all three groups the pulmonary capillary wedge pressure (PCWP) increased following infusion at 30 minutes; the increment was significantly greater in both HBOC-201 groups compared to control, (Table 2, Figure 1.2-d), never reaching the predefined critical level of 20 mmHg. There were no significant changes in calculated left ventricular stroke work index.

A significant decrease in mixed venous saturation (SVO2) was noticed following IV HBOC-201 (baseline: 77.4%±7.7%, 30 minutes: 70.7%±8.3%, p=0.002); in seven patients below the level of 65 %. However, the index of systemic oxygen consumption (VO2), assuming an arterial oxygen saturation ($SaO_2$) of 97% in all patients, did not change from baseline (calculation, see online-only data supplement).

## Coronary haemodynamic effects

The effects of IV HBOC-201 on the diameter of coronary arteries (reference vessel) and on flow velocity before and after IV adenosine administration are shown in Table 3. Intravenous administration of HBOC-201 caused no significant changes in the resting APV, coronary-artery diameter or coronary vascular resistance. The coronary blood flow velocity reserve tended to increase and this

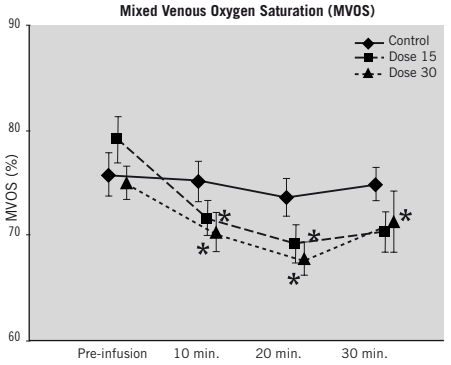



*Figure 2. Relative change SVO2 with respect to baseline values. Measurements were made at baseline (pre-infusion) and at three different time-points during a 30 minute infusion period: 10', 20' and 30'=end of infusion. Values are shown as means±standard error.*

**Table 2. Systemic and pulmonary haemodynamic variables at baseline and at the end of the study drug infusion period.**

| | 15 g HBOC-201 (n=17) | | | 30 g HBOC-201 (n=11) | | | Control (n=16) | | |
|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **Baseline** | **Post Infusion** | **P value (+)** | **Baseline** | **Post Infusion** | **P value (+)** | **Baseline** | **Post Infusion** | **P value (+)** |
| Systolic Blood Pressure (mmHg) | 145±24 | 153±30* | 0.34 | 140±15 | 158±26* | 0.006 | 126±25 | 123±20 | 0.49 |
| Mean Arterial Pressure (mmHg) | 100±12 | 111±15* | 0.02 | 97±11 | 112±16* | <0.001 | 90±13 | 90±13 | 0.95 |
| Pulmonary Arterial Pressure (mmHg) | | | | | | | | | |
| Systole | 24±7 | 29±7 | 0.002 | 23±7 | 30±8 | 0.003 | 21±5 | 24±5 | 0.13 |
| Diastole | 12±5 | 16±7 | 0.006 | 12±5 | 15±4 | <0.001 | 11±3 | 12±4 | 0.30 |
| Mean | 17±5 | 22±6 | 0.001 | 17±5 | 21±5 | <0.001 | 14±3 | 17±4 | 0.06 |
| Pulmonary-capillary wedge pressure (mmHg) | 9±4 | 14±4* | <0.001 | 10±3 | 15±3 | <0.001 | 9±3 | 11±3 | 0.09 |
| Heart rate (beats/min) | 69±8** | 60±8 | 0.001 | 57±9 | 57±12 | 0.46 | 60±8 | 59±7 | 0.36 |
| Cardiac index (litres/min/$m^2$) | 2.87±0.49 | 2.51±0.56* | 0.008 | 2.66±0.36 | 2.45±0.55* | 0.16 | 2.64±0.44 | 2.94±0.59 | 0.002 |
| Systemic-vascular resistance index (dyn.sec.cm-5) | 1339±270 | 1820±527* | <0.001 | 1409±236 | 1799±370* | <0.001 | 1289±369 | 1177±395 | 0.02 |
| Left Ventricular Stroke Work Index (g.m/$m^2$) | 51±11 | 54±11 | 0.52 | 55±5 | 59±20 | 0.29 | 49±11 | 57±13 | 0.07 |

Data is represented as numbers and percentages or mean values with standard deviations

n: Number of patients per indicated group

(+): P values calculated with the mixed linear analysis of variance model

*: Different from control (P<0.05). Calculated with analysis of covariance with baseline value as covariate

**: Different from control and HBOC-201 30 g (P<0.05). Calculated with one-way analysis of variance

Average for baseline/post infusion is derived from matched data

In the high dose treatment group, data were available for 11 out of 12 patients

**Table 3. Coronary haemodynamics at baseline and at the end of the study drug infusion period.**

| Variable | HBOC-201 (n=20) Baseline | Post infusion | P value (+) | Control (n=11) Baseline | Post infusion | P value (+) |
|---|---|---|---|---|---|---|
| Diastolic Systolic Velocity Ratio – at rest | 1.78±1.03 | 1.50±0.65* | 0.03 | 1.62±0.40 | 1.91±0.87 | 0.19 |
| Average Peak Velocity – hyperemic (cm/sec) | 45±18 | 57±25* | 0.01 | 36±16 | 34±14 | 0.59 |
| Average Peak Velocity – at rest (cm/sec) | 18±8 | 22±12 | 0.09 | 19±8 | 18±4 | 0.60 |
| Coronary Flow Reserve | 2.64±0.93 | 2.70±0.72 | 0.74 | 2.10±0.98 | 1.97±0.81 | 0.67 |
| | HBOC-201 (n=15) | | | Control (n=10) | | |
| Mean Arterial Pressure – at rest (mmHg) | 97±10 | 116±14 | <0.001 | 102±14 | 99±11 | 0.37 |
| Coronary Blood Flow – at rest (mL/min) | 28±13 | 33±20 | 0.26 | 28±13 | 25±15 | 0.72 |
| Coronary Artery Diameter by QCA (mm) | 2.72±0.68 | 2.63±0.77 | 0.35 | 2.53±0.50 | 2.35±0.49 | 0.43 |
| Coronary Vascular Resistance – at rest (mmHg/ml/min) | 4.32±2.28 | 4.78±2.82 | 0.68 | 4.52±2.30 | 5.00±2.60 | 0.64 |
| | HBOC-201 (n=19) | | | Control (n=10) | | |
| Coronary Vascular Resistance index | 0.47±0.16 | 0.49±0.21 | 0.36 | 0.35±0.14 | 0.35±0.14 | 0.99 |

Data is represented as mean values with standard deviations followed by number of observations. *: Different from control at (P<0.05). Calculated with analysis of covariance with baseline value as covariate. (+) P value calculated with mixed linear analysis of variance model. Mean±SD followed by number of observations. Coronary Vascular Resistance: – At baseline 6 missing values (4 missing reference diameter, 2 missing Mean Arterial Pressure/Average Peak Velocity); – At post infusion 7 missing values (5 missing reference diameter, 2 missing Mean Arterial Pressure/Average Peak Velocity); For mean arterial pressure, coronary blood flow and coronary artery diameter, only patients with an existing value for coronary vascular resistance are included.

increase may be related to a significant augmentation in driving pressure. A detailed QCA analysis of the reference vessel did not show any angiographic coronary vasoconstriction brought about by the study drug (Table 1, online-only Data Supplement). Coronary flow studies were terminated early (n=31) after a futility analysis by the DSMB considering the presented data and the potential patient burden of this invasive procedure.

## Safety and tolerability

This study was aimed at providing as much safety information as possible about the IV administration of HBOC-201 in acute cardiology and PCI. The mean [±SD] amount of study drug solution infused in this study was: 238.1 (±34.2) ml for the 15 g HBOC-201group, 230.3 (±3.0) ml for the 30 g HBOC-201 group and 247.9 (±67.2) ml for the Voluven only group. One patient accidentally received two units of Voluven. In none of the patients did the study drug infusion have to be stopped for pre-defined safety reasons.

Patients were followed up for 30 days post PCI. During this period, no additional SAE occurred. The number of patients who experienced at least one adverse event was higher in the active treatment groups (75.9% pooled), as compared to the control group (62.5%) (Table 4), the difference is not significant statistically (p-value=0.49). In total, eighteen adverse events were considered to be study drug related,

**Table 4. Reported adverse events (serious and non-serious).**

| | | Control (n=16) Ne,Np (%) | 15 g HBOC-201 (n=17) Ne,Np (%) | 30 g HBOC-201 (n=12) Ne,Np (%) | Pooled HBOC-201 (n=29) Ne,Np (%) |
|---|---|---|---|---|---|
| Adverse events | Total | 15,10 (63) | 19,11 (65) | 23,11 (92) | 42,22 (76) |
| | Product-related | 0 | 6,6 (35)* | 12,8 (67)* | 18,14 (48)* |
| | Procedure-related | 5,5 (31) | 2,2 (12) | 6,5 (42) | 8,7 (24) |
| Serious adverse events | Total | 2,2 (13) | 3,2 (12) | 4,4 (33) | 7,6 (21) |
| | Product-related | 0 | 1,1 (6) | 0 | 1,1 (3) |
| | Procedure-related | 0 | 1,1 (6)¶ | 1,1 (8) | 2,2 (7) |
| Serious adverse events as coded by ICD-9 code | Abdominal pain | 0 | 1,1 (6) | 0 | 1,1 (3) |
| | Cardiac arrest | 0 | 1,1 (6)¶ | 0 | 1,1 (3)¶ |
| | Chest pain | 1,1 (6) | 0 | 0 | 0 |
| | CVA | 0 | 1,1 (6)¶ | 0 | 1,1 (3)¶ |
| | GI haemorrhage (low) | 0 | 1,1 (6)¶ | 0 | 1,1 (3)¶ |
| | Haematemesis | 0 | 0 | 1,1 (8) | 1,1 (3) |
| | Hypertension[GDube1] | 0 | 1,1 (6) | 0 | 1,1 (3) |
| | Non-ST-segment elevation acute coronary syndrome | 1,1 (6) | 0 | 3,3 (25) | 3,3 (10) |
| | Malaise & fatigue | 0 | 0 | 1,1 (8) | 1,1 (3) |
| | Nausea & vomiting | 0 | 0 | 1,1 (8) | 1,1 (3) |

n: number of patients; Ne=number of events; Np=number of patients that experienced an event; %: percentage of patients that experienced the event; CVA: Cerebro Vascular Accident; GI: Gastro Intestinal; ¶: the same patient; *: different from control (P<0.05). Calculated with Fisher's Exact Test. Hypertension: table only includes hypertensive episodes reported by the investigators (table 4 bis: incidence of critical elevations of blood pressure adjudicated by CEC, online version only)

one of which (a hypertensive episode) was serious. The difference in the number of events between the IV HBOC-201 treatment groups and the Voluven groups was mainly driven by the rise in liver (n=6) and/or pancreas enzymes (n=1) and the number of hypertensive episodes (n=10) (SBP>180 mmHg). In addition, one HBOC-201-treated patient experienced abdominal pain.

One patient suffered a periprocedural electromechanical dissociation (EMD), which followed a prolonged wedging of the guiding catheter during the PCI procedure. The patient required a prolonged resuscitation in the catheterisation laboratory. The clinical evolution was complicated by a watershed cerebral infarction and lower gastrointestinal bleeding. The patient experienced a full recovery. This incident was subject to detailed investigation by the DSMB supported by an independent neurologist while patient enrolment in the study was temporarily suspended. The EMD, reported as an SAE, was adjudicated to the procedure and not to the study drug; the neurological event reported as an SAE was putatively attributed to the period of hypotension experienced during the prolonged cardiac resuscitation of this patient. The cardiac arrest and "watershed infarction" were counted as one event.

No clinically significant changes were noted in haematological or chemical values following IV HBOC-201, except for the cardiac markers and liver transaminases. A significant rise in CK-MB levels >3 times ULN was documented in one patient, but this enzyme abnormality was not likely due to HBOC-201 treatment as the patient suffered procedure related serious complications and had a prolonged resuscitation period.

Through hospital stay, patients in both the HBOC-201 and control group had a similar incidence of increased liver alanine transaminase (31% vs 31%, respectively, NS); 10% of the patients in the active HBOC-201 group had elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) or lactate hydrogenase (LDH) enzymes (>3 times ULN) compared with none in the control group (Table 5). No patients had an abnormal total bilirubin (>3.0 mg/dl and ≥ 100% increase) or Alkaline Phosphatase (>250 IU/L and ≥ 100% increase) value, and no jaundice or hyper bilirubinaemia was reported. Two patients in the treatment group showed an increase in pancreatic enzymes (serum amylase >1.5 ULN). No effect of the drug was observed on the renal function (Table 5). Overall, there was a slight increase in plasma methaemoglobin level following IV HBOC-201 (average value pre-HBOC: 0.50% / 6-8 hours post-HBOC: 0.75%, P= 0.007 and post 18-24 hours 0.90%, P<0.001) with two patients above the cut-off level of 1.0% (data not shown).

The IV HBOC administration was associated with a statistically significant differential increase in inflammatory markers (IL-6, and CRP), measured at 18-24 hours after HBOC infusion, between the treatment arms and the control group, without any clear dose response relationship (Figure 3).

## Discussion

We report on the first study in which HBOC-201 has been administered to patients with acute coronary syndromes undergoing PCI.

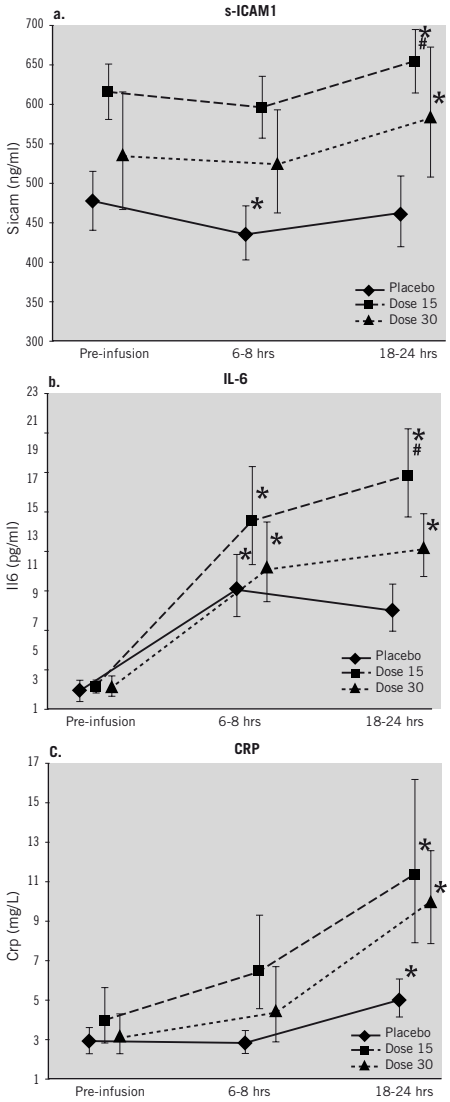



*Figure 3. Effect of control or IV HBOC 15 g and 30 g on s-ICAM1 (a), IL-6 (b) and CRP (c). A dose relationship could not be established for any of these markers in the active IV HBOC-201 arms. Statistical analysis is performed on log-scale. For presentation, the geometric mean±the standard-error is given on the original scale.*
** Significantly different from pre-infusion (P<0.05). Effect of time.*
*# Significantly different from control at 18-24 hours (P<0.05). Effect of treatment.*

**Table 5. Laboratory testing on organ function (liver/kidney)**

| | Control (n=16) N (%) | 15 g HBOC-201 (n=17) N (%) | 30 g HBOC-201 (n=12) N (%) |
|---|---|---|---|
| Peak AST > 3x ULN* | 0 | 2 (13) | 1 (8) |
| Peak ALT (SGPT) 1-3x ULN*# | 5 (33) | 4 (25) | 2 (17) |
| Peak ALT (SGPT) > 3x ULN* | 0 | 2 (13) | 1 (8) |
| Peak ALP >2x ULN* | 0 | 0 | 0 |
| Increase in serum Creatinine (Cr) >0.5mg/dl | 0 | 0 | 1 (8) |
| Decrease in eGFR>25% from baseline | 1 (7) | 0 | 3 (25) |
| ↑Cr >0.5mg/dl or ↓eGFR>25% | 1 (7) | 0 | 3 (25) |

*ULN: upper limit of normal; AST: aspartate aminotransferase; ALT: alanine transaminase; ALP: alkaline phosphatase; eGFR: estimated glomerular filtration rate.
Cut-off levels for total bilirubin, serum alanine aminotransferase and alkaline phosphatase levels were chosen according to the definition of drug-related hepatotoxicity.[25] The mean change in ALT expressed as a ratio (24 hrs follow up/Baseline) was 0.71 (control, P=0.02) vs 1.01 (HBOC-201, P=0.91), the mean change in ALP expressed as a ratio (24 hrs follow up/Baseline) was 1.07 (control, P=0.02) vs 1.11 (HBOC-201, P=0.09).
# All 11 patients in this group had elevated ALT values at the baseline

Several haemoglobin-based oxygen carriers are currently being studied in clinical trials for various indications. Most are derived from human or bovine blood and have been chemically modified, resulting in molecules that differ in size, molecular weight, oxygen affinity, viscosity, and oncotic activity. Every formulation should be considered a unique drug with its own physical characteristics, pattern of biological activity, and profile of adverse reactions.

HBOC-201 is a cell free, endotoxin free, glutaraldehyde cross-linked bovine polyhaemoglobin in solution with an average molecular weight of 250 kDa (molecular weight ranging 130-500 kDa) and a viscosity less than plasma (1.3 centipoise at 37°C). Only trace amounts (2%) of unmodified haemoglobin and stabilised tetramer (molecular weight 65 kDa) are detected. HBOC-201 has an oxygen dissociation curve that is right-shifted with a $P_{50}$ of 40 mmHg, compared to 27 mmHg for native human haemoglobin. These features provide excellent oxygen-transport properties.

The pathobiological effects of cell-free plasma haemoglobin are a concern.[12] Vascular homoeostasis is dependent on the compartmentalisation or physical separation of haemoglobin from the endothelium.[13] However, unlike single haemoglobin molecules, polymerised-HBOCs like HBOC-201, that are mostly in the form of large soluble haemoglobin complexes (98% is ≥ 130 kDa), are not expected to readily cross the intercellular endothelial junctions of blood vessels to exacerbate vasoconstrictive effects.

HBOC-201 is a colloid solution, and avoidance of circulatory overload is another important consideration. In our study population, a volume of up to 250 ml HBOC-201, equivalent to 30 g haemoglobin glutamer-250 bovine, was infused over a 30 minute time period. In none of the patients did the study drug infusion have to be discontinued for pre-defined safety reasons, such as an excessive increase in pulmonary wedge pressure.

IV HBOC-201 in this study population resulted in an increase in systolic blood pressure, a decrease in CO, and an increase in calculated SVR suggesting a vasoconstrictive effect. A critical elevation in SBP could be reversed by the intravenous administration of a nitric oxide donor, nitroglycerin, consistent with a putative role of nitric oxide scavenging in vasoregulation.[14-17]

The increase in SVR (afterload) in patients receiving HBOC-201 most likely contributed to the differential increase in PCWP between the control and treatment groups. The increase in preload observed after HBOC-201 must be interpreted as a normal physiological compensatory reaction to an increase in afterload (only observed in the HBOC-201 group) and to an increase in plasma volume expansion (induced in both groups). This increase in filling pressure does not reflect an intrinsic myocardial depressing effect of the compound nor a detrimental effect on the myocardial systolic function, since the Left Ventricular Stroke Work Index (LVSWI) remained unchanged regardless of the treatment received.

A decrease in mixed venous saturation was observed in both treatment arms and in some patients saturation went below 65% (Mean $SVO_2$ at baseline 77.4, at 30 minutes 70.7, p=0.002). The most plausible explanation for this phenomenon is a reduction in resting cardiac output associated with study drug infusion; consequently the arterio-venous $O_2$ difference would have to increase by lowering the mixed venous saturation. The metabolic demand of patients lying at rest on the cath lab table was probably unchanged and hence not a factor contributing to the fall in SvO2. There is no indication that IV HBOC-201 affected global oxygen consumption.

Our data clearly show that IV HBOC-201 had no effect on resting and hyperaemic coronary blood flow. This suggests that the autoregulatory mechanism of the coronary circulation was not adversely affected by the infusion of HBOC-201. In addition, there was no angiographic coronary vasoconstriction observed in the major epicardial vessel brought about by this drug.

This safety and feasibility study was designed to detect as many safety signals as possible; the DSMB was prospectively informed about the potential side effects of IV-haemoglobin solutions. The multitude of endpoints specifically scrutinised by either the investigators or the DSMB and CEC may have contributed to the apparently large number of adverse events reported.

Systemic removal of bioavailable nitric oxide has already been shown to contribute to clinical morbidities, including severe oesophageal spasm and dysphagia, abdominal pain and thrombosis.[17-19] The low incidence of these nitric oxide-related

clinical side effects in the present study, as compared to the literature, may be explained either by the lower dose of IV HBOC-201 used, by a concomitant use of nitric oxide donors and/or by the unique properties of the investigational drug.

A transient rise in concentrations of liver transaminases and/or pancreatic enzymes was seen in 10% of the patients following IV-HBOC-201. These patients were typically asymptomatic and without clinical sequelae during the 30 day follow-up. Since the liver is the normal Hb catabolic site, the absorption-distribution-metabolism and excretion (ADME) of HBOC-201 also involves the hepato-pancreatic systems, possibly inducing an upregulation of enzyme activity in response to an increased metabolic load. Elevations of transaminases and lipase have been observed in previous animal studies and clinical trials with HBOC-201. These enzyme elevations are generally not associated with hepatic or pancreatic dysfunction. The potential clinical importance of the increases in liver transaminases should be the subject of further investigation.

No adverse effect of the drug on renal function was observed. Nevertheless, given the recognised nitric oxide scavenging potential of the haemoglobin solutions, caution should be exercised when administering active HBOC-201 to patients with known renal dysfunction or in circumstances where the renal plasma flow is known to be reduced (i.e., NSAID use).

Nitric oxide reacts with oxyhaemoglobin to rapidly form the oxidation product, nitrate (NO3-), and methaemoglobin which is inactive.[20] The comparatively slow reduction of methaemoglobin back to the active form makes the formation of methaemoglobin of potential clinical importance. In this study, the plasma level of methaemoglobin increased slightly following IV HBOC-201, remaining within the physiological range in most of the patients. When the circulating methaemoglobin values in both treatment doses were pooled, a significant difference was found between the pre-infusion value versus the 18-24 hour value (ratio 1.76, p=0.003). This difference is not considered clinically significant.

In our study, the circulatory levels of hs-CRP, IL-6 and s-ICAM in the whole population remained in the broad range of variability observed in patients with ACS undergoing PCI.[21] The differential rise in circulatory levels of inflammatory markers following IV HBOC-201 compared to the control treatment is in accordance with previous observations indicating pro-inflammatory properties of plasma haemoglobin and heme.[22] Heme stimulates the expression of the adhesion molecules ICAM-1 (intracellular adhesion molecule-1), VCAM-1 (vascular cell adhesion molecule-1) and E-selectin on endothelial cells *in vitro*.[23,24] The clinical significance and extent of our observations has to be established in further work.

Study limitations: These results reasonably apply to medium- to low-risk patients suffering CAD and cannot be extrapolated to patients with an evolving or recent transmural myocardial necrosis or haemodynamic instability because such patients were excluded from this study. IV HBOC-201 might provoke more pronounced systemic haemodynamic effects in patients with other cardiovascular conditions or different baseline characteristics. The favourable profile of HBOC-201 in this trial warrants additional animal studies and clinical trials, including in particular, studies in higher risk ACS (STEMI) patient populations. The current trial did not focus on myocardial oxygen consumption or tissue oxygenation during IV HBOC-201. Investigation of HBOC-201 oxygen transport properties and the potential for this therapeutic to preserve myocardial tissue oxygenation in humans is currently under way.

In conclusion, despite its known vasopressor effect, intravenous administration of HBOC-201 does not interfere with the autoregulation of coronary blood flow both at rest and after maximal hyperaemia. The safety profile of HBOC-201 in this study reflects many of the known side effects of haemoglobin based solutions. When clinically contextualised, the SAEs observed in the HBOC-201-treated patients arose from other factors and, with the exception of increased blood pressure, were not considered product related. However, some adverse events (AEs) of cell-free plasma haemoglobin observed in this study remain a concern and need further investigation. This work provides a first step towards exploring a new pharmacological strategy that could broaden the temporal window for PCI, particularly in patients suffering a STEMI. While we recognise that this small population study did not include STEMI patients, investigated only two doses of HBOC-201 and was not aimed at demonstrating efficacy or beneficial effects of this oxygen carrier during ischemia, the results are encouraging enough to pursue additional studies to gather that information.

## Acknowledgements

The authors would like to thank Ms. Samantha Young for her assistance with the preparation of the manuscript.

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# CHAPTER 3.3

## COR-0002: Proof-of-Concept Trial to Evaluate Hemoglobin Based Oxygen Therapeutics in Elective Percutaneous Coronary Revascularization. Rationale, protocol design and hemodynamic results

Meliga E, Vranckx P, Regar E, Kint PP, Duncker DJ, Serruys PW,

*EuroIntervention*. 2008; **4**: 99-107. [**original research paper**]

EuroIntervention

# Proof-of-concept trial to evaluate haemoglobin based oxygen therapeutics in elective percutaneous coronary revascularisation. Rationale, protocol design and haemodynamic results

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*All authors have no conflict of interest to declare.*

**KEYWORDS**
*HBOC-201, percutaneous coronary interventions, oxygen donor*

## Abstract

**Aims:** To test the hypothesis that intracoronary infusion of pre-oxygenated HBOC-201 during brief, total coronary artery occlusion would preserve left ventricular function.

**Methods:** Immediately following a successful PCI, the target coronary artery was occluded without ("dry occlusion") –or with– infusion of pre-oxygenated HBOC-201 distal to the stent via the guidewire shaft of an over-the-wire balloon for up to three minutes at an infusion rate of 48 ml/min. A cross-over design was applied. Early signs of myocardial ischaemia were evaluated by left ventricular pressure-volume loops and intracoronary ECG. A 12-lead Holter ECG was activated before the PCI and deactivated four hours after the study period. Primary endpoints were change in left ventricular relaxation indices and in the sum of ST segment deviations.

**Results:** None of the measured parameters differed significantly from their respective baseline values during HBOC-201 infusion. By contrast, ejection fraction (EF), cardiac output (CO) and minimal rate of LV pressure change ($dP/dT_{MIN}$) decreased significantly and the end diastolic pressure (EDP) and time constant of relaxation increased significantly during dry occlusions ($P < 0.05$). The end diastolic pressure-volume relationship (EDPVR) at the fixed pressure level of 30 mmHg ($V_{30}$), an index of myocardial compliance, reflected greater myocardial stiffness during dry occlusions compared to occlusions with HBOC-201 infusion.

**Conclusions:** Intracoronary infusion of oxygenated HBOC-201 is capable of preserving left ventricular function, likely through maintenance of myocardial oxygenation. It is hypothesised, that in an acute setting, HBOC-201could serve as an oxygen bridge to reperfusion by PCI extending the "golden" time period during which permanent myocardial damage is unlikely.

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## Introduction

HBOC-201 is a cell-free, endotoxin-free, glutaraldehyde-polymerised haemoglobin solution produced by chemical modification of bovine haemoglobin. Initially developed as an alternative to red blood cells for anaemic surgical patients, HBOC-201 has the ability to restore tissue oxygenation in persistently ischaemic tissue. By facilitating oxygen diffusion and convective oxygen delivery, HBOC-201 may act as a direct oxygen donor and increase oxygen transfer between red blood cells and between RBCs and tissues[1,2]. These mechanisms could improve tissue oxygenation[3], especially in post-stenotic areas that free plasma, but not RBCs, is capable of reaching. HBOC-201 can be stored at room temperature for a period of up to three years and does not require cross-matching.

Because HBOCs can deliver oxygen, they have been considered as an adjunct treatment in ACS. Studies conducted in animal models demonstrated that both the prophylactic (before induction of ischaemia) and late (after ischaemia onset) HBOC infusion are well tolerated and effective[4-8].

The safety and tolerability of HBOC up to 230 ml in low to moderate risk cardiac patients scheduled for elective PCI has recently been investigated in the COR-001 trial[9]. This study showed that intravenous HBOC-201 administration did not compromise autoregulation of coronary blood flow, despite the known vasoconstrictive properties of this drug, or myocardial function as assessed by the left ventricular stroke work. A transient increase in the mean arterial blood pressure (MAP) and systemic vascular resistance was observed, consistent with the purported nitric-oxide scavenging activity of the drug.

The present study is a first step towards establishing the efficacy and safety of oxygenated HBOC-201 in preserving myocardial function using PCI techniques to induce brief coronary artery occlusion in humans. Additional safety information regarding intracoronary delivery of oxygenated HBOC-201 has also been collected.

## Methods

### Study design

The COR-0002 pilot trial is a single-centre, phase II, placebo-controlled, crossover, single-blind study conceived to test the hypothesis that HBOC-201 administration improves myocardial "oxygenation" and myocardial function during brief coronary occlusion. Enrolled subjects underwent coronary balloon occlusion, with and without oxygenated HBOC-201 intracoronary infusion (11-12 g/dl at 48 ml/min up to 3 min). The study was approved by the Medical Ethics Committee of the Erasmus Medical Centre (Rotterdam, The Netherlands) and was performed in accordance with the International Conference on Harmonisation of Good Clinical Practice (ICP/GCP) guidelines.

### Patients

Patient inclusion and exclusion criteria are summarised in Table 1. In brief, patients were eligible for the study if they were admitted for either documented silent ischaemia, stable angina or unstable angina (Braunwald class I-IIIB)[10]. To optimise safety and size of the area at risk, eligibility was further constrained to patients with a target lesion in the proximal part of the left anterior descending coronary artery, in the absence of associated angiographically visible collateral vessels. Further, a successful index PCI, with focal stenting of the target lesion during the same cath lab session, was required prior to initiating the study period.

The pre-PCI standard 12-lead ECG recording corresponds to the baseline for quantitative dynamic analysis of ST changes over time during the study period. Written informed consent was obtained from all patients before the initiation of any study-specific procedures, including pre-treatment sedation.

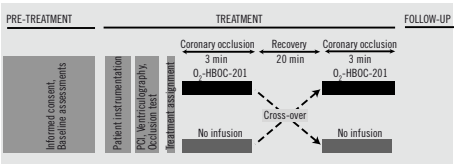


*Figure 1. The COR-0002 trial was divided into three phases: a preparation period (pre-treatment phase), a treatment phase and a follow-up phase. The study period began after the lesion was successfully treated (PCI and stenting). Continuous 12-lead HOLTER ECG was recorded from pre-PCI to four hours after the study period ended (follow-up). PCI: percutaneous coronary intervention.*

### Study procedures

Data collection points and study design are depicted in Figure 1. All subjects were followed from study inclusion to hospital discharge. An independent physician was appointed to monitor safety and welfare of the study subjects and review the clinical events during the study period.

### Concomitant treatment

Standard medications used in the management of subjects with ischaemic heart disease were not withheld per study protocol with the exception of analgesics. Use of analgesics was restricted as much as possible and were not administered immediately before study drug infusion.

#### PRE-TREATMENT PHASE

Laboratory testing, including haematology (haemoglobin, haematocrit, platelets and INR) and blood chemistry (creatinine, LDL, AST, ALT, amylase, troponin T, CK total and CK-mb), was performed at pretreatment baseline (within 24 hours of the study period) and eight hours post PCI. HBOC-201 was pre-oxygenated within 24 hours of the study period using a proprietary system designed and validated for this purpose (Figure 2).

Continuous 12-lead Holter monitoring. On arrival in the cath lab, the patient was connected to a continuous 12-lead Holter ECG recording device which was activated before the PCI and deactivated four hours after the study period. The Holter data were sent to an independent ECG core laboratory (Cardialysis, Rotterdam, The Netherlands) where ST segment changes over time

**Table 1. Key inclusion/exclusion criteria.**

| **Inclusion criteria** |
|---|
| – Males or females between 18 and 80 years of age |
| – Stable angina pectoris (CCS- Class 1, 2, 3, 4) or unstable angina (Braunwald class I-III, B) or documented silent ischaemia. |
| – Baseline ECG with stable sinus rhythm and no signs of myocardial ischaemia, with no Q waves, bundle branch block or intra ventricular conduction disturbances. |
| – Normal left ventricular wall motion with preserved (ejection fraction ≥ 55%) systolic global left ventricular function. |
| – Non-occlusive stenosis, located in the proximal segments of the left anterior descending artery and/or circumflex artery or right coronary artery requiring PCI with coronary stenting. |
| – Secondary inclusion criteria to be assessed after completion of stenting procedure. |
| **Key exclusion criteria** |
| – Non-ST segment elevation myocardial infarction (patients with any troponin T elevation within the last 5 days). |
| – History or ECG evidence of prior myocardial infarction in the territory supplied by the vessel undergoing PCI, intraventricular conduction defects/baseline ST-segment abnormalities on the surface ECG. |
| – Moderate to severe aortic or mitral valve disease. |
| – Angiographically visible collateral vessels to the target vessel. |
| – Hypertension not adequately controlled by anti-hypertensive therapy at the time of study entry (> 140/100 mmHg). |
| – Uncompensated congestive heart failure or signs of pulmonary oedema. |
| – Significant haemodynamic compromise and/or cardiogenic shock requiring inotropic or pressor support. |
| – Known history of COPD with $FEV_{1s}$ <1.0 L |
| – Serum creatinine > 1.6 mg/dL. |
| **Secondary exclusion to be assessed upon completion of coronary stenting procedure** |
| Active myocardial ischaemia |
| Coronary spasm |
| TIMI in treated vessel < 3 |
| Any deterioration in subject's status between informed consent and randomisation, ie SBP > 180 mmHg, PCWP or LVEDP > 20 mmHg |

CCS: Canadian Cardiovascular Society Scale; PCI: percutaneous coronary intervention

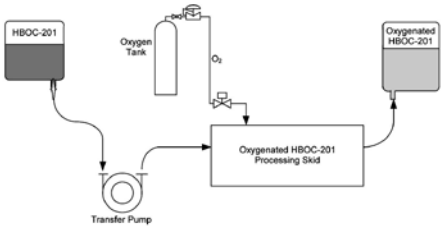


*Figure 2. In vitro oxygenation system. In this closed circuit system, HBOC-201 is pumped across a liquid-gas exchange apparatus in which the gas side is supplied with a continuous stream of medical-grade oxygen. The exiting oxygenated HBOC-201 is collected into pre-sterilised bags at a concentration of 11-13 g/dl.*

were analysed by an experienced, independent analyst who has no knowledge of the order of study treatments. ST-segment shift compared to baseline was analysed in the lead that demonstrated the most severe alterations as well as in all leads showing ST-segment changes ≥ 1 mm (at 60 ms after the J-point).

Patient instrumentation. Vascular access was obtained using the femoral approach with a standard Seldinger technique. Usually, a 6 or 7 Fr arterial sheath was selected. Prior to starting the PCI procedure, a conductance catheter was inserted into the left ventricle by an additional 8 Fr arterial sheath (details concerning the haemodynamic data acquisition are provided below in "Left ventricular haemodynamics"). A Swan-Ganz catheter was placed in the pulmonary artery via the femoral vein for cardiac output determinations by thermal and hypertonic saline (NaCl 10%) dilution methods.

## INDEX PCI PROCEDURE PHASE

An index PCI procedure was performed according to standard institutional practices. All patients were pretreated with aspirin and clopidogrel (300 mg) 2-8 hours prior to the intervention. PCI procedural success was defined as successful stent deployment in the target lesion with a residual percent in-stent diameter stenosis of < 15% and TIMI 3 flow of the target vessel without the need for bypass surgery and in the absence of death.

## THE STUDY PHASE

Upon successful completion of the index PCI procedure, a short over-the-wire (OTW) balloon (Helios 1.5, Goodman, Japan) was positioned inside the stent using a conventional 0.014 inch guidewire (Balance Middle Weight, Guidant, Indianapolis, IN, USA). The OTW balloon was used to temporarily re-occlude the stented segment and to perform the study-specific, selective intracoronary infusion. Before any study drug infusion, an occlusion test was performed with contrast injection through the guiding catheter to confirm that complete occlusion could be achieved. A conventional 0.014-inch guidewire (Balance Middle Weight, Guidant, Indianapolis, IN, USA) was inserted outside the OTW balloon, distal to the stent (in the "region of interest") to allow for continuous "online" intracoronary ECG monitoring (Figure 3). Printouts of these ECG recordings were collected and sent to the independent ECG core laboratory (Cardialysis, Rotterdam, The Netherlands).

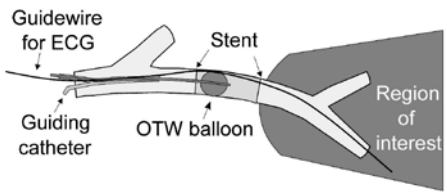


*Figure 3. A short over-the-wire balloon was positioned inside the stented segment using a long conventional 0.014 inch guidewire (Balance Middle Weight, Guidant, Indianapolis, IN, USA). ECG signs of myocardial ischaemia were assessed by an intracoronary lead positioned in the guidewire shaft of the over-the-wire balloon catheter and placed distal to the stent in the region of interest. OTW: over-the-wire.*

Study occlusion and fluid infusion: All subjects underwent two intrastent balloon occlusions (balloon inflation pressure=0.5 atm). During one occlusion, a continuous intracoronary infusion of pre-oxygenated HBOC-201, warmed to 37°C, was administered through the OTW lumen at a rate of 48 ml/min (maximum volume infused is 144 ml). HBOC-201 was warmed via an in-line clinical fluid warmer (Astotherm®plus, Model AP220S, Futuremed America, Inc., Granada Hills, CA, USA) positioned immediately proximal to the intracoronary OTW helios balloon catheter. HBOC-201 was contained within the sterile, high-pressure infusion line wrapped around the heating coil of the clinical fluid warmer. The infusion rate of 48 ml per minute was selected, based on the efficacy of intracoronary oxygenated HBOC-201 in swine subjected to simultaneous coronary occlusion. The infusion rate employed in this preclinical study was extrapolated to a corresponding rate in man after adjustment for differences in the average body weights of the animals and subjects of the COR-0002 trial.

The control occlusion period was performed similarly, but without infusion (termed "dry occlusion"). Subjects were assigned to receive pre-oxygenated HBOC-201 during the first occlusion period and no-infusion during the second period or vice versa. Each occlusion and infusion period lasted for up to three minutes. Three patients received oxygenated HBOC-201 during the first coronary occlusion and two patients received a dry occlusion as the first experimental intervention. Pre-determined criteria for premature interruption of the balloon occlusions were:

- ≥ 100% increase of left ventricular end-diastolic pressure (LVEDP) from baseline
- Sustained ventricular arrhythmias (ventricular tachycardia or ventricular fibrillation)
- Intolerable chest pain (angina)
- Significant hypertension (systemic blood pressure rise to > 180 mmHg)
- Significant LV dysfunction (EF decrease to less than 35%)

Once the balloon had been deflated and the infusion stopped, a "resting period" of 20 minutes followed for all recorded parameters to return to baseline (in particular LVEDP). The treatment period concluded after the second deflation, once all parameters had returned to their baseline values. A control angiogram was performed immediately after each balloon deflation to allow off-line quantitative coronary angiography (QCA)[11] of the region of interest.

## Left ventricular haemodynamics

Left ventricular haemodynamic data were recorded before, during and after the procedure by online left ventricular pressure-volume signals obtained by a 7 Fr combined pressure-conductance catheter (CD Leycom, Zoetermeer, The Netherlands) introduced into the left ventricle via the femoral artery. The catheter was connected to a Cardiac Function Lab (CFL-512, CD Leycom, Zoetermeer, The Netherlands) for display and acquisition of pressure-volume loops. Parallel conductance and cardiac output were determined by multiple injections of hypertonic saline solution and thermodilution, respectively, in order to calibrate the volume signals of the conductance catheter. Data analysis was performed off-line by custom-made software. Cardiac function was quantified by cardiac output and stroke volume, stroke work, end-diastolic and end-systolic volume, LV ejection fraction, end systolic and end diastolic pressure, maximal and minimal rate of LV pressure change (dP/dtMAX and dP/dtMIN). The isovolumic relaxation period (defined as the period between the time point of dP/dtMIN and the time point where dP/dT reached 10% of the dP/dtMAX value) was analysed using phase-plot analysis and the time constant of relaxation (Tau) was then determined. The end diastolic pressure-volume relationship (EDPVR) was estimated using the method adopted by Klotz et al[12]. The change in diastolic distensibility was calculated by the relative left and rightward shifts of the EDPVR at the fixed pressure level of 30 mmHg (V30). Systemic haemodynamics were quantified by systolic, diastolic and mean systemic arterial pressure recorded every three minutes through the guiding catheter for the duration of the study period to investigate any possible hypertensive effects of HBOC-201 infusion.

## Objectives

The main objectives of this study (Table 2) were early signs of myocardial ischaemia during intrastent balloon inflation defined as changes in left ventricular relaxation (Tau and $dP/dT_{MIN}$) and changes in the sum of ST segment deviations (assessed by continuous 12-lead Holter ECG monitoring) compared to baseline. Secondary objectives included changes in the cardiac performance measured by LV pressure volume loop analysis, clinical signs of myocardial ischemia and changes in coronary vascular tone measured by QCA.

Because of the crossover study design, it is not possible to make a direct comparison between treatment modalities (HBOC-201 vs. dry occlusion). However, it was possible to assess treatment safety

**Table 2. Study endpoints.**

| **Primary endpoints** |
|---|
| The change in left ventricular relaxation indices (relaxation time constant Tau [ms] and pressure-half time [ms] as measured by left ventricle pressure-volume loop analysis) and the change in the sum of ST segment deviations (as assessed by continuous 12-lead Holter ECG monitoring) compared to baseline. |
| **Secondary endpoints** |
| – Left ventricular haemodynamics as assessed by left ventricle pressure-volume loops. Parameters taken into account are:<br>- heart rate<br>- left ventricle end-systolic pressure and volume,<br>- left ventricle end-diastolic pressure and volume,<br>- maximal and negative dP/dt (mmHg/s),<br>- left ventricle ejection fraction (%),<br>- left ventricle stroke work (mmHg.ml). |
| – The change of ST segment as recorded at intracoronary ECG measures during balloon inflation. |
| – The local (vasoconstrictive) effect of HBOC-201(r) on coronary artery diameters as assessed with off-line quantitative coronary analysis based on angiograms performed before and immediately after study drug infusions. |
| – Safety endpoints as measured by in-hospital occurrence of:<br>- thrombotic events by: abrupt vessel closure (angiographic)<br>- anaphylactic type of reactions by: clinical signs<br>- life-threatening cardiac arrhythmias (sustained ventricular tachycardia, ventricular fibrillation, asystole, 2nd or 3rd degree atrial-ventricular block) as recorded by the 12-lead Holter ECG<br>- any (serious) adverse events |

from the haemodynamic responses, intracoronary and Holter 12-lead ECG monitoring and QCA measurements during the treatment period. Holter 12-lead ECG monitoring continued for four hours after conclusion of the study period and a 12-lead ECG was recorded at discharge or four days post treatment, whichever was earlier. Blood chemistry (LDH, ALT, AST, amylase, CK, CK-MB, troponin T) was collected 6-8 hours post-treatment for comparison to pre-index PCI baseline values. Additional safety endpoints included the in-hospital occurrence of adverse events.

## Statistical analysis

Variables with normal distribution were analysed using parametric tests while variables with a non-normal distribution were analysed with non-parametric tests. Continuous variables are expressed as mean±SD or median ± inter-quartile range (IQR) and differences were compared using Student *t* test or Mann Whitney test. Categorical variables are expressed as counts and percentages.
All values were normalised in order to account for baseline variability. Normalisation was done by dividing each response to treatment (HBOC-infusion or dry occlusion) by the respective baseline. This method of normalisation was selected because it was an appropriate strategy to minimise the variability associated with differences in baselines between subjects. Differences were assessed by T- test or chi-square test. All statistical tests were two-tailed. All analyses were performed using SPSS version 12 statistical software (SPSS Inc., Chicago, IL, USA). A P value <0.05 was considered significant. Due to the descriptive nature of this study, no sample estimation was utilised.

## Results

Subject baseline characteristics are described in Table 3. Patients (n=5) of mean age of 54.4±14 years underwent stent implantation for proximal (n=5) and/or mid LAD lesion (n=1) and were enrolled in the present study. Stent per patient ratio was 1.8±1.3. Diagnosis at admission was class II stable angina for all five patients. Hypertension was present in two patients, hypercholesterolaemia in three and familiar risk factor in one patient. No patient was diabetic. The mean ejection fraction (EF) was 66±10% and the mean EuroSCORE was 1.1±0.32%. Procedural and haemodynamic results are illustrated in Figures 4, 5 and 6. None of the measured haemodynamic parameters differed significantly from their respective baseline values during HBOC infusion. When data obtained during HBOC infusion and dry occlusion phases were compared, a statistical difference was shown for all systolic and diastolic performance indexes evaluated except dP/dTMAX. EF, CO and dP/dTMIN decreased significantly during dry occlusions from median values of 0.98 (IQR 0.09), 1 (0.06) and 0.99 (0.08) to 0.78 (0.22), 0.9 (0.16) and 0.85 (0.16), respectively. EDP and Tau

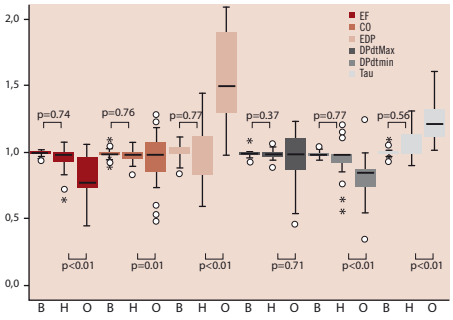


*Figure 4. Box plot illustrating the changes in haemodynamics that occurred during HBOC infusion (H) and dry occlusion (O) compared to baseline values (B). Solid lines inside the boxes: median; box ends: IQR. Stars and circles: outsiders.*

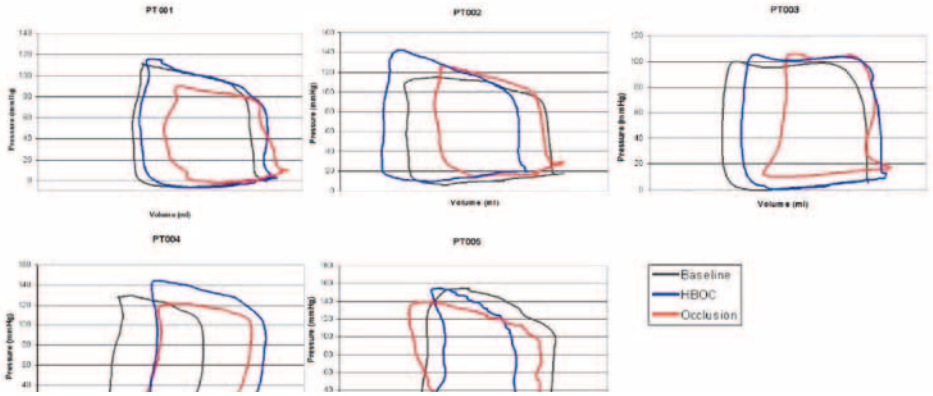


*Figure 5. Pressure-volume loops derived from the five patients at baseline, during HBOC-201 infusion and dry occlusion. An important rightward shift of the PV loop occurred in all patients except PT005 during dry occlusion. By contrast, HBOC-201 infusion increased ESV and EDV in only one patient (PT004).*

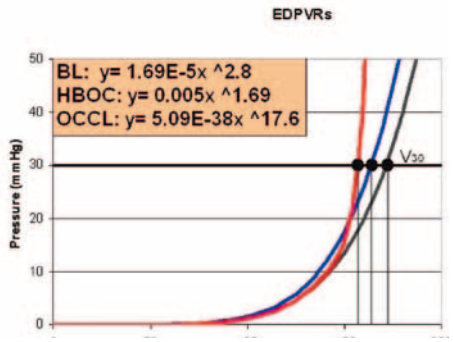


*Figure 6. Mean EDPVR and V30 at baseline, during HBOC-201 infusion and dry occlusion.*

**Table 3. Baseline characteristics.**

| | |
|---|---|
| Age | 54.4±14 |
| Men | 5 (100) |
| Arterial hypertension | 2 (40) |
| Hypercholesterolaemia | 3 (60) |
| Current Smoking | 0 (0) |
| Diabetics | 0 (0) |
| Familiar risk factor | 1 (20) |
| Previous AMI | 0 (0) |
| Previous PCI | 1 (20) |
| Previous CABG | 0 (0) |
| Previous cerebrovascular event | 1 (20) |
| Stable angina | 5 (100) |
| Class II | 5 (100) |
| LVEF | 66±10 |
| Lesion location | |
| proximal LAD | 5 (100) |
| mid LAD | 1 (20) |
| Stent/patient | 1.8±1.3 |
| EuroSCORE | 1.1±0.32 |

AMI: acute myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; LVEF: left ventricular ejection fraction; LAD: left anterior descending.
Data are number (%) or mean (±standard deviation).

increased significantly during dry occlusions from median values of 1 (0.39) and 1 (0.16) to 1.5 (0.71) and 1.21 (0.23), respectively. The change in dP/dTMAX was not statistically significant (from 1 (0.04) to 1 (0.28), p=0.71). During dry occlusion, an important rightward shift of the PV loop occurred in all patients but PT005, while during HBOC infusion, ESV and EDV did not increase with the exception of PT004. V30 decreased from 172 ml at baseline to 164 ml and 156 ml during HBOC infusion and dry occlusion, respectively (p=0.21).

Intrastent occlusions performed with infusion of pre-oxygenated HBOC-210 all lasted the intended three minutes duration; specifically, criteria for premature interruption of the inflation were never met. However, mean duration for dry occlusions was 2.13 ± 0.12 min and premature termination of the occlusion was necessary in all subjects. Table 4 identifies the reason(s) for terminating the dry occlusion in each patient.

Intracoronary ECG data were available in four out of five patients. Data from patient two (PT002) were considered not analysable by the independent core laboratory. ST segment changes are shown in Figure 7. During HBOC infusion, ST segment showed no significant changes from baseline while it was found to be significantly elevated during the dry occlusion phase in patients three, four and five. Of note, transthoracic ECG did not show any significant change both during the study phase and during the occlusion period.

**Table 4. Reasons for premature interruption of dry occlusion phase.**

| | Premature (Y/N) | Time (min) | Main reason | Additional reason |
|---|---|---|---|---|
| PT001 | Y | 2.15 | LVEF<35% | multiple extrasystoles |
| PT002 | Y | 2.05 | EDP>20mmHg | multiple extrasystoles |
| PT003 | Y | 2.46 | LVEF<35% | |
| PT004 | Y | 2 | VT | |
| PT005 | Y | 2.31 | Chest pain | multiple extrasystoles |

LVEF: left ventricular ejection fraction; EDP: end diastolic pressure; VT: ventricular tachycardia

QCA of the arterial segment distal to the stent (Table 5) did not show major differences in reference vessel diameter (RVD), minimal lumen diameter (MLD) and diameter stenosis (DS) during infusion of HBOC compared to baseline values.

From a safety point of view, mean systolic blood pressure (SBP) increase during the HBOC infusion was 10.8±10.5 mmHg. SBP never reached the critical values defined prospectively for protocol-specified pharmacological intervention with nitrates and/or nifedipine. There were no noteworthy findings in the clinical chemistry parameters and no serious adverse events in any patient through the 4-day follow-up phase occurred.

## Discussion

The main results of this study are: 1) Intracoronary infusion of oxygenated HBOC-201 maintained left ventricular haemodynamic status during total proximal LAD occlusion; 2) LV systolic and diastolic properties were not affected during HBOC-201 infusion while they significantly deteriorated during the dry occlusion; 3) intracoronary ECG showed no significant ST segment changes during HBOC infusion; 4) QCA indicated no conduit coronary vasoconstriction by the study drug; 5) HBOC-201 did not cause any adverse event or significantly alter blood chemistry parameters through the follow-up period.

The COR-0002 study was designed to test the hypothesis that pre-oxygenated HBOC-201 is capable of supporting myocardial metabolism and preserving function during total coronary occlusion in humans. The experimental design selected is a sequential intrastent angioplasty balloon inflation model with intracoronary infusion of pre-oxygenated HBOC-201 compared to the same occlusion with no infusion. Parameters of systolic and diastolic function and ST segment changes were measured to determine whether intracoronary delivery of oxygenated HBOC-201

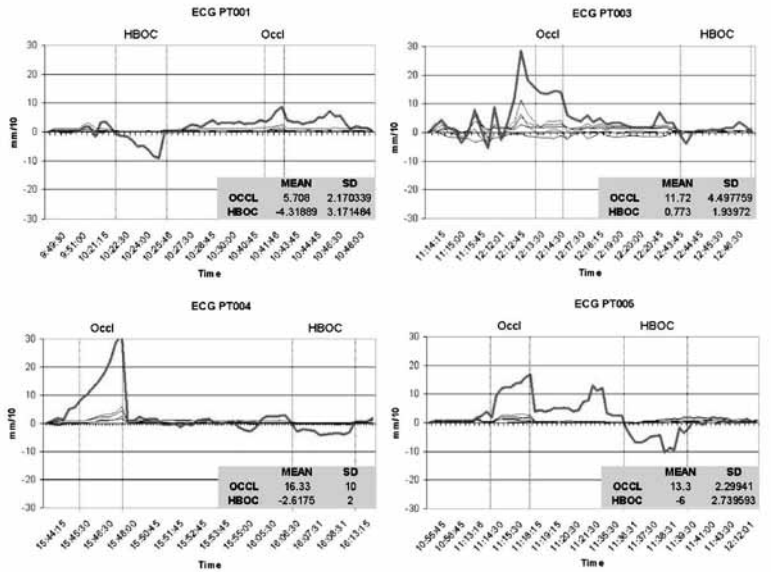


*Figure 7. Intracoronary (red line) and surface (grey lines) lead changes in ST segments during the dry occlusion and HBOC-201 infusion interventions. During HBOC infusion, ST segment showed no significant changes from baseline while it was found to be significantly elevated during the dry occlusion phase in patients three, four and five.*

**Table 5. Quantitative coronary angiography (QCA) analysis.**

| | RVD (mm) | | | MLD (mm) | | | DS (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| PT | B | O | H | B | O | H | B | O | H |
| 001 | 3.1 | 2.68 | 2.77 | 2.5 | 2.23 | 2.27 | 19 | 16 | 18 |
| 002 | 3.11 | NA | 3.23 | 2.44 | NA | 2.27 | 22 | NA | 30 |
| 003 | 2.28 | 2.23 | 2.07 | 1.7 | 1.86 | 2 | 25 | 17 | 3 |
| 004 | 2.22 | 2.23 | 2.22 | 1.94 | 1.97 | 1.84 | 13 | 12 | 17 |
| 005 | 2.86 | 2.67 | 2.28 | 1.95 | 1.76 | 1.78 | 32 | 34 | 22 |

PT: patient; RVD: reference vessel diameter; MLD: minimal lumen diameter; DS: diameter stenosis; B: Baseline; O: occlusion phase; H: HBOC infusion.

to myocardium at risk mitigates ischaemia. Local delivery of oxygenated autologous blood to the myocardium at risk through the central lumen of a dilated balloon catheter has previously proven to be safe, feasible and effective in patients in the setting of routine coronary angioplasty[13]. A one minute coronary occlusion and simultaneous infusion of blood at 60 ml/min reduced, but did not eliminate, arrhythmias and angina associated with control occlusions performed in the absence of infusion. Higher infusion rates tested only in vitro resulted in concerning levels of haemolysis and potassium release, events that are obviated with infusion of HBOC-201. As in this prior study, we selected a comparable, low-risk CAD patient population scheduled for elective PCI to assess the impact of intracoronary pre-oxygenated HBOC-201.

Percutaneous coronary angioplasty provides a unique opportunity to study the response of the human myocardium to brief periods of controlled ischaemia and reperfusion and the potential impact of study drugs. The present study involved repeated intracoronary balloon inflations with an intervening period of normal perfusion following successful deployment of a stent in an isolated proximal LAD stenosis. Acute recruitment of collateral vessels and ischaemic preconditioning may be a major confounding factor during successive balloon inflations in PTCA studies[5,14-16]. Previous studies have shown that if the duration of the first balloon inflation is longer than a "threshold" of ~ 60 to 90 seconds, indicators of myocardial ischaemia including chest pain severity, abnormalities of left ventricular regional wall motion and ST-segment elevation are attenuated during subsequent balloon inflations. These observations provide evidence of myocardial adaptation induced by the first period of ischaemia[17-19]. We anticipated this potential interference by using an alternating crossover clinical trial design. Furthermore, patients with angiographically evident collateral vessels supplying the area of interest were excluded[20].

The evaluation of early signs of myocardial ischaemia in this trial relied on continuous, invasive recording of PV loops, a technique able to provide detailed, reliable data on ventricular and myocardial performance[21] throughout the entire cardiac cycle. isovolumic relaxation was evaluated by the peak rate of pressure decline (dP/dTMIN) and by the ventricular relaxation time constant Tau ($\tau$). During the dry occlusion phase, early after balloon inflation, dP/dTMIN significantly decreased while $\tau$ significantly increased, both early indicators of myocardial ischaemia. During HBOC infusion, neither dP/dT nor Tau changed significantly from baseline values, suggesting HBOC substantially mollified the ischaemia otherwise induced by balloon inflation. Alterations of the isovolumic relaxation phase are the earliest and most sensitive signs of ischaemia-induced left ventricular dysfunction. Early asynchronous segment re-extension and regional non-uniformity also contribute to early onset and slower rate of ventricular pressure fall and might contribute to these diastolic disturbances[22]. Passive ventricular characteristics are well described by the end-diastolic pressure-volume relationship (EDPVR). Myocardial ischaemia often results in elevated left ventricular end diastolic pressures and in changes of the slope and position of the entire EDPVR[23-25]. Such shifts, when they occur, reflect a volume-independent increase in chamber stiffness.

In this series of subjects, LVEDP did not significantly increase during HBOC infusion, but increased continually in all subjects during the dry occlusion. Consistent with these results, $V_{30}$ decreased more evidently during dry occlusion than during HBOC infusion, indicating greater myocardial stiffness during dry occlusion. It is interesting to note that the slope of the EDPVR remained unchanged during coronary occlusion with HBOC infusion compared to the dry occlusion phase, suggesting worsening of diastolic properties predominantly due to a reduction of myocardial distensibility. The pathophysiological mechanisms of this shift are not completely understood but it is thought to be due to an increased level of intracellular Ca++ during diastole[26] and to impaired myosin-actin cross-bridge inactivation secondary to elevated ADP concentrations[27-29]. Ventricular interactions and pericardial constraints may also contribute to these shifts.

Akin to diastolic function, systolic functions are importantly influenced by ischaemia. HBOC largely averted systolic dysfunction. Ejection fraction (EF) and stroke volume (SV), major indexes of the ejection phase properties, did not show significant variations from baseline during coronary occlusions with HBOC infusion while they were significantly reduced during the dry occlusion phase. These results were achievable despite the fact that the occlusions were performed in the proximal part of the LAD coronary artery which supplies a large "area at risk." Consistent with these results, $dP/dT_{MAX}$, commonly used as an isovolumic phase index of cardiac contractility, did not vary significantly from baseline during HBOC infusion suggesting preservation of systolic myocardial performance. It is also noteworthy, however, that the $dP/dT_{MAX}$ values did not differ from baseline even after the onset of ischaemic conditions during dry occlusions, notwithstanding a wide IQR and outliers. It is likely that the shortness of the ischaemic period (criteria for premature interruption of the ischemic period were met in all subjects) and the load-dependence of $dP/dT_{MAX}$ mitigated the real effect of ischaemia on the myocardium.

Early electrical signs of ischaemia in the area of interest were detected by using intracoronary ECG, a technique able to detect early signs of ischaemia with high sensitivity[30]. In this series of patients, HBOC infusion did not cause any significant alteration of the ST segment. The non-significant changes that occurred during the infusion phase, moreover, were only negative alterations (ST depression), suggesting that the myocardial wall was efficiently and protected by the drug. On the contrary, a significant ST elevation, a sign of transmural ischaemia, was detected in three out of four patients during dry occlusion phase. In PT001, the ST elevation did not reach significant levels most likely because the occlusion was interrupted relatively early, due to severe EF impairment (EF<35%) and the presence of multiple extra-systolic beats. In all patients, ST tended to remain elevated even after the balloon deflation while no ST alterations occurred during the resting periods following HBOC infusion.

In the COR-0001 clinical trial[9] the major side effect of the study drug was an increase of systemic vascular resistance, a mechanism not completely understood but possibly related to putative NO scavenging by HBOCs. Importantly, however, intravenously administered HBOC-201 had no effect on conduit or microvascular coronary tone in COR-0001 subjects. In the present study, QCA analysis demonstrated that the intracoronary infusion of HBOC also failed to alter conduit coronary artery tone, as indicated by a lack of effect on RVD, MLD and DS. The absence of coronary vasoconstriction, despite exposure to undiluted HBOC-201, further supports the potential utility of HBOC-201 in complicated patient subsets such as those with coronary artery disease.

## Limitations

The present pilot study reports the results from a small series of five patients. Therefore, caution must be exercised in the interpretation of these data.

Although oxygenated HBOC-201 substantially preserved LV function, ameliorated or prevented cardiac arrhythmia and sharply reduced or eliminated coronary angina, treatment with study drug in this clinical trial was not fully optimised. In swine studies, intracoronary infusion of oxygenated HBOC-201 at 30 ml/min preserved approximately 80% of LV regional wall motion during coronary artery occlusion (unpublished data). Lower infusion rates yield proportionately less protection against coronary occlusion and higher infusion rates achieved full preservation of regional wall motion in swine. Extrapolating the 30 ml/min infusion rate in pigs to the average patient weight in the current clinical trial yields an infusion rate of 48 ml/min, the rate administered to subjects in this trial. Hence, higher intracoronary infusion rates based on individual body weights or coronary flows may have provided even greater LV protection against interruptions in coronary blood flow.

In summary, intracoronary oxygenated HBOC-201 represents a new category of pharmacologic strategies that may have utility in patients undergoing PCI. The results of this exploratory trial provide preliminary evidence that HBOC-201 can effectively preserve myocardial mechanical and electrical properties in the face of total coronary occlusion. This represents an important next step in the clinical development program for this product as a treatment for acute myocardial ischaemic syndromes. Future studies will be required

to determine if intracoronary and/or intravenous oxygenated HBOC-201 can enhance treatment efficacy in more complicated patient populations including STEMI and in cases where lesion access is difficult or when microvascular pathology contributes to low TIMI flow.

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# APPENDIX 3.1

## Pre-oxygenated hemoglobin-based oxygen carrier HBOC-201 annihilates myocardial ischemia during brief coronary artery occlusion in pigs

te Lintel Hekkert M, Dubé GP, Regar E, de Boer M, Vranckx P,
van der Giessen WJ, Serruys PW, Duncker DJ.

*Am J Physiol Heart Circ Physiol.* 2010;**298**:H1103-13. [**original research paper, only provided as a reference** ]

Because of their ability to perfuse remote regions and deliver oxygen, hemoglobin-based oxygen carriers (HBOCs) may be considered in the treatment of several ischemic conditions such as acute coronary syndromes or high-risk percutaneous intervention. Here we studied the effects of intracoronary infusion of ex vivo pre-oxygenated HBOC-201 during brief total coronary artery occlusion (CAOs) on myocardial oxygenation and left ventricular (LV) function in a large animal model and investigated the influence of HBOC-201 temperature and infusion rate on these effects. Thirteen open-chest anesthetized swine were instrumented for measurement of global and regional LV function and metabolism. CAOs were induced by inflating an intracoronary balloon catheter; pre-oxygenated HBOC-201 (12 g/dL) was infused distally through the central lumen of the balloon catheter. Animals underwent consecutive 3-min CAOs interspersed by 30 min of reperfusion, accompanied by different HBOC-201 infusion rates (0, 15, 23, 30, 40, and 50 ml/min) and/or two infusion temperatures (18 degrees C or 37 degrees C) in random order. CAO elicited immediate loss of systolic shortening (SS) in the ischemic region (19 +/- 1% at baseline vs. -3 +/- 2% at end of CAO), resulting in decreases in maximum rate of rise in LV pressure (15 +/- 5%) and stroke volume (12 +/- 4%; all $P < 0.05$). Balloon deflation resulted in marked coronary reactive hyperemia (to 472 +/- 74% of baseline), increases in coronary venous concentrations of adenosine + inosine (to 218 +/- 26% of baseline; both $P < 0.05$) and rapid restoration of SS toward baseline. HBOC-201 ameliorated the CAO-induced changes in SS, stroke volume, reactive hyperemia, and coronary venous adenosine + inosine. The effects were temperature and flow dependent with full preservation of SS at 50 ml/min HBOC-201 of 37 degrees C. In conclusion, intracoronary pre-oxygenated HBOC-201 preserved myocardial oxygenation and LV function in swine during CAO in a dose- and temperature-dependent manner. In our study setting, pre-oxygenated HBOC-201 can match the oxygen delivery role of endogenous blood in the heart on an almost equivalent-volume basis.

# [ PART 4 ]

**performance.**

## PERCUTANEOUS ADVANCED MECHANICAL CIRCULATORY SUPPORT TO THE FAILING HEART

# CHAPTER 4.1

## The Tandemheart, Percutaneous Transseptal Left Ventricular Assist Device. A safeguard in High-risk Percutaneous Coronary Interventions. The 6 year Rotterdam experience

Vranckx P, Meliga E, De Jaegere P, Van den Ent M, Regar E, Serruys PW.

*EuroIntervention* 2008; **4**:331-337. [**original research paper**]

EuroIntervention

# The TandemHeart®, percutaneous transseptal left ventricular assist device: a safeguard in high-risk percutaneous coronary interventions. The six-year Rotterdam experience

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*None of the authors have a conflict of interest to declare.*

**KEYWORDS**
*Heart-assist device, angioplasty, TandemHeart®*

## Abstract

**Aims:** Percutaneous coronary interventions (PCI) in high-risk cardiac patients are preferentially referred to specialised myocardial intervention centres (MIC). Included in this group are patients with a haemodynamic collapse or high likelihood of haemodynamic collapse, either during balloon inflation or with acute vessel closure. The TandemHeart®, a percutaneous transseptal left ventricular assist (PTVA®) that can be introduced using standard catheterisation laboratory techniques, offers interesting perspectives to reduce procedural risks.

**Methods and results:** Between September 2000 to July 2006, The TandemHeart®, supported the circulation of 23 patients (age: range 46-74, mean 59) admitted to our centre for high risk, either emergency or elective, PCI. Successful implantation was achieved in 100% of patients. The mean time for implementation of circulatory support was 35 minutes (range 16-62). The index PCI was successful in all patients except two. A pump flow up to 4L/min was achieved with significant reduction of left ventricular filling pressures, pulmonary capillary wedge pressure and with significant increase of systemic arterial pressures. Duration of support ranged from 1-222 hours (mean 31±49.8 hours). Five patients died with the TandemHeart® in place, four of whom were in irreversible cardiogenic shock at admission. Mild to moderate access site bleeding was seen in 27% of patients. One patient experienced a loge syndrome of the leg. Core temperature (Ct) decreased to <36.5°C in six patients, profound hypothermia (Ct < 35°C) was observed in two patients. There was no technical device failure.

**Conclusions:** The TandemHeart® - PTVA® provides effective, total left ventricular support in very high risk PCI settings. The rate of device related cardiac and vascular complications was acceptable.

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## Introduction

With increasing operator experience, refinement in technology and adjunctive pharmacological treatment, percutaneous coronary intervention (PCI) is now considered the treatment of choice for many high-risk subgroups in which PCI was previously contra-indicated. PCI may even be a valuable option for those patients where coronary bypass grafting (CABG) is clinically contra-indicated[1-3]. Many of these procedures are elective.

In general the benefits of a specific (percutaneous) procedure should be weighed against the risks involved; taking into account alternative treatment strategies, the interventional and intensive care team experience[4] and taking in consideration the individual patient risk scores, that may aid the operator in selecting or avoiding adjunctive pharmacotherapy or specific devices[5-9].

Patients in whom it is considered that PCI poses a significantly high risk include these with high likelihood of haemodynamic collapse, either during balloon inflation or with acute vessel closure[4]. In general, these are the patients in whom a large amount of the viable myocardium is supplied directly or indirectly by the affected artery. The development of a percutaneous ventricular assist device (VAD) that could be easily and quickly inserted prophylactically or in case of an haemodynamic collapse proves invaluable in this setting.

The TandemHeart®, a percutaneous transseptal left ventricular assist device (PTVA®) system (CardiacAssist Inc., Pittsburgh, PA, USA), has been demonstrated to effectively reverse cardiogenic shock after myocardial infarction[11] and to play an important role for bridging to another definitive therapy[12]. This system allows for rapid implementation of circulatory support using standard interventional techniques in the catheterisation laboratory and is designed to deliver up to 4.5 litres of blood flow per minute. In this report, we will report on a single centre six year clinical experience with the TandemHeart® in high risk PCI procedures.

## Methods

### Patients selection

Since 2000, the Thoraxcenter, Erasmus University Medical Centre, Rotterdam, The Netherlands started a program evaluating percutaneous left ventricular assist devices (LVAD) during high risk PCI. Between September 2000 to July 2006, twenty-three patients admitted to our centre for acute coronary syndromes (ACS)/ ST segment elevation myocardial infarction (STEMI) or for elective PCI, were treated with TandemHeart®.

In non-elective patients, the indication for TandemHeart® support was based on already established haemodynamic instability before the index PCI procedure, defined as typically with low cardiac output (cardiac index < 2.2 L/min/m$^2$), peripheral signs of tissue hypoperfusion (decreased urine output and/or cold extremities), systemic hypotension (systolic blood pressure < 100 mmHg) despite vasopressor therapy and in the presence of appropriate left ventricular filling pressures (pulmonary capillary wedge pressure, PCWP ≥ 15 mmHg). In case of presence of an intra aortic balloon pump (IABP) haemodynamic measurements were done with the IABP paused for 60 seconds.

In patients who underwent elective PCI, circulatory assist was indicated in procedures which had a presumed high risk of ischaemic/haemodynamic complications, based on the presence of severely depressed left ventricular (LV) function and planned treatment of ≥ one complex lesions in vessels supplying a large amount of myocardium. CABG was not considered a treatment option in any of these patients. Major exclusion criteria were predominant right ventricular failure requiring right ventricular support, severe aortic insufficiency, severe sepsis and anoxic brain damage.

## System description

The TandemHeart® PTVA® (Figure 1-2) incorporates arterial perfusion cannula configurations ranging from 9 to 17 Fr, an unique 21 Fr venous transseptal cannula, and a centrifugal blood pump. Oxygenated blood from the patient's left atrium is supplied to the pump by the trans-septal cannula and than returned to the patient's systemic arterial circulation. The centrifugal pump contains a single moving part (rotor/impeller) that is suspended by a thin lubricating film of fluid to reduce heat and friction, thereby reducing the risk of thrombus formation. The pump connects to a microprocessor-based controller that displays PTVA speed and flow. These parameters are controlled by adjustment of a single knob. The controller also provides automatic system monitoring and alarms indicating conditions that require action. The system is designed to deliver up to 4.5-5 litres (L) of blood flow per minute, depending on the size of the arterial cannulation and the filling conditions of the left atrium, while operating at a relatively low speed (7500 revolutions per minute, RPM).

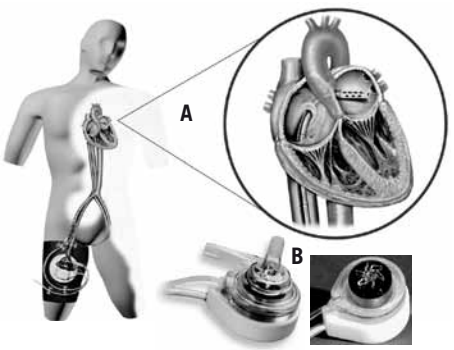


*Figure 1. Schematic of the system deployed. The Tandemheart® removes oxygenated blood from the left atrium via a 21 Fr transseptal cannula that is advanced from the femoral vein trough the inter-atrial septum into the left atrium (A). The oxygenated blood is returned into the arterial vascular system via a 15 up to 17 Fr arterial cannula by means of a centrifugal pump (B). The centrifugal pump contains a single moving part (rotor/impeller) that is suspended by magnetic force on a thin lubricating film of fluid to reduce heat and friction, thereby reducing the risk of thrombus formation.*

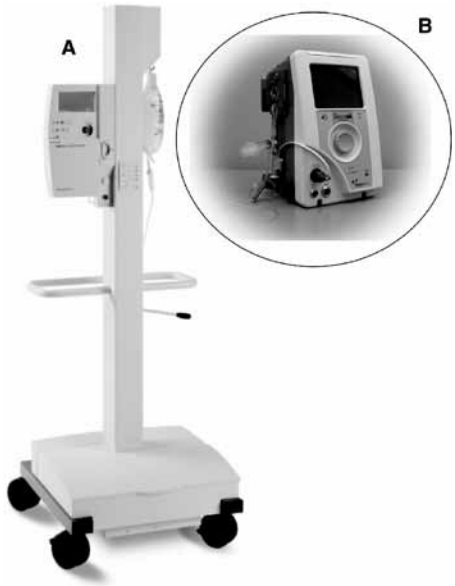


*Figure 2. Microprocessor-based controller used in this series (A) displaying PTVA speed and flow. These parameters are controlled by adjustment of a single knob. The controller includes extensive self-diagnostic and alarm features to ensure patient support without the need for constant operator surveillance. Panel (B) shows the recently introduced Escort Controller. This light (21 pound or 9.53 kg) weight controller can be mounted at the patient's bedside and includes an easy-load infusion system. The latter allows the lubrication fluid infusion line to be installed in seconds.*

## Insertion technique

A standard transseptal puncture technique, using an Inoue guidewire, was used to gain access into the left atrium from the right femoral vein. Transseptal puncture was carried out by an experienced operator only. The inter-atrial septum was dilated with an 2-stage 14/21 Fr dilator and the venous inflow cannula was inserted (proper positioning in the left atrium was checked by either angiography and/or transesophageal echocardiography). One 15 Fr or 17 Fr perfusion catheter (Bio-medicus cannula, Medtronic, Minneapolis, MN, USA) was inserted into the femoral artery and advanced to the common iliac artery. An ileac angiography was performed before the placement of the perfusion catheter to delineate the arterial anatomy and size and to disclose eventual luminal obstructions. In three patients a dual femoral approach with Y connection was used for arterial access. Both arterial and venous cannula were fixed to the skin with multiple sutures in order to secure their position. The pump was placed on the upper leg of the patient. After checking the central venous pressure, priming and cautious de-airing of the entire system, the arterial and venous cannulas sets were connected to the pump by a heparin-coated tygon tubing (up to 30 cm length) and the pump was activated to its maximum rotation speed. Output pump flow was measured by an external electromagnetic flow meter (HT 311, transonic).

## Device weaning and removal

A predefined weaning protocol was initiated at the moment vasoactive drugs were reduced to a stable minimal level (dobutamine up to 4 µg/kg/min., norepinephrine up to 0.1 4 µg/kg/min.) provided stable haemodynamic parameters (mixed venous or central venous saturation > 65%). A stepwise reduction of pump assist was performed, by reducing pump speed from 7500 to 3500 RPM (steps of 500-1,000 mL/min), adapted to the medical condition of each patient individually. The final removal decision was based on medical judgement. A weaning period up to six months was respected for most patients. The pump was not stopped until immediately before removal. No specific instructions on access site closure were issued.

## Concomitant treatment

The index coronary intervention was performed after TandemHeart® implantation and functioning. Arterial access was obtained via the contra-lateral femoral artery and the interventional strategy was left to the operator, according to standard techniques. Standard intensive care was provided to each patient. Patient sedation and intubation was considered for clinical and/or comfort reasons. A balloon tipped pulmonary artery (PA) catheter was placed via the contra lateral femoral vein for haemodynamic monitoring purposes if clinically indicated. Cardiac output determinations were made using standard thermodilution techniques.

During the index procedure, a constant flow (10 ml/h) of heparinised infusate is maintained providing a localised concentration of heparin in the interior of the pump in order to obtain localised anti-coagulation thereby minimising systemic heparinisation, the risk of bleeding and thrombus formation. Additional boluses of heparin were administered peripherally to maintain the activated coagulation time to approximately 200 seconds during routine support (400 seconds during insertion) or an activated partial thromboplastin time of between 65 and 80 seconds.

## Predefined safety endpoints and time periods

The following predefined clinical events related to the use of the TandemHeart® were assessed in each patient: any minor or major TIMI bleeding[9], laceration of the insertion vessel/limb ischaemia, device related thromboembolic events. infective complications, residual atrial septum defect after device removal, device malfunction or failure.

The insertion time was defined as the time from providing of the Brockenbrough needle to the 'full' heparinisation following connection of the femoral cannula to the pump. The duration of support was defined as the time from 'full' heparinisation at time of connection to the pump till the removal of the femoral cannula.

## Statistical analysis

Variables with normal distribution were analysed using parametric tests while variables with a non-normal distribution were analysed with non-parametric tests. Continuous variables are expressed as mean ±SD or median ±SD and differences are compared using

Student t test or Mann Whitney test. Categorical variables are expressed as counts and percentages. Differences were assessed by Fisher exact test or chi-square test, as appropriate. All analyses were performed using SPSS version 12 statistical software (SPSS Inc., Chicago, IL, USA). A two-tailed p value < 0.05 was considered significant for hypothesis testing.

## Results

### Baseline characteristics

Baseline clinical and procedural characteristics are listed in Table 1. Mean age was 59 ± 9.4 years, 19 patients (83%) were men. The ejection fraction was <30% in 16 patients (70%). Fifteen patients (65%) suffered a three vessel disease, six of whom with left main involvement. The indications for TandemHeart® support were elective/high risk PCI in 15 patients and non-elective (emergency) in eight patients with ACS and acute heart failure. Eight patients experienced an evolving (< 36 hours) myocardial infarction, five of which were complicated by acute heart failure/cardiogenic shock (CS). Eight patients needed intubation and mechanical ventilation as part of their medical treatment and 11 were on inotropic support at the start of the implant procedure. Standard EuroScore in our patients ranged between 2 and 14 (mean 6.5) providing a surgical risk of mortality between 1.5% and 46.6% (mean: 11.3±11.6%). Very high risk patients (EuroScore > 9) were nine[13].

### Haemodynamic effects

The TandemHeart® showed good performance, achieving flow rates up to 4.0 L/min. Mean systemic arterial pressure was 74.8±18 mmHg at baseline and 85.6±19 mmHg after pump functioning (p= 0.023).

**Table 1. Baseline characteristics; n (%)**

| | | |
|---|---|---|
| Age (mean±SD) | | 59±9.4 |
| Sex | M | 19 (82.6) |
| | F | 4 (17.4) |
| Previous MI | | 11 (47.8) |
| Previous CABG | | 4 (17.4) |
| Clinical presentation | STEMI&CS | 5 (21.7) |
| | STEMI | 3 (13) |
| | NSTEMI | 1 (4.3) |
| | UA | 5 (21.7) |
| | Angina/dyspnea | 8 (34.7) |
| | Scheduled PCI | 1 (4.3) |
| CAD extension (23 pts) | 1VD | 3 (13) |
| | 2VD | 5 (21.7) |
| | 3VD | 9 (39.1) |
| | 3VD + LM | 6 (26) |
| EF | <20% | 11 (47.8) |
| | 20-30% | 5 (21.7) |
| | 30-50% | 3 (13) |
| | >50% | 4 (17.4) |
| Indication for PTVA | elective | 15 (65.2) |
| | emergency | 8 (34.7) |
| Intubation | | 8 (34.7) |
| Inotropic support | | 11 (47.8) |
| EuroScore (mean±SD) | | 6.5±3.4 |
| | HRP (>6) | 3 (13) |
| | VHRP (>9) | 9 (39.1) |

Pulmonary wedge pressure was 16.8±5.6 mmHg at baseline and 13.6±6 after pump functioning (P= 0.002). The pulse pressure was reduced on support from 39.7±17.7 to 31.5±17 (p<0.001) (Table 2). In two patients the initial period after implantation of the TandemHeart® was characterised by a complete non- pulsatile arterial blood pressure (pulse pressure < 7 mmHg). In one patient with the recovery of the heart function < 24 hours after implantation, increasing pulse pressures became evident. Modulation of pulsatility with low amplitude to the non-pulsatile blood flow produced by the PTVA could be achieved by varying pump flow. One patient did not show recovery of pulsatile blood flow and he died with the TandemHeart® *in situ*.

**Table 2. Hemodynamic effects of PTVA.**

| | Baseline | PTVA | P value |
|---|---|---|---|
| MSBP (mean±SD) | 74.8±18 | 85.6±19 | 0,023 |
| Pulse P (mean±SD) | 39.7±17.7 | 31.5±17 | 0,001 |
| PCWP (mean±SD) | 16.8±5.6 | 13.6±6 | 0,002 |

A pulmonary artery catheter was inserted in 20 out of 23 patients. The hemodynamic measurements reported were immediately before Tandem Heart® insertion and at the end of the PCI procedure (before the patient was transferred to the cardiac intensive care department)

### Procedural and clinical outcomes

Procedural and clinical outcomes are summarised in Table 3.

Index-PCI procedural success was achieved in 42 lesions (96%). A total of 44 lesions were treated (one up to four lesions per patient), all including stent implantation (mean stent per patient rate: 2.3). The mean time for insertion of the TandemHeart® was 34±12 minutes (range 16-62), the procedural success was 100%. The circulatory assist period ranged from 1h to 222h, mean 31±49.8h One patient with a severe femoral artery stenosis needed PTA and stenting of the iliac artery vessel prior to cannulation.

Seventeen patients were successfully weaned from the TandemHeart®. In-hospital death occurred in six patients. In total five patients died with the device *in situ*, four of which were considered in irreversible CS at admission. Another patient admitted for CS was initially stabilised after 222 hours on TandemHeart®

**Table 3.**

| | | |
|---|---|---|
| PCI Results; n (%) | | |
| PCI success rate | | 96% |
| Number of treated lesions | | 44 |
| Stent per patient | | 2,3 |
| PTVA Insertion success rate | | 100% |
| PTVA Insertion Time (mean±SD) | | 34±12 |
| Assist period, hours (range/mean±SD) | | 1-222/31±49.8 |
| Death | In hospital | 6 (26) |
| | with PTVA in place | 5* (22) |
| | at 6 months FU | 9 (39) |
| | at 12 months FU | 10 (43) |
| | at 2 years | 11 (47) |
| | at 5 years | 11 (47) |

* 4/5 patients suffered cardiogenic shock

support. However, this patient developed abrupt circulatory failure after removal of the pump and died a few hours later. No further invasive treatment was possible due to the abrupt worsening of his clinical condition. During the follow-up period, three patients were lost and one patient died due to progressive heart failure < 30 days. An uneventful six months follow-up was observed in 13 patients.

## Complications

Potential complications related with the use of TandemHeart® are summarised in Table 4. In this series of patients, no procedural complications during device insertion were noted and no cardiac tamponade, thromboembolic events nor device failure occurred. In two elective cases (8.7%) the weaning needed to be postponed due to the occurrence of profound hypothermia (core temperature 32.7 °C and 34.2 °C) and the need for active re-warming. Minor to mild access site bleeding complications occurred in 26% of patients (n=6), none required specific treatment. Lower limb ischaemia complicated by a loge syndrome occurred in one patient with pre-existing severe peripheral vascular disease. This patient needed a fasciotomy. Dislocation of the venous cannula occurred in one patient and required pump removal.

Most pumps were surgically removed in the operation theatre (n=12, 52%). A closure device (Prostar) failed to close completely the puncture site in two out of three attempts. A local compression device (Femostop, Radi) was used successfully in these patients as well as in three others without any complication.

**Table 4. Potential complications of PTVA; n(%)**

| | |
|---|---|
| Puncture of aortic root, coronary sinus, posterior free wall | 0 (0) |
| TandemHeart pVAD system failure | 0 (0) |
| Thromboembolism | 0 (0) |
| Neurologic dysfunction | 0 (0) |
| Hemolysis | 0 (0) |
| Cardiac tamponade | 0 (0) |
| Deep venous thrombosis | 0 (0) |
| Arrhythmias | 0 (0) |
| Systemic hypothermia (35-36.5) | 4 (17.4) |
| Profound hypotermia (<35) | 2 (8.7) |
| Bleeding | 6 (26) |
| Cannulation site infection | 0 |
| Cannula dislogment | 0 |
| Distal leg ischaemia | 1 (4.3) |
| Total no. of events | 13 |

**Table 5. Exclusion criteria for this study were:**

- Participation in another trial with an investigational drug/ device during the last 60 days
- Concomitant disease that interferes with the prognosis.
- Contra indications to standard drugs for coronary intervention and coronary heart disease.
- Coagulopathy-chronic anticoagulant therapy / uncontrolled active bleeding.
- CNS damage resulting in fixed dilated pupils not related to pharmacologics.
- Severe aortic/mitral valve stenosis, significant aortic valve insufficiency.
- Rupture of the ventricular wall
- Right heart failure, defined as the need of a right ventricular assist device.
- Severe peripheral vascular disease (e.g. aorto-iliac occlusive disease).
- Stroke of haemorrhagic or unknown origin
- Non-haemorrhagic stroke, that took place within the past 30 days
- A transient ischaemic attack, that took place within the past 30 days.

## Discussion

PCI in high-risk coronary patients with (potential) haemodynamic compromise is challenging and may be considered a special dimension of MIC[14]. Active circulatory support using VAD constitutes a valuable safeguard to reduce potential fatal intervention-related complications in this setting and is nowadays considered part of the current therapeutic armamentarium.

IABP is currently the most widespread mechanical device used to support and to improve coronary perfusion in patients with acute heart failure. IABP implantation is easy and its use is safe and associated with a low incidence of serious complications. IABP may provide a lot of diastolic augmentation of coronary flow in patients in shock, however only limited forward output augmentation (up to about 0.5 L/min). This level of support has been shown to be scarcely able to improve clinical outcomes in the setting of complete hemodynamic collapse[15].

Active circulatory support using VAD combines the beneficial effects of the myocardial unloading and an increase in tissue perfusion pressure. Theoretically, this technique should also allow very early decompression ("unloading") of the left ventricle in massive myocardial infarction, thus enhancing the chances of recovery of the jeopardised ischemic non-infarcted areas[16]. In animal models, LV unloading prior to revascularisation of the infarcted artery led to significant myocardial salvage in comparison to the implementation of unloading after reperfusion[17]. A trial testing this concept, including one patient reported in this series, was stopped early due to poor recruitment. However, the concept could nicely be illustrated by echo contrast imaging in one of our patients (Figure 3). Our data confirmed that TandemHeart® support was associated with significant decreases in left ventricular filling pressures, mean systolic blood pressure and arterial pressures. The blood flow, up to 4.5 L/min, provided by the device may be sufficient to both optimally unload the LV and to prevent and even reverse organ dysfunction in cardiogenic shock patients[11,18].

Patient selection is the single most crucial factor in determining a successful outcome in patients who receive temporary mechanical circulatory support. Rapid diagnosis and treatment are essential but are often based on limited information. The patient's history and overall clinical setting should be considered in the decision process to initiate circulatory support. A pulmonary-catheter was used in the majority of the patients as adequate left ventricular filling conditions are essential for proper functioning of (preload to) the device. Haemodynamic data, including mixed (or central) venous oxygen saturation, may help to guide the overall patient selection, the

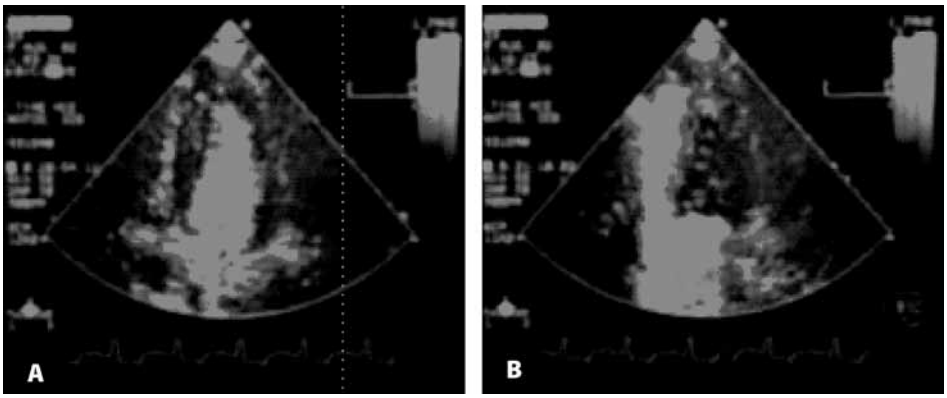


*Figure 3. Echocardiographic contrast perfusion images in a patient on Tandemheart(r) circulatory support. Panel A: low circulatory support (high wall tension, poor myocardial perfusion, contrast remains in the ventricle cavity). Panel B: Full circulatory support with effective unloading of the left ventricle (low wall tension, good myocardial perfusion).*

management and potential weaning decisions. In our series five patients died while on TandemHeart® support, four were in profound CS at the time of treatment initiation. Patients beyond the 'irreversible edge' of CS prove bad candidates for this technique in this and other series[11]. Of interest, only three out of the successfully weaned patients (n=17) deceased during the FU period, suggesting this device may have a tangible impact on the long-term survival as well.

The TandemHeart® can be used prophylactically and in bail-out situations. In experienced hands cardiovascular support can be implemented in less than 35 minutes. The most important drawback of the technique may be the difficulty of cannula insertion. Substantial atherosclerotic changes in the iliac artery and the consequent peripheral vascular disease are most common in the group of coronary patients who most benefit from the effects of the pump. In this series, a total number of 13 device-related in-hospital adverse events rate were observed, 0.6 events per patient. Many of them were access site complications. One patient developed a loge syndrome requesting a fasciotomy, but no other iatrogenic arterial insufficiency was noticed. Mild to moderate groin bleeding was encountered in six out of 23 patients (27%), none needing a specific treatment. Most pumps were surgically removed in the operation theatre in order to allow optimal local haemostasis and proper inspection of the cannulation site. A local compression or closure device may provide a valuable alternative given a clean puncture technique. Access site complications may be minimised by prior iliac angiography and by implementing an ultrasound guided puncture technique of the (common) femoral artery[13]. When necessary, the use of distal perfusion and antegrade cannulation of the superficial femoral artery may obviate peripheral vascular complications as well.

As opposed to other modalities of percutaneous cardiopulmonary support (CPS) used in this indication[19,20], the TandemHeart® system keeps the patient's lungs as its own ventilator and may be used to support patients for a longer period of time without major haematological or pulmonary complications (up to 10 days in our series). No thrombi formation was noticed either during the support or after the removal of the device and no thromboembolic event occurred. Evidence of clinical relevant haemolysis, which was a particular concern, was looked for but absent in our series (data not shown). Also this observation is in line with the Leipzig series[11].

Systemic hypothermia (<36,5°C) was observed in 25% of patients (n=6) but the temperature decreased below 35°C only in two cases. Contact of the system circuit with room temperature may have contributed to a cooling effect on the blood flowing through the pump. Other factors that may have contributed to heat loss are the use of general anaesthetic agents and neuromuscular blockers leading to vasodilatation and the loss of muscular tonus. Correcting measures may be straightforwardly introduced to avoid or rapidly detect this complication in the future.

## Conclusion

Our results create optimism for more widespread introduction of the TandemHeart® in the MIC setting. The concept of closed chest left heart bypass, with left atrial to femoral artery bypass, constitutes a relatively safe and reliable safeguard in high risk PCI and acute heart failure. TandemHeart® PTLA® can be rapidly and percutaneously implanted in the catheterisation suite using standard interventional techniques in both a prophylactic or emergency settings. The TandemHeart® provides more haemodynamic support than the IABP and is effective in stabilising haemodynamics. Access site complications remain the Achilles' heel of this technique.

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# CHAPTER 4.2

## Assisted Circulation using the Tandemheart during very high-risk PCI for Unprotected Left Main Coronary Artery disease in patients declined for CABG

Vranckx P, Schultz CJ, Valgimigli M, Eindhoven JA, Kappetein AP, Regar ES, Van Domburg R, Serruys PW.

*Catheter Cardiovasc Interv* 2009, **74**: 302-310. [**original research paper**]

The Tandemheart during high risk PCI-part II

# CORONARY ARTERY DISEASE

## *Original Studies*

# Assisted Circulation Using the Tandemheart® During Very High-Risk PCI of the Unprotected Left Main Coronary Artery in Patients Declined for CABG

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**Objectives: In a single center experience, we retrospectively evaluated the short-term safety and efficacy of the TandemHeart® percutaneous transseptal left ventricular assist (PTVA®) system to deliver extracorporeal circulatory support during catheter based treatment of the unprotected left main coronary artery (ULMCA). Background: Percutaneous Coronary Intervention (PCI) of the ULMCA usually has been restricted to patients who are hemodynamically unstable or ineligible for coronary artery bypass grafting (CABG). High-risk patients for CABG should be considered at increased risk for PCI as well. In these patients the TandemHeart PTVA System (p-LVAD) may provide a valuable safeguard to reduce procedural risks. Methods and Results: Between July 2002 and May 2008 the TandemHeart was used in 9 very high risk patients (Logistic Euro score: 13.64 (7.46–29.67); Syntax score:43 (41–50); Mayo Clinic Risk score (MCRS) 7 (6–8); age: median 65 (range 55–71) undergoing elective PCI for the novo lesions on the ULMCA. All patients were declined for CABG by a heart team. A "true" percutaneous insertion technique was used in all patients, technical success rate was 100%. The median (range) time for implementation of circulatory support was 27 min (24–30). A median (range) pump flow up to 4.36 (3.40–5.54) L/min was achieved with significant reduction of left ventricular filling pressures, pulmonary capillary wedge pressure and a small increase of systemic arterial pressures. Median (range) duration of support was 93 min (50.4–102). Successful weaning was achieved in all patients. There was no in hospital death, survival at 6 months was (89%), whereas vascular access site complications were seen in 4 patients (44.4%). Conclusions: In very high risk PCI, assisted circulation using the TandemHeart-PTVA provides effective, total left ventricular support and may contribute to a reduced procedural risk and improved survival. The rate of device related cardiac and vascular complications was acceptable.** 

**Key words: heart-assist device; tandemheart; percutaneous coronary intervention; high-risk; unprotected left main coronary artery disease**

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Conflict of interest: Nothing to report.

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Received 10 January 2009; Revision accepted 18 January 2009

DOI 10.1002/ccd.22011
Published online 9 April 2009 in Wiley InterScience (www.interscience.wiley.com).

## INTRODUCTION

Because of concern about periprocedural risk and long-term durability, PCI of the ULMCA usually is currently recommended to patients who are hemodynamically unstable or declined for surgery because of high-risk comorbid conditions [1,2]. Indeed, catheter-based ULMCA treatment may prove a challenging task, with historical event rates reported to be high, especially in patients who were previously declined by cardiac surgeons [3]. Importantly, high-risk patients for CABG have been repeatedly shown to be at greater risk for adverse outcome after PCI as well which calls for dedicated strategies to offer a safe and effective percutaneous revascularization in this difficult patient subset [4].

The TandemHeart® PTVA® (CardiacAssist, Pittsburgh, PA) has been demonstrated to effectively reverse cardiogenic shock after myocardial infarction [5]. This system allows for rapid implementation of circulatory support, delivering up to 4.5 L of blood flow per minute, using standard interventional techniques in the catheterization laboratory [6,7].

We herein report a single center expertise implementing the TandemHeart, left atrial-to-femoral arterial, extracorporeal circulatory support during very high risk catheter-based treatment of the ULMCA in patients turned down for CABG.

## PATIENTS AND METHODS

### Patients

Between July 2002 and May 2008, the TandemHeart PTVA was used in a series of 9 patients who underwent elective PCI for de novo lesions in the ostium, shaft or distal ULMCA in the Thoraxcentre, Erasmus University Medical Centre Rotterdam (The Netherlands). All patients had confirmed myocardial ischemia related to ULMCA disease and were declined for CABG due to comorbid clinical conditions (Table I). The contraindication to surgery was assessed and agreed to in writing by the attending cardiologist and a senior staff cardiothoracic surgeon (the so called "heart team").

Patients were stratified into risk classes with the European System for Cardiac Operative risk evaluation (euroscore) [8]. Subjects with a EuroSCORE $>6$ were defined as high perioperative risk, and those with a EuroSCORE $>9$(logistic $\geq 20$) as very high risk [9]. In addition, information about the risk of mortality and morbidity was generated with the Mayo Clinic Risk score [10]. The Syntaxscore, a comprehensive angiographic scoring system for contemporary coronary intervention, scored by two independent investigators, was added to the analysis to objectively quantify the complexity of the coronary anatomy [11,12].

### The Tandemhart (Insertion Technique)

The Tandemheart PTVA (CardiacAssist, Pittsburgh, PA) (Fig. 1a) incorporates arterial perfusion cannula configurations ranging from 9 to 17 french, an unique 21 french venous transseptal cannula, and a centrifugal bloodpump (Fig. 1b). Oxygenated blood from the patient's left atrium is supplied to the pump by the transseptal cannula and than returned to the patient's systemic circulation. The pump connects to a microprocessor-based controller that displays PTVA speed and flow. These parameters are controlled by adjustment of a single knob. The controller also provides automatic system monitoring and alarms indicating conditions that require action. The system is designed to deliver up to 4.5–5 L of blood flow per minute, depending on the size of the arterial cannulation and the filling conditions of the left atrium, whereas operating at a relatively low speed (7,500 RPM).

A standard transseptal puncture technique was used to gain access into the left atrium from the right femoral vein. Transseptal puncture was carried out by an experienced operator only. In all cases, an ileac angiography was performed before the placement of the perfusion catheter to delineate the arterial anatomy and size and to disclose eventual luminal obstructions. Details on the Tandemheart circulatory support and implementation are reported elsewhere [5]. Weaning from the Tandemheart was performed in a stepwise protocol, with progressive reduction of pump assist, by reducing pump speed from 7,500 to 3,500 rates per minute (Pump flow $\pm$400 mL), and adapted to the medical condition of each patient individually. The pump was not stopped until immediately before removal. The final removal decision was based on medical judgment.

### Anticoagulation

A constant flow (10 mL/hr) of heparinized infusate is maintained providing a localized concentration of heparin in the interior of the pump to obtain localized anticoagulation thereby minimizing systemic heparinization, the risk of bleeding and thrombus formation.

### Index Procedure and Concommitant Medications

The index coronary intervention was performed after Tandemheart PTVA implantation and functioning. The interventional strategy, including adjunctive therapies, is performed according to the concurrent guidelines using appropriate device(s). Angioplasty strategy, the use of periprocedural GPIIb/IIIa inhibitors, predilatation device, intravascular ultrasound guidance and the use of a vascular closure device were at the discretion of the operator. All patients were pretreated with aspirin

**TABLE I. Baseline Characteristics**

| Age | Sex | Length | Weigth | BSA | Previous MI | Previous stroke | Previous PCI | Hyper cholesterolemia/ statin use | Hypertension (SBP > 130 mm Hg) | DM-II | Clinical syndrome | Elective procedure |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 65 | Male | 179 | 83 | 2.2 | N | N | N | N | N | N | STEMI anterior (Late presentation) | SE |
| 71 | Male | 168 | 83 | 1.93 | Y | N | N | Y, atorvastatin 20 mg | Y | N | UA | Y |
| 74 | Male | 175 | 88 | 2.04 | Y | N | Y | Y, atorvastatin 20 mg | Y | N | UA/dyspnoe | Y |
| 54 | Male | 173 | 70 | 1.83 | Y | N | Y | Y, pravastatin 40 mg | Y | N | NSTEMI :VT Myocardial ischemia | Y |
| 46 | Female | 175 | 64 | 1.78 | N | N | N | N, simvastyatin 40 mg | Y | Y | UA | Y |
| 69 | Male | 175 | 75 | 1.9 | Y | N | Y | Y, atorvastatin 20 mg | Y | N | UA | SE |
| 55 | Male | 196 | 100 | 2.33 | Y | N | N | Y, rosuvastatin 10 mg | N | N | UA | Y |
| 60 | Male | 185 | 134 | 2.62 | Y | N | Y | Y, atorvastatin 10 mg | Y | Y | UA | Y |
| 89 | Female | 170 | 70 | 1.78 | N | TIA | Y | Y, simvastatin 10 mg | Y | N | Heart failure | Y |

| Extent of CAD | EF (%) | General anaesthesia | Inotropic support | Treated segments | Number of stents | Total stent length (mm) |
|---|---|---|---|---|---|---|
| LM trifurcation/RCA 100% | 20 | N | N | 5,6,7,11,12 | 4 | 55 |
| LM bifurcation, CFX, RCA 100% | 30 | N | N | 5,6,11 | 4 | 84 |
| LM,RCA, (LIMA-LAD) | >50% | Y | N | 1,2,3,4,5 | 6 | 97 |
| LM,CFX,LAD, RCA100%, | <20% | N | N | 5,6 | 2 | 48 |
| LM bifurcation, CFX, LAD, RCA | >50% | Y | N | 2,5,6,11 | 4 | 87 |
| LM bifurcation, LAD, RA, RCA 100% | 30–50% | N | N | 5,6,7,13,14 | 5 | 79 |
| LM, CFX 100%, LAD (segment 7), RCA 100% | 20–25% | N | Y | 5,7,8 | 4 | 111 |
| LM bifurcation, CFX-M1 70–90%, RCA | 30% | N | Y | 5,6,11 | 3 | 53 |
| LM, LAD, D1, CFX, CFX-M1, RCA | 20–25% | N | N | 5,6 | 2 | 31 |

Hypercholesterolemia, Low-density lipoprotein cholesterol >3.36 mmol/L; MI, myocardial infarction; DM-II, Type II diabetes mellitus; TIA, Transient ischemic attack; SBP, Systolic blood pressure; Clin. Syndr., Clinical syndrome at presentation; UA, unstable angina; A, angina; SE, semi elective (<24 hr after admission); CAD, coronary artery disease; LM, left main; CFX, circumflex coronary artery; RCA, right coronary artery; LAD, left anterior descendens coronary artery; RA, ramus angularis; D1, first diagonal branch (segment 9); CFX-M1, first lateral branch (segment 12).

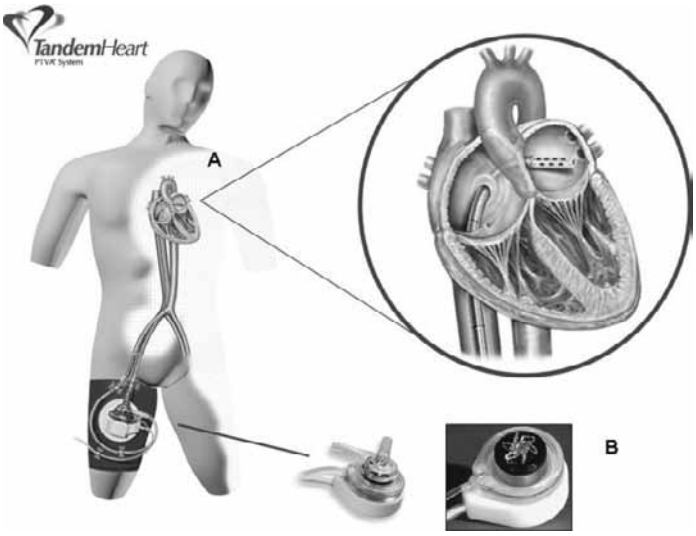


**Fig. 1. Tandemheart pVAD system (A). The left atrial cannula is positioned by transseptal approach (higher magnification at the right) and the pump itself (B) are shown. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]**

75–325 mg and a loading dose of clopidogrel 300–600 mg before the wire crossing the lesion per the site standard of care. Unfractionated heparin was started in the catheterization laboratory immediately following the transseptal puncture. During the index PCI procedure the patients received weight adjusted intravenous heparin to achieve an activated clotting time of >250 sec for the duration of the procedure. All patients were advised to maintain aspirin lifelong, and clopidogrel was prescribed for 6 months in both groups.

Standard intensive care was provided to each patient. The index procedure was performed under dissociated anesesthesia, sedation, and analgesia without intubation and ventilation, which was initiated in the catheterization suite. Patient sedation and intubation was only considered for clinical and/or comfort reasons. A balloon tipped pulmonary artery catheter was placed via the contra lateral femoral vein for hemodynamic monitoring purposes if clinically indicated. Cardiac output determinations were made using standard thermodilution techniques.

### Definitions

Total stent length was calculated as the sum of the length of each single stent placed to treat LMCA, provided at least one stent strut was in direct contact with the left main stem at visual estimation. Technical success was defined as the successful deployment of the stent(s) in the target lesion. Procedural success was defined as left main revascularization with a $\leq$30% residual diameter stenosis by visual analysis and the presence of thrombolysis in myocardial infarction (TIMI) flow grade 3.

The Tandemheart PTVA insertion time was defined as the time from providing of the Brockenbrough needle to the "full" heparinization following connection of the femoral cannula to the pump. The duration of support was defined as the time from "full" heparinization at time of connection to the pump till the removal of the femoral cannula.

### Data Collection and Follow-Up

All data relating to hospital admissions, procedures, and in-hospital outcomes were collected within the hospital recording network. Information regarding clinical status was collected at clinic visits and by telephone interview. At 6 months the clinical follow-up was 100%. Endpoints were measured in terms of the patient-oriented composite endpoint of all case death, myocardial infarction and any repeat revascularization procedures at 30 days and 6 months of follow-up. Patients with more than one event have been assigned

the highest rank event, according to the previous list. All deaths were considered to be of cardiac origin unless a noncardiac origin was established clinically or at autopsy. Myocardial infarction was diagnosed by an increase in the creatine kinase level to more than twice the upper normal limit and with an increased creatine kinase-MB fraction. Data analysis was performed with the approval of the institutional ethics committee.

### Statistical Analysis

Categorical variables are described as counts and percentages. Continuous variables are expressed as median and range or mean ± SD as appropriate. Pre- and post pumping hemodynamic variables were compared by paired Student's *t*-tests. Statistical significance was achieved at $P < 0.05$.

## RESULTS

### Baseline and Procedural Characteristics

The baseline characteristics of the patient population are shown in Table I. Nine patients were included in this series, 7 were male, the median (range) age was median 65 years (55–71), 2 (22.2%) were diabetics, 6 (66.7%) patients had a history of myocardial infarction (MI), 5 (55.5%) had had a previous PCI, and 1 (11.1%) had previously undergone CABG. The most common admission diagnosis was unstable angina (6, 66.6%), followed by nonfatal MI (2, 22.2%), and acute heart failure diagnosed in 1 patient (11.1%).

The patient risk in our series was mainly driven by renal function and the left ventricular systolic dysfunction (Table II). The median (range) calculated logistic EuroScore was 13.64 (7.46–29.67). The median (range) risk of mortality and morbidity or mortality calculated by the Mayo clinical risk score was 7 [6–8]. The median (range) syntax score was 43 (41–50). Figure 2 shows the calculated relative risk for future cardiovascular events according to the different risk scores tested and their interaction.

Detailed procedural and angiographic characteristics are shown in Table III. Elective PCIs comprised 77.7%, and emergent PCIs comprised 22.2% of procedures. Lesions were more frequently distal (55.5%) than ostial/shaft (44.4%). The median (range) total stent length was 79 mm (53–87), and median (range) the stents/patient ratio was 4 (3–4). All patients had multivessel treatment. More than half of the patients (55.5%) had an occluded right coronary artery. One patient had a simultaneous retrograde aortic revalving (CoreValve ReValving System®) procedure.

Implementation of circulatory support was successful in all patients. Median (range) time for TH® implantation was 27 min (24–30). The median (range) duration on circulatory assist was 93 min (50.4–102). The median (range) systemic arterial pressure (MBP) was 82 mm Hg (80–88) at baseline and 99 mm Hg (92–101) after pump functioning (*t*-testing). The median (range) support of the TH was 4.36 (3.40–5.54) L/min and the effective cardiac index was increased by (data limited to 4 patients). Two patients needed general anaesthesia.

The median (range) systemic blood pressure, pulse pressure, and heart rate pre-TH® implantation was: 82 (54–94), 60 (23–76), 63 (54–77); and at the time of the first balloon inflation: 99 (73–120), 30 (7–57), 66 (54–76).

### Clinical Course in Hospital and 6 Months and Overall Outcomes

Technical and procedural success of the index PCI was 100%. The TH (implantation procedure was uneventful in all patients. Access site complications occurred in 4 patients. A pseudoaneurysm was seen in 1 patient. After compression with a femoral compression system (FemoStop II Plus, RADI Medical Systems) and a mild reduction of the heparin dose, the pseudoaneurysm thrombosed. Another patient had a failure of the vascular preclosure device resulting in local bleeding. Surgical closure was then successfully performed. Two patients (22.2%) suffered major leg ischemia after (day 1 and 4) TH® removal and required surgical intervention to resolve limb ischemia. Both patients had pre-existing peripheral vascular disease and were treated with a 15 french arterial cannula. There were no perprocedural or in hospital death. The 6-month mortality rate was 11.1%. One patient died at 11 days after the index procedure, 4 days after a staged procedure (Target vessel, nontarget lesion). In total, 3 patients died during follow-up, 1 patient following a subacute stent thrombosis (Table IV: follow-up and MACE table).

## DISCUSSION

This is the largest series of assisted circulation using the TH during (semi-)elective PCI of the ULMCA in a very-high-risk, "no-surgical option," patient population. The main findings of this study are: (i) despite the attendant high procedural complexity procedural success was high; (ii) the cumulative in hospital and 6 months cardiac mortality compared favorable with the predicted risk; (iii) one patient suffered a definitive ST. (iiii) TH circulatory support could easily be implemented by an experienced operator. In terms of safety, access site complications remain an important hurdle

**TABLE II. Risk Scores**

| SYNTAX score | Mayo clinical risk score | EURO score (Standard) | EURO score (Logistic) | Age | Gender | Chronic pulmonary disease[a] | Extracardiac arteriopathy | Neurologic dysfunction[b] | Previous cardiac surgery | Serum creatinine: >200 m micromol/L | Active endocarditis |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 35 | 6.5 | 7 | 6.4 | 65 | M | N | N | N | N | 104 | N |
| 43 | 8.5 | 8 | 9.44 | 71 | M | N | N | N | N | 177 | N |
| 65 | 5 | 13 | 39.98 | 74 | M | N | N | N | Y | 170 | N |
| 41 | 8 | 5 | 4.48 | 54 | M | N | Y | N | N | 74 | N |
| 27 | 6 | 15 | 29.67 | 46 | F | N | Y | N | N | Dialysis, 966 | N |
| 59 | 8 | 9 | 14.68 | 69 | M | N | Y | N | N | 74 | N |
| 47.5 | 7 | 7 | 7.46 | 55 | M | N | N | N | N | NA | N |
| 41 | 6 | 9 | 13.64 | 60 | M | Y (COPD, fibrosis) | Y | N | N | 90 | N |
| 50 | 10 | 14 | 45.28 | 89 | F | N | N | Y | N | 93 | N |

| Critical preoperative state | Unstable angina | LVEF | MI <90days | PAPsyst >60 mm Hg | Emergency | Ao valve surgery | Mitrakl valve surgery | Reason to turn down for CABG |
|---|---|---|---|---|---|---|---|---|
| Y | STEMI | <20% | Y, STEMI | N | Y | N | N | Poor LV function |
| N | Y | 30% | N | N | N | N | MI2-3 | Poor LV function + mitral valve disfunction, Comorbid conditions |
| N | Y | >50% | N | N | N | N | N | Comorbid conditions |
| Y | Y | <20% | N | N | N | N | N | Poor LV function |
| N | N | >50% | N | N | N | N | N | No VG material |
| N | Y | 30% | Y, NSTEMI | N | N | N | N | Poor LV function, Comorbid conditions |
| N | Y | 20–25% | N | N | N | N | Y | Diffuse CAD, no option for landing with bypass |
| N | Y | <20% | N | N | N | N | N | Poor LV function, Pulmonary function |
| N | Acute HF | 20–25% | N | N | N | PAVI | N | Age, diffuse CAD, Ao valve disease |

LVEF, left ventricle ejection fraction (Estimated by Echocardiography); LV, left ventricle; NSTEMI, non-ST segment elevation myocardial infarctio; STEMI, ST-segment elevation myocardial infarction; VG, venous graft; PAVI, percutaneous aortic vallve replacement; MI, myocardial infarction; HF, heart failure.

[a]Long-term use of bronchodilators or steroids for lung disease.

[b]Severely affecting ambulation or day-to-day functioning.

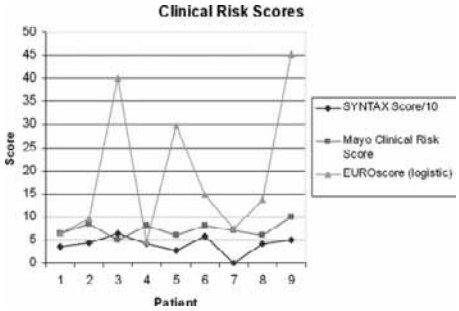


**Fig. 2. Clinical risk scores. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]**

in this specific patient population with a large atherosclerotic burden.

In this study, we only considered patients signed off by "the Heart-team" to be at "No-Option" for CABG due to comorbid clinical conditions. Whether catheter-based treatment of ULMCA should be strictly reserved for poor surgical candidates or offered with less restriction to patients known to be at low risk for future cardiac events is beyond the scope of this work and subject of ongoing research. The important role of a dedicated heart team for patient triage cannot be over emphasized. At all times the benefits of a specific (percutaneous) procedure should be weighed against the risks involved, taking into account alternative treatment strategies, the individual operators and overall institutions (interventional and intensive care team) experience [13]. As in this highly symptomatic patient subset, very high-risk procedures are sometimes inevitable because of the inherent risk of the underlying disease. Published estimates of risk for an individual patient may aid the operator in selecting or avoiding adjunctive pharmacotherapy or specific devices. Both LVEF, pretreatment angiographic criteria expressed by the Syntax score and specific anatomical characteristics of the LMCA lesion [3] may have great potential in this regard. They may allow to identify the patients at high likelihood of hemodynamic collapse, either during balloon inflation or with acute vessel closure.

The procedural success was 100% without any in hospital death. The 1 year overall MACE rate was acceptable. Survival at 6 months was 88.5%, as compared to a 89.5% in an "all comers" unprotected left-main population in our centre in the same time period [14]. Our completive results also compare favorable with the preprocedural median logistic EuroSCORE and to the Mayo Clinical Risk Score. These results,

**TABLE III. Procedural Characteristics**

| Insertion time (minutes) | Sheat type (French) | Time on support (Hours:minutes) | Pump flow (Max.) | MBP-pre | SBP/ DBP-pre | PP-Pre | Hr-pre | MBP-post | SBP/ DBP-pre | PP-post | Hr-post | PCWP-pre | PCWP-post | CI-pre | CI-post | Access site complication | Access site bleed | Closure device |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 43 | 17 | 2:35 | 3.41 | 94 | 135/67 | 67 | 73 | 101 | 135/84 | 51 | 71 | 20 | 18 | 1.7 | 3.3 | Y | Yes | Surgical |
| 27 | 15 | 1:21 | 3.831 | 54 | 85/40 | 45 | 63 | 73 | 81/65 | 16 | 54 | 8 | 3 | 2.7 | 3.12 | Yes acute ischemia right leg 4days following TH explant | N | Proscar |
| 30 | 14 | 77:56 | NA | 90 | 141/65 | 76 | 69 | 113 | 146/99 | 47 | 72 | 8 | 8 | 2.4 | 2.4 | N | N | FS |
| 24 | 17 | 5:15 | 4.01 | 82 | 116/67 | 49 | 68 | 99 | 117/97 | 20 | 76 | 13 | NA | NA | NA | N | N | Surgical |
| 25 | 15 | 2:50 | NA | 68 | 100/51 | 49 | 54 | 92 | 97/90 | 7 | 56 | 23 | 13 | 1.8 | 2.6 | Y loge syndrome right D1 post TH explant. Fasciotomia | N | Surgical |
| 30 | 17 | 2:20 | 4.361 | 88 | 132/63 | 69 | 60 | 99 | 123/85 | 38 | 63 | NA | NA | NA | NA | N | N | Prostar |
| 23 | 17 | 1:03 | 5.21 | 80 | 94/71 | 23 | 60 | 94.6 | 110/87 | 23 | 66 | NA | NA | NA | NA | Y, pseudoaneurysma Re | Y | Prostar |
| 20 | 17 | 1:24 | 4.71 | 82 | 128/60 | 68 | 60 | 84 | 122/65 | 57 | 61 | NA | NA | NA | NA | N | N | Prostar |
| 31 | 15 | 2:37 | 5.541 | 87 | 127/67 | 60 | 77 | 120 | 140/110 | 30 | 70 | NA | NA | NA | NA | N | N | Prostar |

MBP, mean systemic blood pressure; HR, heart rate; PCWP, pulmonary capilary wedge pressure; CI, cardiac index; PP, pulse pressure; FS, Femostop.

**TABLE IV. Follow-Up and MACE Table**

| Patient | Date TH PCI | Date first event | Survival 11/08 | MACE |
|---|---|---|---|---|
| 1 | 25/04/2006 | 19/09/2006 | 01/11/2008 | TLRischemia driven |
| 2 | 4/07/2006 | 16/07/2006 | 11/07/2006 ✝ | Death, TLR, AMI, Stent Thrombose |
| 3 | 23/04/2002 | 22/11/2002 LC | ✝ | Death |
| 4 | 31/01/2006 | | 01/11/2008 | No |
| 5 | 6/08/2002 | 28/01/2003 | 21/03/2007 ✝ | Death, TLR |
| 6 | 6/02/2008 | | 01/11/2008 | No |
| 7 | 5/02/2008 | | 01/11/2008 | No |
| 8 | 11/12/2007 | 30/06/2008 | 01/11/2008 | TLRischemia driven |
| 9 | 20/05/2008 | | 01/11/2008 | No |

LC, last medical control; TLR, target lesion revascularisation.

against the background of preserved periprocedural hemodynamics in this patient series, supports the hypothesis that TH support allows for a safe and optimal treatment technique.

As opposed to other modalities of percutaneous cardiopulmonary support (CPS) used in this indication, [15,16] the TandemHeart system keeps the patient's lungs as its own ventilator and may be used to support patients for a longer period of time without major haematological or pulmonary complications (up to 10 days in our experience) [7]. In our series, only two patients required general anaesthesia, the device was well tolerated. TH insertion requires transeptal puncture. Direct visualization of the interatrial septum by intracardiac ultrasound (AcuNav ICE, Siemens Medical Systems, Mountain View, CA) may have contributed to the safety and increased efficacy of this procedure [17,18]. The most important drawback of the technique may be the difficulty of cannula insertion. Substantial atherosclerotic changes in the peripheral vascular (PV) bed are most common in the group of coronary patients who most benefit from the effects of this device. Four patients in this limited patient series developed an access site complication. Two patients developed limb ischemia requesting a surgical intervention. A vascular preclosing device was used in most patients. In case of severe PV disease, surgical removal should be considered to allow for optimal local hemostasis and proper inspection of the cannulation site. A local compression or closure device may provide a valuable alternative given a clean puncture technique. Access site complications may be minimized by prior iliac angiography and by implementing a true percutaneous, ultrasound guided, puncture technique of the (common) femoral artery [5]. When necessary, the use of distal perfusion and antegrade cannulation of the superficial femoral artery may obviate peripheral vascular complications as well.

Important limitations of this study should be acknowledged. The results of this study are encouraging, but they cannot be conclusive. The present study is a single-center experience from a tertiary referral center and lacks the clear advantages of a multicenter randomized study. Another limitation is the length of clinical follow-up. Studies with larger sample sizes and more prolonged clinical follow-up are clearly in demand to confirm our findings.

## CONCLUSIONS

Assisted circulation using the TH during complex catheter based revascularization involving the ULMCA preserved hemodynamic stability, regardless of the intrinsic cardiac function, and may have contributed to a high procedural success. Circulatory assistance through TH insertion may be considered in patients undergoing high-risk PCI to stabilize hemodynamic conditions and/or avoid acute circulatory collapse during intervention. Whether TH may more effectively replace IABP in these relatively rare yet high risk procedures warrants further investigation.

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# CHAPTER 4.3

## Assisted Circulation using the Tandemheart, Percutaneous Transseptal Left Ventricular Assist Device, during Percutaneous Aortic Valve implantation: The Rotterdam experience.

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*EuroIntervention.* 2009;**5**:465-9. [**original research paper**]

EuroIntervention

# Assisted circulation using the Tandemheart®, percutaneous transseptal left ventricular assist device, during percutaneous aortic valve implantation: the Rotterdam experience

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*The authors have no conflict of interest to declare.*

**KEYWORDS**
*Heart-assist device, TandemHeart, valves, aortastenosis, valvuloplasty*

## Abstract

**Aims:** The morbidity and mortality of surgical aortic valve replacement are increased in elderly patients with multiple high risk comorbid conditions. Percutaneous prosthetic aortic valve replacement (PAVR) via the femoral arterial approach is feasible in selected patients, who are poor operative candidates, with satisfactory short term outcomes. It is conceivable that patients with poor LV function may benefit from periprocedural cardio-circulatory support. We evaluated the short-term safety and efficacy of using the TandemHeart® PTVA® System (p-LVAD) to deliver extracorporeal circulatory support in patients undergoing PAVR.

**Methods and results:** Between April 2006 and May 2007 the TandemHeart® was used in 10 patients (age: range 64-85, median 80) undergoing elective PAVR using the CoreValve™ Revalving System. The median (range) time for implementation of circulatory support was 32 (22-40) minutes. A pump flow up to 4.6 L/min was achieved. Systemic haemodynamics were maintained in all but one patient. The median (range) systemic arterial pressure (MBP) was 77 (67-89) mmHg at baseline and 76 (61-91) mmHg after pump functioning. A major systolic blood pressure drop (systolic blood pressure < 70 mmHg, pulse pressure < 10 mmHg, occurred in one patient due to PAVR related pericardial tamponade. Median (range) duration of support was 64 (60-93) minutes. Successful weaning was achieved in all patients. There was one in hospital death. Survival at 12 months was 90%, at 15 months 70%. Vascular access site complications were seen in two patients. One patient suffered a mild to moderate access site bleeding, one a local wound infection. There was no technical device failure.

**Conclusions:** The TandemHeart-PTVA® may provide a valuable safeguard during high risk PAVR procedures and enables precise delivery of the CoreValve prosthesis. The rate of device related cardiac and vascular complications was acceptable.

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## Introduction

Degenerative aortic stenosis (AS) is a frequent heart valve disease in Western countries, of which the prevalence steadily increases with age[1,2]. Open heart surgery with mechanical or bioprosthetic valve replacement is the reference standard therapeutic approach for patients with severe aortic valve disease, offering symptomatic relief and improving long-term survival in most patients. The Euro Heart Survey, however, revealed that one-third of elderly patients with severe, symptomatic AS are not referred or declined for surgery by the attending practitioner[2]. This is particularly the case for very elderly patients, patients with reduced left ventricular (LV) function and/or associated comorbid conditions. Since the prognosis of medically treated patients and those who underwent 'plain' balloon valvuloplasty is poor[3,4], a less invasive techniques for treatment of high-risk patients such as PAVR may be an alternative. The CoreValve Revalving™ System (Medtronic, Minneapolis, MN, USA) consists of a porcine valve mounted in a self expanding nitinol frame that is implanted by slowly pulling back a protective sheath. The implantation technique allows delicate and minute adjustments for correct valve positioning[5-7]. Initially, with the introduction of the PAVR technique, the clinical protocol recommended the use of mechanical circulatory support (MCS) during implantation to maintain adequate systemic circulation. This was realised by the use of femoro-femoral cardiopulmonary bypass (CBP).

To reduce the surgical trauma, to render PAVR truly percutaneous and to increase patient comfort, we started using the TandemHeart®, which is a Percutaneous Transseptal Left Ventricular Assist Device (PTVA®) system (CardiacAssist Inc., Pittsburgh, PA, USA) instead of CBP. This system allows for rapid implementation of circulatory support, delivering up to 4,5 litres of blood flow per minute, using standard interventional techniques in the catheterisation laboratory[8]. We report the Rotterdam single centre expertise with assisted circulation using the TandemHeart® PTVA System during PAVR. We performed a post hoc analysis of prospectively (on PAVR procedures[9]) collected data.

## Patients and methods

### Patients

From April 2006, the TandemHeart® percutaneous circulatory support was used in a series of 10 consecutive patients treated with the CoreValve Revalving™ System (CRS) in the Thoraxcentre, Erasmus University Medical Centre, Rotterdam (The Netherlands). Patients were considered for this analysis if a clinical follow-up of 12 months or more could be established.

Patients were considered for PAVR provided: 1) a symptomatic severe stenosis (valve area $< 1\ cm^2$, $0.6\ cm^2/m^2$ as by echocardiographic measure) of the native aortic valve, 2)[10,11] reflecting a high peri-operative risk and 3) a contraindication to surgery because of concomitant comorbid conditions assessed and agreed to by both an independent cardiologist and a senior cardiovascular surgeon. Exclusion criteria for the PAVR study protocol included: hypersensitivity or contraindication to aspirin; heparin; thiënopyridines; nitinol or contrast media that could not adequately pre-medicated; sepsis or active endocarditis; excessive femoral, iliac, or aortic atherosclerosis; calcification or tortuosity; aortic aneurysm; bleeding diathesis or coagulopathy. Any condition considered contraindicated to extracorporeal assistance. This study was approved by the local Medical Ethics Committee, and all patients and their closest relatives signed informed and written consent.

### Percutaneous valve implantation procedure

The technique of PAVR using the CoreValve™ Revalving System has been described in detail elsewhere.[6,7,8,22] In the present series of 10 patients, the 21 Fr revalving system was used in the first three patients, while the 18 Fr system was used in the remaining six patients. Vascular access, via the common iliac artery or common femoral artery, was obtained by surgical cut-down in four patients, and echo-guided vascular access was obtained in six with the use of vascular 'pre'-closing device (a 10 Fr Prostar XL). A 5 Fr pigtail was put in place via the left radial artery into the ascending aorta for pressure recording and angiography to guide valve positioning and assessment of the final result. Clinical and haemodynamic outcomes were assessed serially during the procedure. Valve implantation was performed under general anaesthesia in four and dissociated anaesthesia in six (sedation and analgesia, but no intubation and ventilation).

### The Tandemheart (insertion technique)

The Tandemheart®PTVA® (CardiacAssist, Pittsburgh, PA, USA) (Figure 1a) incorporates arterial perfusion cannula configurations ranging from 9 to 17 Fr, an unique 21 Fr venous transseptal cannula, and a centrifugal blood pump (Figure 1b). Oxygenated blood from the patient's left atrium is supplied to a centrifugal pump by the transseptal cannula and than returned to the patient's systemic circulation. The pump connects to a microprocessor-based controller that displays PTVA speed and flow. These parameters are controlled by adjustment of a single knob. A standard transseptal puncture technique, using an Inoue wire, was used to gain access into the left atrium from the right femoral vein. Transseptal puncture was carried out by an experienced operator only after clear delineation of the inter-atrial septum using ICE (Intra Cardiac Echocardiography, ACUNAV, Siemens, Germany). Details on the of the Tandemheart circulatory support and implementation are reported elsewhere[12]. At the moment

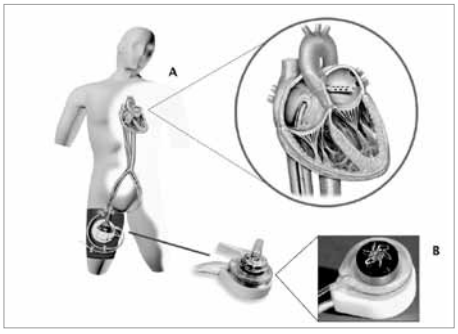


*Figure 1. The Tandemheart®PTVA® incorporates arterial perfusion cannulae, a 21 Fr venous transseptal cannula, and a centrifugal blood pump.*

of valve crossing with a straight Kimal wire, the Tandemheart was tuned down to a stand-by-mode. The stand-by-mode entails the reduction of the RPM to the lowest RPM value possible (± 3500 RPM) resulting in a minor to insignificant circulatory support. A fully active pump may reduce the already impaired leaflet motion, and enhance the difficulty of crossing the stenotic valve. At the moment of balloon valvuloplasty and CoreValve™ positioning and placement, the pump was returned to full circulatory support. Weaning from the Tandemheart was performed in a stepwise protocol, with progressive reduction of pump assist, by reducing pump speed from 7500 to 3500 rates per minute (Pump flow +/- 400 ml/min), and adapted to the medical condition of each patient individually. The pump was not stopped until immediately before removal. The final removal decision was based on medical judgement.

### Anticoagulation

A constant flow (900 units/hr.) of heparinised infusate is maintained, thus providing a localised concentration of heparin in the interior of the pump in order to obtain localised anti-coagulation, thereby minimising systemic heparinisation, the risk of bleeding and thrombus formation. During the PAVR, the patients received weight adjusted intravenous heparin to achieve an activated clotting time of 300 to 350 seconds for the duration of the procedure. Post-implantation, a dual antiplatelet strategy of aspirin 75-160 mg and Plavix 75 mg, each daily, for six months, followed by aspirin 75-160 mg, indefinitely, was prescribed.

## Statistical analysis

Categorical variables are described as counts and percentages. Continuous variables are expressed as median and quartiles. Statistical significance was achieved at $p<0.05$. The insertion time was defined as the time from providing of the transseptal puncture needle to the 'full' heparinisation following connection of the femoral cannula to the pump. The duration of support was defined as the time from 'full' heparinisation at time of connection to the pump till the removal of the femoral cannula. Statistical analysis was performed by Cardialysis, Rotterdam (The Netherlands) with SAS 8.2 software (SAS Institute Inc, Cary, NC, USA).

## Results

From April 2006 to May 2007, 10 symptomatic patients (five men, five women; median age 80 years; range 64-82) had a PAVR supported by the Tandemheart®. Baseline characteristics are listed in Table 1. The median (range) calculated logistic EuroSCORE was 22.59 (range 21.56 to 26.40).

The left ventricular systolic function (echocardiographic estimated ejection fraction, EF) was reported good (EF > 50%) in six, moderate (EF 30-50%) in two and poor (EF < 30%) in another two patients. The patient risk in our series was mainly driven by age, renal function and EF (Table 1).

Implementation of circulatory support was successful in all patients. Median (range) time for TH® implantation was 32 (22-40) minutes. The median (range) duration on circulatory assist was 64 (60-93) minutes. The median (range) systemic arterial pressure (MBP) was 77 (67-89) mmHg at baseline and 76 (61-91) mmHg after pump functioning. A major systolic blood pressure drop (systolic blood pressure < 70 mmHg, pulse pressure < 10 mmHg, occurred in one patient due to pericardial tamponade following crossing of the valve with a straight Kimal wire. A needle pericardiocentesis was needed. A valve prosthesis was nevertheless correctly implanted. The patient died at day six due to severe sepsis and end-organ (renal) failure. An iliac artery rupture occurred in one patient during revalving. The procedure was aborted, the TandemHeart® was weaned and the patient was sent for surgical vascular repair and had a further uneventful hospital recovery. The latter patient was excluded from further outcome analysis in our series. Overall procedural success was 78% (Table 2). The final aortic regurgitation rate was < 2 in all patients. There was no neurologic event nor any need for permanent pacing reported in this patient series. The median (range) clinical follow up was 585 days (405-628). As already indicated, there was one in hospital death at eight days following PAVR. Survival at 12 months was 90%, at 15 months 70%. Mild access bleeding occurred in one patient, local wound infection in another. Local homoeostases was provided by a vascular pre-closure device (Prostar®XL) in both these patients.

## Discussion

This is the largest report investigating the haemodynamics and outcomes of patients undergoing PAVR with the Tandemheart. The main results of this study can be summarised as follows: The TandemHeart® PTVA® System could easily and quickly be implemented by an experienced operator using intracardiac echocardiography, the procedure and Tandemheart related complications were low. The Tandemheart provided a valuable

**Table 1. Baseline patient characteristics.**

| Age (Years) | Length (Cm) | Weight (Kg) | BSA (m²) | Sex | Previous MI | Previous CABG | Previous PCI | DM-II | Serum creatinine >200 umol/L | EF (%) | EuroSCORE logistic | Reason to turn down for surgery |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 85 | 175 | 53 | 1,64 | male | Y | N | Y | N | N | > 50 | 21,6 | Age |
| 75 | 168 | 57 | 1,64 | male | N | N | N | N | N | > 50% | 11,66 | Porcelain aorta |
| 72 | 160 | 83 | 1,86 | female | Y | N | Y | Y | N | 30-50% | 23,92 | Severe lung disease |
| 80 | 162 | 53 | 1,55 | female | N | N | N | N | N | > 50% | 21,56 | Age, mental status |
| 78 | 168 | 78 | 1,88 | male | Y | Y | N | Y | Y | < 30% | 79,99 | Age, LV-EF, concomitant disease |
| 82 | 164 | 58 | 1,63 | female | N | N | N | N | Y | > 50 | 37,61 | Age, concomitant disease |
| 64 | 173 | 78 | 1,92 | male | N | Y | Y | Y | Y | < 30% | 22,59 | Previous CABG, LV-EF, critical condition |
| 80 | 167 | 90 | 1,99 | female | N | Y | Y | Y | N | > 50% | 19,2 | Age, previous CABG |
| 79 | 158 | 73 | 1,75 | female | N | N | N | N | N | > 50% | 26,4 | Severe lung disease |

BSA: body surface area; MI: myocardial infarction; LV-EF: left ventricle ejection fraction; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; EF: ejection fraction; DM-II: diabetes mellitus

**Table 2. Procedural characteristics.**

| Insertion time (min) | Sheath type (Fr) | Duration of support (min) | MBPpre (mmHg) | | MBPpost (mmHg) | | Pump Flow | TandemHeart access site complication | Access site bleed | Closure device | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 40 | 17 | 66 | 95 | 136/95 | 61 | 78/50 | NA | N | N | surgery | 26 months |
| 40 | 12 | 152 | 52 | 93/29 | 85 | 127/59 | 3,3 | N | N | perclose | (13 months*) |
| 32 | 17 | 150 | 76 | 142/82 | 95 | 145/70 | 2,95 | Y, infection | N | perclose | 21 months |
| 29 | 17 | 60 | 85 | 120/67 | 63 | 133/28 | 3,8 | N | N | prostar | 21 months |
| 22 | 17 | 64 | 83 | 123/62 | 71 | 122/71 | 4,07 | N | N | surgery | 14 months |
| 16 | 17 | 61 | 76 | 123/49 | 63 | 75/59 | 3,8 | N | N | prostar | (8 days*) |
| 19 | 17 | 93 | 66 | 97/48 | 60 | 107/41 | 4,3 | N | N | surgery | 20 months |
| 33 | 17 | 54 | 78 | 122/55 | 77 | 114/56 | 3,9 | N | N | perclose | 20 months |
| 40 | 17 | 54 | 68 | 98/57 | 93 | 126/77 | 4,6 | N | N | prostar | (1 3months*) |

MBPpre: mean systemic blood pressure (baseline); MBPpost: mean systemic blood pressure (Tandemheart on), post-percutaneous balloon valvuloplasty; *: patient died

safeguard during PAVR and allowed for precise positioning of the CoreValve prosthesis in a high risk population. The one year mortality in this high risk patient population was relatively low. Vascular access was performed in a "true percutaneous fashion" in the majority of patients with the aid of vascular 'pre'-closing device. An ultrasound-guided transseptal puncture technique, integrating different imaging modalities available in the catheterisation suite, intracardiac echocardiography (AcuNav ICE, Siemens Medical Systems, Mountain View, CA, USA), was tested and implemented in this patient series may provide excellent therapeutic applications in other, 'complex' anatomical settings.

Transvascular, retrograde implantation of aortic heart valves is an emerging and promising technology that may benefit patients with high risk features for surgery. The experience with these systems continuous to grow, with leading centres and investigators contributing meaningful information toward the application and development of the latest technologies. Device and procedural enhancements are required to assure reliable and safe prosthesis delivery, positioning, deployment, anchoring, function and durability. We introduced the concept of 'stand-by' circulatory support during native valve crossing and re-activation during correct CoreValve™ positioning. The latter is crucial, not only for its proper function but also in respect to mitral valve function and preservation of coronary flow[13,14]. Cardiac motion and (trans-) aortic flow may impede precise positioning and expansion of the valve.

Also during balloon valvuloplasty, prior to device placement, we prefer MCS (mechanical circulatory support) over rapid ventricular pacing (RVP) of the right ventricle as advocated by other operators[5]. In case of adequate capture burst pacing at a rate of 220 $min^{-1}$ will sufficiently lowers systemic blood pressure and (trans-) aortic flow but only provides a limited time window to position and expand the stent without any room for adjustments. RVP might obliterate the left ventricular outflow track and make positioning of the valve impossible. Moreover, rapid ventricular pacing, may induce asystole or malignant ventricular arrhythmia, which occasionally may lead to refractory haemodynamic collapse, especially in patients with structural heart disease as result of age or long lasting pressure overload[15,16]. MCS allows titration to the haemodynamic needs of individual patient and the stage of the procedure. It may reduce the risk of global ischaemia and death in a very high risk patient population.

For reasons of logistics, safety and efficacy, we prefer the TandemHeart® PTVA® System to deliver extracorporeal circulatory support to provide a preserved right ventricular and pulmonary function, rather than full CPB or related systems. However, this requires transseptal puncture technique. Direct visualisation of the inter-atrial septum by intracardiac ultrasound may improve safety and increase efficacy of this procedure[17,18]. In experienced hands, circulatory support up to 4.5 l/min. can be provided in less than 30 minutes. Centrifugal flow provides for ease of set-up and operation (no synchronisation) by the cardiology-intervention team without requiring the assistance of a full trained perfusionist. The flow rates provided by the device might even be sufficient to prevent, and even reverse, organ dysfunction in cardiogenic shock patients[19]. As opposed to other modalities of percutaneous circulatory support (CPS) used in this indication[20,21], the Tandemheart system keeps the patients lungs as its own ventilator, and may be used to support patients for a longer period of time without major haematological or pulmonary complications or haemolysis[12]. The device was well tolerated by the awake patient. No adverse effects were observed during the use of the Tandemheart other than vascular access site complications in two patients (minor bleeding, n=1; local wound infection, n=1). It is unclear whether this was related to the extra vascular access needed for the p-LVAD, the PAVR or the percutaneous closure of the femoral vessels. The device was considered lifesaving in one of our patients at the moment of a PAVR procedure related acute cardiac tamponade. The preload to the left atrium, and the pump, at that time was preserved by volume loading and increasing the heart rate. A needle pericardiocentesis was requested. Survival at one year in our series was 90%, as compared to 87% for the overall patients treated with AVR and 62% for the patients treated with PAVR in our centre in the same time period[22]. These competitive results compare favourably with the pre-procedural median logistic EuroSCORE, and even to surgical reports of high risk patients undergoing AVR[23,24].

Several important limitations of this study should be acknowledged. First, the present investigation was performed at a single experienced centre; a multicentre study is required to more fully understand the generalisability of the present results. As to this time of development, in most patients PAVR is feasible without CPS. However, the Tandemheart should still be considered in some high-risk patients, particularly in those who present with acute heart failure and/or that need concomitant (high-risk) PCI. Even in patients with combined valvular

and complex coronary artery disease, those that are poor candidates for PAVR, the Tandemheart may fit into a hybrid treatment approach[25]. More detailed haemodynamic studies may help to identify those patients that potentially benefit the most of assisted circulation during aortic revalving procedures. At all times the haemodynamic benefit related to implementation Tandemheart® support should be weighted against potential risk involved, with a special focus on risks related to placement of the transseptal and the arterial cannula. In analogy with the literature, we used the logistic EuroSCORE for perioperative risk calculation in PAVR. However, the logistic EuroSCORE might overestimate mortality risk in this patient group. It may be clear that in the future that more appropriate risk models will be needed.

## Conclusion

The elective use of the Tandemheart for circulatory support during PAVI procedures preserved haemodynamic stability in our patients, regardless of the intrinsic cardiac function, and allowed for a precise delivery of the self-expanding, nitinol framed, CoreValve prosthesis.

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# CHAPTER 4.4

## Use of the Impella Recover LP 2.5 left ventricular assist device during high risk percutaneous coronary interventions; clinical and hemodynamic findings

Valgimigly M, Steendijk P, Serruys PW, Vranckx P, Boosma F, Onderwater E, Vaina S, Lighthart M, Mc Fadden E, van der Ent M, de Jaegere P, Serruys P.

*EuroIntervention* 2006, **1**: 91-100. [**original research paper**]

EuroIntervention

# Use of Impella Recover® LP 2.5 left ventricular assist device during high-risk percutaneous coronary interventions; clinical, haemodynamic and biochemical findings

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*None of the authors have declared any conflict of interest*

**KEYWORDS**
*Left ventricular assist device, high-risk percutaneous coronary intervention, pressure - volume loop*

## Abstract

**Aim:** To investigate in terms of clinical, haemodynamic and biochemical profile the safety and efficacy of the Impella Recover® LP 2.5 left ventricular assist device during elective high risk percutaneous coronary interventions (HR-PCI).

**Methods and results:** Ten out of twelve patients were initially enrolled to receive PCI supported by the Impella catheter; eight underwent pressure-volume (PV) loop analysis while one patient was monitored by intra-cardiac echocardiographic. Free haemoglobin (fHb), B-type natriuretic pepetide, catecholamines, aldosterone, angiotensin II, and endothelin were assessed before, every 40 minutes as average during the procedure and at 3, 12, 24 and 48 hours after intervention. The Impella catheter was used for 144±88 min [median (IQR) 108 (85-198)], and was removed immediately after the procedure in all but one patients. In 6, 3 and 2 patients, fHb levels increased above 1, 5 and 10 times the upper limit of normal (ULN), respectively. No significant effect was found on the tested biomarkers in Impella-supported procedures. The PV analysis showed the occurrence of an acute volume increase in the majority of patients immediately after Impella insertion that tended to persist even at maximal pump speed. This was confirmed by the intracardiac echocardiography that was performed in one patient.

**Conclusions:** Our data, although preliminary due to the limited sample size, does not encourage the routine use of Impella Recover® LP 2.5 in HR-PCI. Additional studies are required to confirm and elucidate the mechanisms responsible for the acute LV volume loading and to quantify the degree of haemolysis induced by the pump in a broader set of patients.

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## Introduction

The need for haemodynamic support in high risk percutaneous interventions (HR-PCI) remains widely debated and controversial. It is well recognized that elective HR-PCI can be safely performed without percutaneous cardiopulmonary support or on intra-aortic balloon pump (IABP) in most circumstances. However, in patients with a borderline haemodynamic status, ongoing ischaemia or cardiogenic shock, insertion of an IABP just before coronary instrumentation has been associated with improved outcomes[1,2].

In view of the lack of prospective randomized data, the recently published ACC/AHA/SCAI PCI guidelines recommend the use of cardiopulmonary support for patients only at the extreme end of the spectrum of haemodynamic compromise, such as those patients with extremely depressed left ventricular function or patients with cardiogenic shock[3]. Therefore the decision to proceed with IABP or other devices before percutaneous coronary intervention (PCI) remains a clinical judgement made by the physician based on the high-risk characteristics of coronary anatomy and the overall status of the patient[3-5]. The limited effectiveness of actual support and device-related complications have so far hampered a more widespread use of these devices in our daily practice.

The Impella Recover® LP 2.5 left ventricular assist device (LVAD) (ABIOMED® - Impella CardioSystems GmbH, Aachen, Germany) is a catheter-based miniaturized rotary blood pump (4 mm -12Fr- in outer diameter), that is placed retrograde through the aortic valve and aspirates blood from the LV cavity and expels it in the ascending aorta. Under clinical conditions the pump provides up to 2.5 L/min at its maximal rotational speed. The device is mounted on a 9 Fr pigtail catheter, giving the advantage of percutaneous insertion via a 13 Fr femoral sheath (www.impella.com). We recently reported the case of a single patient with severe LV impairment receiving an Impella-supported coronary intervention. Twelve patients have been considered subsequently for Impella-supported elective HR-PCI as part of a single-centre, investigator-driven protocol. Our complete results, in terms of clinical, haemodynamic and biochemical findings, are presented here.

## Methods

### Patients

Appropriate candidates for this clinical investigation were adult patients of either gender with stable or unstable angina pectoris and a clinical indication for percutaneous coronary revascularisation. In addition, the patients had to have at least one coronary artery stenosis that was amenable to angioplasty as well as left ventricular ejection fraction (LVEF) < 30%, or an angioplasty target vessel supplying > 50% of the viable myocardium, or combined left main and right coronary revascularization or complex lesion(s) in the last remaining patent artery, or refusal of surgical standby because of contraindications to cardiopulmonary bypass. All patients in this study provided written informed consent. The protocol received approval by our local Ethics Committee on Human Research.

### Haemodynamic measurements

A 7 Fr combined pressure-conductance catheter was introduced before positioning of the Impella via the left femoral artery and placed along the long axis of the LV. The catheter was connected to a Cardiac Function Lab (CD Leycom, Zoetermeer, the Netherlands) for online display and acquisition of LV pressure-volume loops. The conductance catheter was calibrated using thermodilution and hypertonic saline dilution, as previously described[6]. Cardiac output was measured by thermodilution catheter (COtd) and by multiplying stroke volume as measured by conductance catheter by heart rate (COlv). The difference between COlv and COtd is mainly due to activation of the Impella pump. The baseline ($T_0$) haemodynamic data was acquired subsequently. Immediately after Impella catheter positioning the minimum level of pump speed [i.e. number of rotations per minutes (rpm)] expected to compensate the spontaneous backflow inside the pump cannula based on the actual pressure gradient between the aorta and LV during diastole was set and all haemodynamic measurements were repeated ($T_1$). The same acquisition scheme was finally performed ($T_2$) after setting the pump at its maximum level of activation (i.e. 50/52,000 rpm), unless suction was detected at console inspection.

Since pump flow is linearly related to motor current, suction was identified as a reduction in motor current at constant level of pump activation. In such cases, the highest pump speed at which no suction occurred was selected for the T2 measurements. In all cases, technical assistance provided by the producing company (ABIOMED® - Impella CardioSystems GmbH, Aachen, Germany) was available to check for the correct positioning and functioning of the Impella device. After obtaining haemodynamic measurements at different levels of pump activation, the procedure was started with active Impella support. In one patient (#8) all haemodynamic measurements were performed at the end of intervention while the baseline ($T_0$) was obtained immediately after Impella catheter removal.

### Intracardiac echocardiographic examination

One patient in whom no pressure-conductance catheter was introduced, underwent intracardiac echocardiographic examination through the AcuNav catheter (Siemens Corp. Germany) inserted in the right ventricle. After obtaining a stable short axis view at the mitral valve papillary muscles level, the baseline LV area was quantified. After Impella catheter insertion, the same echocardiographic measurements were repeated at 35,000, 43,000 and 50,000 rpm. Special care was taken to ensure a stable position of the AcuNav catheter during the whole acquisition process.

### Biochemical measurements

**Free haemoglobin (fHb):** Whole blood was centrifuged, plasma and buffy coat removed and red cell layer washed several times with saline (pH: 7.30) until the supernatant was negative for protein. The resting solution was centrifuged at 1650xg. The stock haemoglobin solution was prepared by diluting the supernatant with Sørensen phosphate buffer (pH: 7.40; M/15) to a concentration of 30 mg per 100 ml. The exact concentration was measured by a photometer that had been standardized for haemoglobin by iron and oxygen-capacity determinants, as previously described[7]. The upper limit of normal reference for fHb was 10 µmol/L.

**Biomarkers:** Blood (2-3 ml) was collected in chilled heparinized tubes containing 3 mg. of glutathione and centrifuged within 15 min

at 4°C (15 min, 3000 x g). Plasma was stored at –70°C. Determination of catecholamines was done by HPLC with fluorimetric detection.[8] Blood for BNP, endothelin and aldosterone measurement was collected in EDTA-tubes; the plasma was stored at –70°C after preparation. BNP was measured by a commercially available immunoradiometric method (Shionoria, Osaka, Japan). Endothelin was measured using a QuantiGlo immunoassay kit from R&D Systems, Abingdon, UK. Aldosterone was measured with a commercially available radioimmunoassay kit (Coat-A-Count, Diagnostic Products Corporation, Los Angeles, CA, USA). For angiotensin II determination blood was collected in chilled tubes containing an inhibitor solution of EDTA, Remikiren and Lisinopril. Determination was performed by Seppak extraction and radioimmunoassay as previously described.[9]

### Statistical analysis

Values are expressed as mean±SD or median and interquartile range (IQR) as appropriate. The effect of Impella-supported intervention on the parameters of interest (i.e. haemodynamic variables and biochemical measurements) was investigated by the use of ANOVA for repeated measures and *Post hoc* comparisons were performed by Tukey's Honest Significance Difference test where appropriate. All statistical tests were 2-tailed. Probability was considered significant at a level of <0.05. Statistical analysis was performed using Statistica 6.1 Software (Statsoft Inc.).

## Results

12 patients were enrolled in the protocol from June 2004 to April 2005. In Patient#4, the sheath of the Impella catheter could not be introduced due to an iatrogenic dissection of the left femoral artery which occurred during arterial access. Similarly, patient#7 underwent treatment without Impella support due to unavailability of the LVAD catheter at the time of the procedure. Thus, 10 patients undergoing intervention supported by the Impella catheter were finally included in the present study. Their baseline and procedural characteristics are summarized in Tables 1 and 2. The overall average left ventricular ejection fraction (LVEF) was below 40%, while LVEF was less than 30% in 6 patients. All patients had experienced a previous myocardial infarction that had involved the anterior wall in 7 patients. Four patients (40%) had a history of symptomatic heart failure, eight (80%) were at high surgical risk according to the EuroSCORE and 5 (50%) patients had been previously refused for cardiac surgery. One patient (#8) with an occluded right coronary artery underwent treatment for a diffusely diseased venous-jump graft anastomosed to the left anterior descending and circumflex arteries, while all others received treatment of the native coronary system, including two patients who underwent treatment for an unprotected distal left main stenosis. On average, there were 2.2 lesions per patient, the majority of which were C-type according to the modified AHA lesions classifications; 3.6 stents per patient were implanted with a total stent length of more than 75 mm.

The positioning of the Impella was uncomplicated in all patients except two, in whom a second attempt to re-position the catheter was needed due to difficulties in removing the guide-wire after the initial positioning of the Impella catheter.

**Table 1. Baseline characteristics**

| Variables | Mean±SD |
|---|---|
| Age (yrs) | 62±10 |
| Males (%) | 8 (80) |
| Body Mass Index (kg/m$^2$) | 28±3 |
| Diabetes n.(%) | 1 (10) |
| Hypertension n.(%) | 7 (70) |
| Hypercholesterolaemia n.(%) | 5 (50) |
| Current Smokers n.(%) | 3 (30) |
| Previous Smokers n. (%) | 3 (30) |
| Family history n.(%) | 3 (30) |
| Creatinine (µmol/L) | 115±56 |
| LV Ejection Fraction (%)* | 37±16 |
| LV Ejection Fraction <40% | 8 (80) |
| LV Ejection Fraction <30% | 6 (60) |
| End diastolic volumes (ml) | 188±44 |
| End systolic volumes (ml) | 125±50 |
| MEDICAL HISTORY N.(%) | |
| PCI | 1 (10) |
| CABG | 2 (20) |
| Myocardial Infarction | 10 (100) |
| Anterior MI | 7 (70) |
| Renal Failure | 5 (50) |
| Heart failure | 4 (40) |
| Peripheral Arterial Disease | 3(30) |
| INDICATION TO REVASCULARISATION | |
| Stable Angina n.(%) | 4 (40) |
| Unstable Angina n.(%) | 4 (40) |
| Myocardial viability n.(%) | 1 (10) |
| Recent cardiac arrest n.(%) | 1 (10) |
| EuroSCORE | 7±3 |
| EuroSCORE >5 n.(%) | 8 (80) |
| Patients refused by surgeon n.(%) | 5 (50) |

**Table 2. Procedural characteristics**

| Variables | Mean±SD |
|---|---|
| | Patients=10 Lesions=22 |
| Native vessel with stenosis, n.(%) | |
| LMCA | 4 (40) |
| LAD | 0 (90) |
| CFX | 7 (70) |
| RCA | 7 (70) |
| Treated Vessel | |
| LMCA | 2 (20) |
| LAD | 6 (60) |
| CFX | 4 (40) |
| RCA | 3 (30) |
| Venous Graft | 1 (10) |
| Patients receiving 2-vessel intervention | 4 (44) |
| Patients receiving 3-vessel intervention | 2 (20) |
| Treated lesions | 2.2±1 |
| > 2 | 3 (30) |
| Type A | 0.18±0.6 |
| Type B1 | 0.27±0.5 |
| Type B2 | 0.5±0.5 |
| Type C | 1.1±0.9 |
| Number of implanted stents | 3.6±1.8 |
| Maximal pressure of stent deployment | 19±3 |
| Total stent length per patient (mm) | 78±35 |
| Moderate to severely calcified lesions | 16 (73) |
| Bifurcated lesions | 6 (27) |
| Bifurcation stenting | 4 (18) |

The duration of LVAD support was 144±88 min (median (range) [IQR]: 108 (60-352) [85-198]); in one patient the Impella was left in place after coronary intervention, while in the other 9 patients it was removed at the end of the procedure.

In patient #8, while receiving intervention in the only remaining open vessel, the arterial pressure remained above 90 mmHg even during a transient (approximately 25 seconds) episode of no-reflow which followed stent expansion (Figure 1). In half of the patients, the maximum level of pump activation (i.e. around 50,000 rpm) could not be maintained during the procedure due to the presence of a suction effect that disappeared in all cases after decreasing the rotational speed to approximately 40,000 rpm.

Groin haemostasis was obtained by manual compression with/without Femostop® in 4 patients, with 10 french Prostar XL 10® in 2 patients, with a single 8 french Angioseal® in 2 patients, with two Angioseals in parallel (one 6 french and one 8 french) in one patient, and through a surgical percutaneous closure in one case. Three patients developed major groin haematoma at the site of Impella insertion. Four patients required red blood cells transfusion of two or more units due to substantial blood loss during and/or after the procedure.

## Impact of Impella on haemolysis

Levels of fHb before, during and after PCI assisted by the Impella catheter are shown in Figure 2. Overall, 6 (60%) patients showed fHb levels beyond the upper limit of normal (red line), while 5 patients had persistent fHb elevation in two or more consecutive samples. In the patient in whom the Impella was left in place after the procedure, the fHb peak occurred at the end of the procedure and not at the time of Impella removal. Similarly, in the patient who showed the highest levels of haemolysis, the peak of fHb (approximately 14 times the upper limit of normal) occurred 30 minutes before Impella removal. On the other hand, in one patient, fHb peaked 3 hours after removal of the Impella. In all of the other patients (n=7) fHb level peaked at the time of Impella removal.

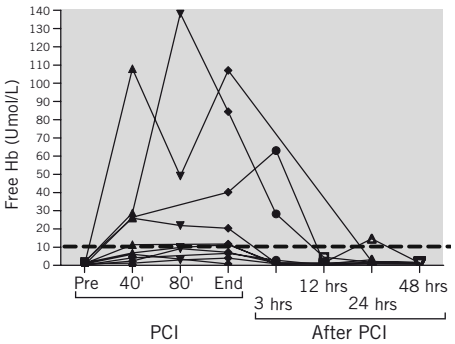


*Figure 2. Free haemoglobin (Hb) levels in relation to timing of intervention (PCI). The red line represents the upper limit of normality of the tested parameter according to the employed photometer test.*

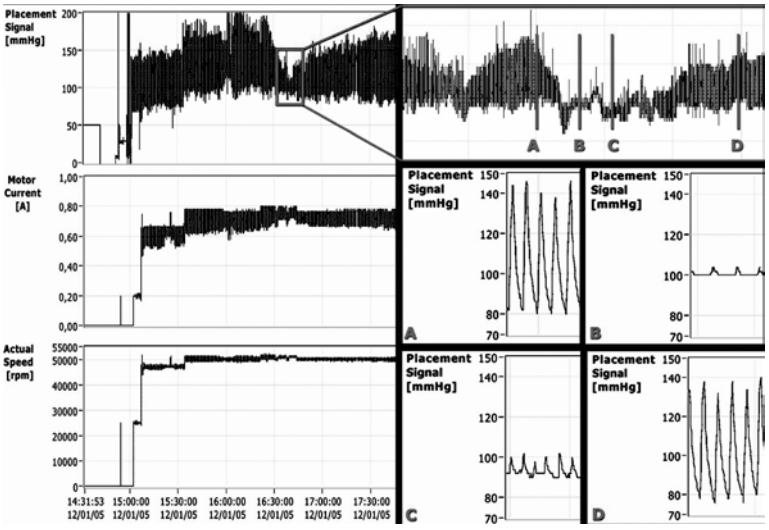


*Figure 1. Aortic pressure (mmHg) signal recorded by a micromanometer positioned near the outlet of the Impella catheter), used for catheter positioning and Impella actual motor current (A) and speed (rpm) during intervention in patient#8. In the top right corner, a magnification of the aortic pressure at the time of a no-reflow phenomenon while treating a graft lesion is shown. Panel A and D: Aortic pressure before and after the occurrence of no-reflow phenomenon. Panel B and C: Aortic pressure during no-reflow phenomenon showing almost absent (especially in figure 2) systo-diastolic excursions as expression of transient depression of left ventricular pumping activity.*

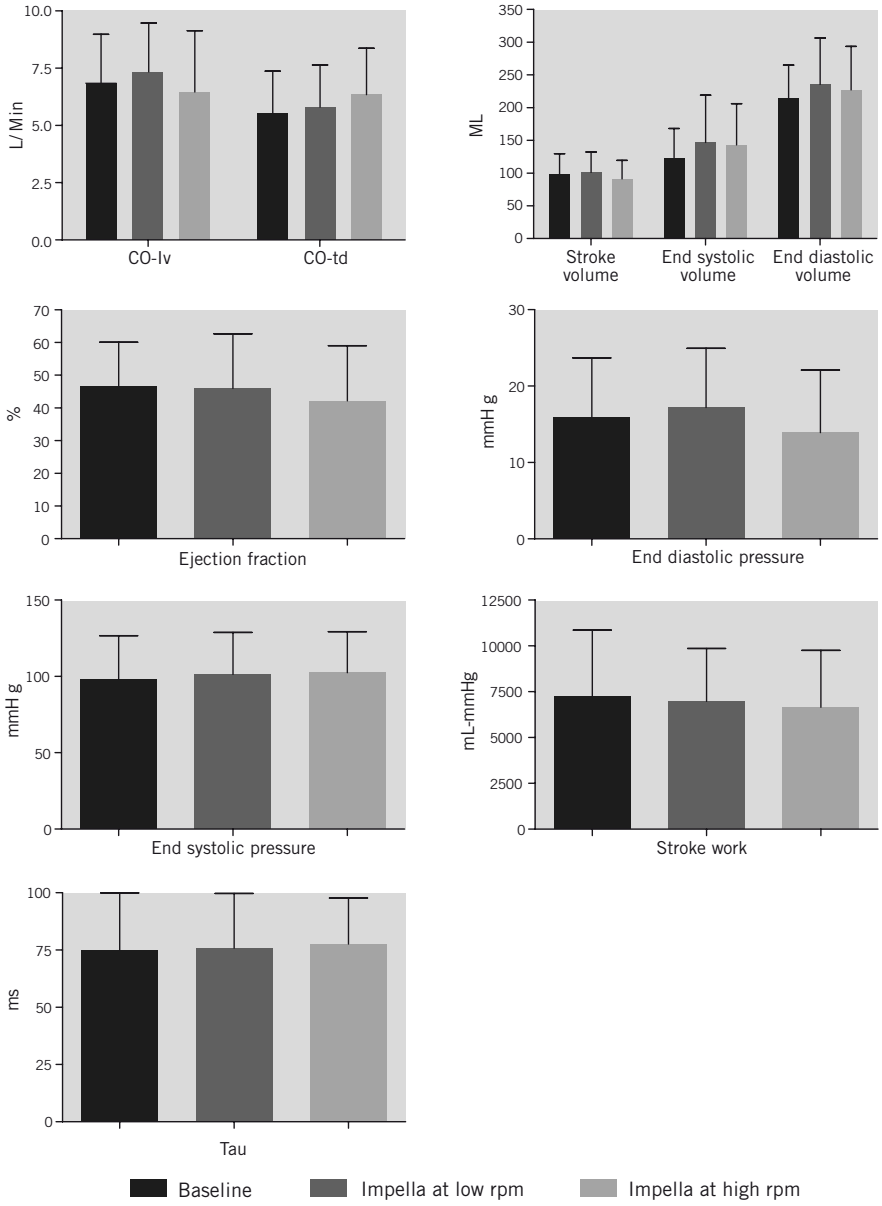


*Figure 3. Haemodynamic variables recorded through the conductance catheter or the thermodilution catheter according to Fick's technique before (baseline), or when the Impella catheter in place during a minimal or maximal level of activation (rpm). COtd: systemic cardiac output measured by thermodilution catheter; COIv: cardiac output according to left ventricle stroke volume as measured by the conductance catheter.*

## Haemodynamic effects of the Impella pump

In the first consecutive nine patients enrolled a 7-Fr combined pressure-conductance catheter was introduced via the left femoral artery and placed along the long axis of the left ventricle directly before positioning of the Impella catheter (8 patients) or immediately after intervention (1 patient, #8). Pressure recordings were judged to be of high quality in all patients included, while in one case (#11) volume-based parameters had to be discarded due to the presence of multiple and diffuse artefacts. There was no significant effect on any of the studied haemodynamic parameters with regards to Impella pump insertion and activation except for end diastolic pressure ($p<0.01$), which showed a slight increase at T1 (17±9 mmHg vs. 15±8 mmHg at T0) followed by a decrease soon after the Impella was maximally activated (13±8 mmHg at T2). The left ventricular cardiac output, stroke volume, end-systolic and end-diastolic volumes) tended to increase when the Impella catheter was inserted and activated at low rpm at T1 -this level of activation was expected to compensate backflow inside the cannula caused by the pressure gradient between aorta and left ventricle during diastole-, followed by an opposite trend as soon as the pump reached the highest possible rpm at T2.

Ejection fraction and systemic cardiac output measured by the thermodilution catheter tended to decrease and increase when going from baseline ($T_0$) to T1 and to T2, respectively, while end-systolic pressure and relaxation time constant tau remained practically unchanged over time. A patient-by-patient analysis based on actual pressure-volume loop analysis is shown in Figure 4. In the majority of the patients (#1, #3, #5, #6, #9 and #10) there was a sudden (detectable immediately after catheter insertion) increase in left ventricular volumes and, in some patients in the end-diastolic pressure as well, as soon as the Impella pump was inserted and activated at low rpm.

The maximal activation of the pump (T2) produced an opposite effect, with variable degrees of LV volume unloading as compared to T1. In all these individual cases, however, a volume increase compared to baseline was still noted at T2. In patient #2 a progressive volume unloading going from baseline to T1 and from T1 to T2 was evident, while patient#8 showed an intermediate pattern of response, with minor volume overload at T1 that was overcompensated with respect to baseline at T2.

Thus the heterogeneity of response to Impella activation may well explain the absence of a net significant haemodynamic effect produced by the pump compared to baseline when all data were pooled.

## Effect of Impella-supported procedure on circulating biomarkers

The change over time of the tested biomarkers in patients undergoing intervention supported by the Impella catheter as compared to baseline is shown in Figure 5. None of the selected parameters showed a significant change over time, despite clear individual heterogeneity in response to the treatment as revealed by the increase in data dispersion (i.e. data range and interquartile range) during and after intervention with respect to baseline.

## Effect of Impella-supported procedure on left ventricular volumes based on the intracardiac AcuNav echocardiographic examination

In the last patient (#12), the effect of the Impella support on LV volumes was investigated by an intracardiac echocardiographic AcuNav catheter examination. The results are given in Table 3 while figure 6 shows four left ventricle short axis views at baseline (A, B) and after activating the Impella support at 43,000 rpm during diastolic and systolic phases, respectively (C, D).

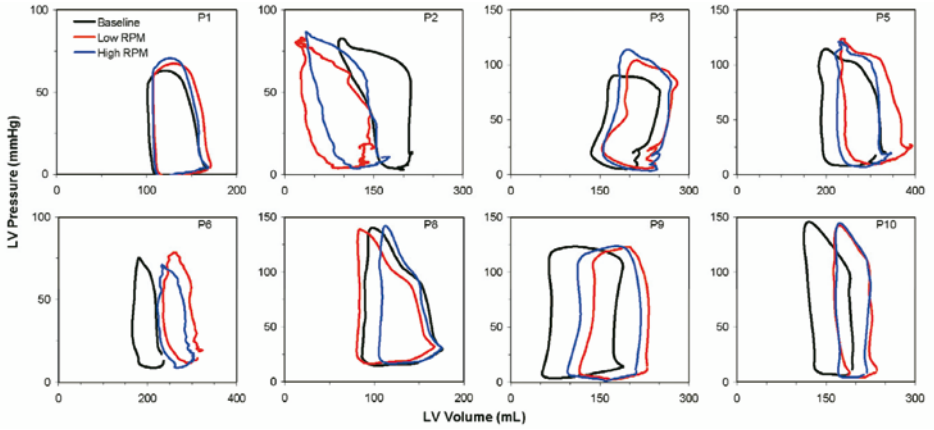


*Figure 4. Individual pressure-volume loops at baseline (black line), immediately after positioning the Impella catheter at minimal level of activation (blue line), and with Impella at maximal speed (red line).*

**Table 3**

| | Systole | | | Diastole | | |
|---|---|---|---|---|---|---|
| | Area ($cm^3$) | Dist_1 (cm) | Dist_2 (cm) | Area ($cm^3$) | Dist_1 (cm) | Dist_2 (cm) |
| Baseline | 4.6 | 2.1 | 2.9 | 25.8 | 5.3 | 6.8 |
| 35,000 rpm | 6.5 | 2.5 | 4.1 | 34.5 | 5.8 | 8.8 |
| 43,000rpm | 5.9 | 2.3 | 3.7 | 31.6 | 5.6 | 8.2 |
| 50,000 rpm | 5.3 | 2.2 | 3.3 | 28.7 | 5.4 | 7.4 |

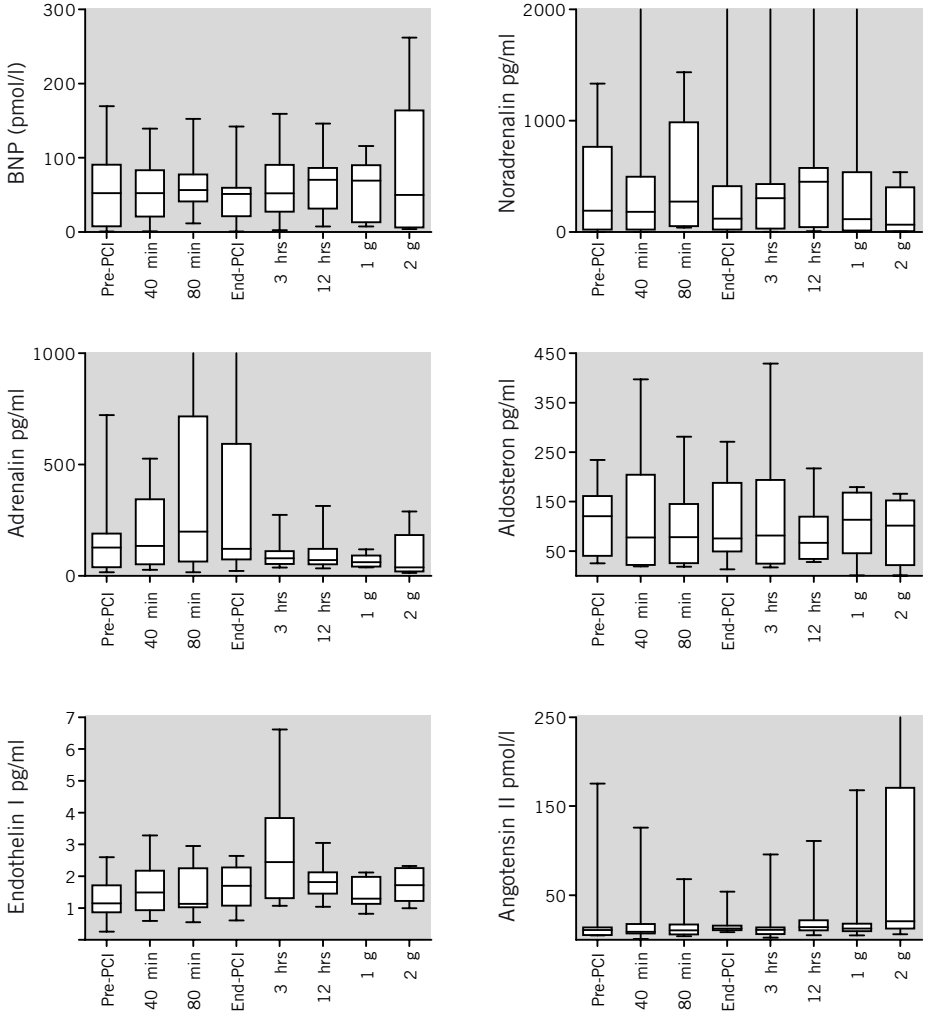


*Figure 5. Levels of tested biomarkers in relation to the timing of intervention. None of the studied parameters were significantly affected by the Impella-supported intervention at the analysis of variance. BNP: B-type natriuretic peptide (g = day).*

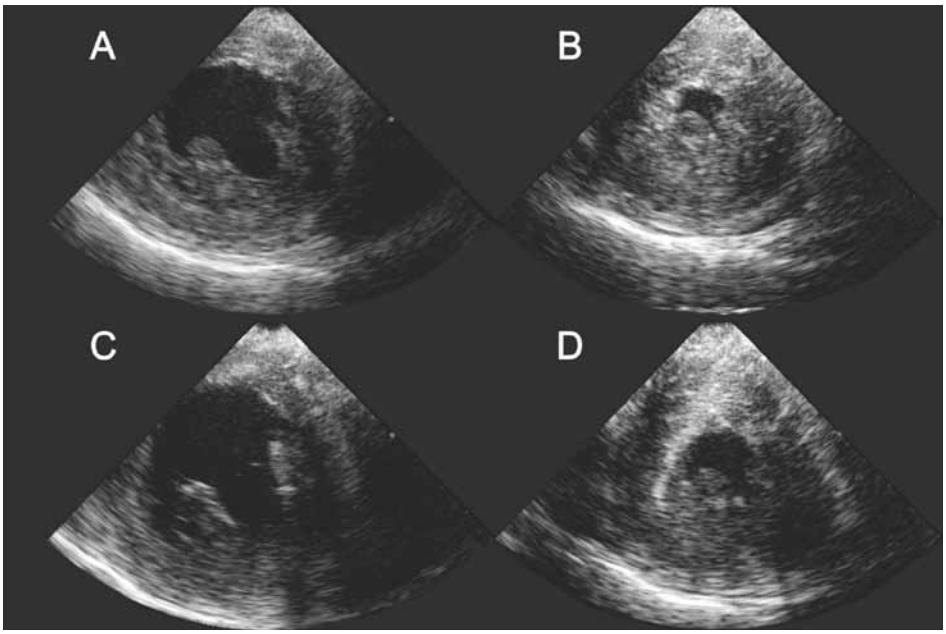


*Figure 6. Effect of Impella support on LV volumes in patient#12, investigated by intracardiac echocardiographic AcuNav catheter. Left ventricle short axis views during diastolic and systolic phases at baseline (A, B) and after activating the Impella support at 43000 rpm,(C, D).*

## Discussion

The Impella LVAD Recover® LP 2.5 is a miniaturized catheter-mounted rotary blood pump that is placed through the aortic valve, aspirates blood from LV cavity, and expels it in the ascending aorta. In clinical conditions the pump provides up to 2.5 L/min at its maximal rotational speed of 50/52,000 rpm. If placed without activation, the catheter would *per se* induce some backflow inside the cannula due to the pressure gradient during the diastolic phase between aorta and left ventricle. The actual amount of flow shunting back to the LV chamber during each diastole and the level of pump activation that is necessary to antagonize this *intra-cannula* insufficiency is dependent on the actual pressure gradient. Based on *in vitro* tests, a level of activation around 30,000 rpm is expected to neutralize the effective backflow (with some minor leak during diastole followed by some minor positive output during the systole) at a typical diastolic gradient between the aorta and the LV of 60/70 mmHg. According to this principle and guided by an engineer who had a major role in developing the Impella device, we set the level of pump activation at T1 in order to have no net flow within the pump cannula during each cardiac cycle. We thus expected to have a comparable haemodynamic profile at T1 as compared to baseline. However our findings indicate that after Impella positioning and with minimal activation at T1, a substantial volume overload occurred with respect to baseline in 7 out of 8 patients studied, with only one individual able to (over) compensate for the initial volume increase during maximal activation of the pump at T2. In the remaining case, a clear LV volume and pressure unloading at each step of Impella catheter activation was noted. Thus, in only 2 out of the 8 patients who underwent pressure-volume analysis in the present protocol, a final LV unloading was detected at T2.

These observations, coupled with the rather limited sample size of the study may explain the observed overall neutral effect of the Impella pump on almost all studied haemodynamic variables and biomarkers, including B-Type natriuretic peptide, whose production and secretion being linked to LV wall stretch, is known to closely reflect the haemodynamic status of the heart.

It could be argued that the simultaneous positioning of 12 Fr (Impella LVAD) and 7 Fr (pressure-conductance) catheters through the aortic valve might theoretically cause significant aortic regurgitation by disturbing adequate valve closure. However a pattern of volume overload was confirmed also by intracardiac echocardiographic examination, during which only the Impella catheter was positioned through aortic valve. Potentially, transseptal positioning of the conductance catheter might be desirable in future investigations. Thus although we cannot fully rule out the possibility that the two catheters in parallel might have increased the magnitude of volume overload due to increased aortic regurgitation, we believe this does not explain our current findings.

Our study focused on elective patients undergoing HR-PCI, who had had their medical treatment optimized. As a consequence, all patients had a normal or near-normal LV end-diastolic pressure before intervention and this may have contributed to the increase of the magnitude of volume regurgitation and LV overload during the diastolic phases of the cardiac cycle at T1. This may also explain the high incidence of suction effect observed in our study. In patients with acute haemodynamic compromise or during the acute phase of ischaemia (such as the transient no-flow phenomenon observed in patient#8) the LV diastolic pressures may be, or become, particularly elevated, thus limiting the degree of volume regurgitation towards the LV, while favouring a forward output towards the aortic arch. As an example, in patient#8, a clear effect of the Impella pump, was observed at the stage in which a dramatic no-flow phenomenon occurred during intervention in the last remaining patent artery. As shown in Figure 1, arterial pressure remained constantly above 90 mmHg while LV function was extremely, although transiently, depressed as shown by the minor systo-diastolic excursion. Indeed the patient remained completely asymptomatic during this phase and no inotropic support was needed.

At this point the reasons behind the immediate volume overloading which followed Impella pump positioning in most cases may only be speculative since our protocol was not designed to investigate this issue. A possible explanation is that while blood is continuously expelled into the aorta from the outlet of the Impella catheter, blood is at the same time regurgitating back into LV due to aortic valve insufficiency *(peri-cannula leak)*. This may be the consequence of the interplay between two factors: 1) The presence of the Impella catheter (4 mm in outer diameter) may interfere with aortic valve closure, particularly when the pump is far from being perpendicular with respect to the aortic valve plane in patients with severely calcified leaflets; 2) in cases where the Impella pump is placed too deeply inside the LV although positioning may appear satisfactory, based on pressure tracing inspection at the device console, the outlet orifices may remain too closely in contact with the aortic valve plane. When the blood is expelled with great velocity out into the ascending aorta, turbulent vortices may be created that may force the aortic valves to open. In this situation, the higher the degree of pump activation, the higher might be the induced aortic regurgitation. This may explain why despite maximal activation of the pump in 6 patients out of 8 studied, the device could not compensate the acute LV volume overload observed at T1.

If our speculations are correct, the haemodynamic effects provided by the Impella catheter depended a great deal on the haemodynamic status of the patient but may also be affected by the actual position of the Impella catheter. Future studies, potentially including transseptal placement of the conductance catheter and slow pull-back of the Impella device after initial positioning, may be needed to substantiate our speculations. Concomitant, transoesophageal echocardiographic examination may provide additional insight.

Finally, two issues deserve attention: a) the occurrence of haemolysis as a consequence of pump activation and b) bleeding at the site of pump insertion.

a) We observed occurrence of haemolysis in 6 out of 10 patients. In five, this was detected in two or more samples collected around 40 minutes apart. In three cases, levels of fHb increased more than 5 times the upper limit of normal (ULN) while in two individuals 10 times the ULN was found. At the same time, we clearly could observe that the degree of observed haemolysis was not strictly related to the duration of pump activation. This may be explained by the fact that the relatively older erythrocytes in the circulating pool may be subject to injury first. Thus after this early peak of haemolysis, the degree of fHb elevation may remain controlled even if the pump remains activated for several hours. Our study could not confirm this hypothesis, which needs to be tested in future investigations. The presence of suction during pump activation would be theoretically able to increase the occurrence of haemolysis due to increase shear stress. However, fHb levels at peak was not different in those with as compared to patients without suction during intervention, which makes the possibility that suction was the explanation for the high rate of haemolysis observed in our series quite unlikely.

b) The need to insert an arterial 13 Fr sheath before Impella pump insertion exposes the patient to a risk of bleeding at the site of puncture, as witnessed by our experience. We believe that echo-guided puncture of the common femoral artery followed by 10 Fr Prostar XL 10® insertion is the best approach in order to ensure effective and safe vascular access when the Impella pump needs to be inserted.

### Study limitations

Our study involved a limited number of patients and no control group was used. According to our protocol, the patient at baseline was supposed to be the internal reference of the study. However this may carry important limitations especially in interpreting our results in terms of biomarkers, which are known to be affected by the coronary intervention itself.

The need to place two catheters simultaneously in place through the aortic valve to obtain PV loop signal might limit the external validity of our findings; transseptal placement of the conductance catheter would be preferable for future studies to avoid interference with aortic valve closure system while the impella catheter is in place.

## Conclusions

Our findings on the safety and efficacy of the Impella Recover® LP 2.5 during HR-PCI, although preliminary due to the limited sample size, cannot support its routine use in this setting. Additional studies are required to confirm and investigate the mechanisms of the acute LV volume overload observed in the majority of the cases enrolled in the present study. Whether and how much the acute LV volume overload affects the haemodynamic support provided by the Impella pump remains unclear based on our data. Similarly, a better quantification of the degree of pump-induced haemolysis in a broader set of patients is warranted.

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## Reviewer comments:

I agree with the statement, in the introduction of the previous case report (Cath and CV Interventions 2005; 65:263-267) as well as this manuscript, that the role of assist devices generally in high-risk PCI is limited and controversial. I believe that is the case because:

a) it is hard to predict which stable patients will 'crash'; this was shown in the cardiopulmonary support registry experience (JACC 1993;21:590-596), and

b) cardiopulmonary support and IABP have significant potential for vascular adverse outcomes (CPRS also has haematologic and pulmonary physiologic effects), and perhaps most important

c) the time one takes inserting and setting up equipment, that neither the operator nor the lab crew use very frequently, can be spent getting the culprit vessel stented in a 'crashing' patient.

I don't think there is any doubt the heart-lung bypass machine can support the entire cardiac output of a patient in full arrest (for example AJC 1989;64:967-970), but it takes a while to get the 12 and 14 F cannulate in place and most lab crews have limited or no regular experience setting it up, priming it, etc, etc.

The IABP provides some forward output augmentation, a little LV unloading and a lot of diastolic augmentation of coronary flow in patients in shock ( for example either Coronary Artery Disease 1991;2:649-660 or Circulation 2000;102:364-365). Most experienced operators have used the IABP enough to have it in place and operational in about a minute or 2, unless there is major vascular issue.

# APPENDIX 4.1

## The ABC&D of cardiac resuscitation in the Cath Lab

Vranckx P, Benit E.

In Handbook of Complications During Percutaneous Coronary Interventions. Taylor & Francis Group. 2006, Chapter 17, 229-44
[**Review, only provided as a reference**]

Cardiogenic shock (CS) complicating ACS remains a common and frequently fatal disorder. The presence of ischemic and/or stunned or hibernating myocardium may have a profound impact on the initial, in-hospital, and post-discharge management and prognosis. The invasive management of the complex cardiac patient with advanced heart failure, CS, and/or potential hemodynamic compromise during and after percutaneous coronary intervention (PCI) has become an element of specialized myocardial intervention centers. Such centers provide state-of-the-art facilities for PCI including experienced senior operators and critical care physicians who are available 24 h per day, 7 days per week, with immediate access to cardiac surgery and mechanical circulatory support (MCS) systems. In this article, we discuss the invasive treatment of acute heart failure syndromes/CS complicating ACS, focusing on the implementation of percutaneous mechanical circulatory support.

# APPENDIX 4.2

## Mechanical Support for Cardiogenic Shock complicating Acute Coronary Syndromes

Vranckx P, Serruys PW. Percutaneous Acute Coronary Syndromes.

*Acute Coronary Syndromes*. 2011;**10**:2-9. [**technical report, only provided as a reference**]

# [ PART 5 ]

## PREVENTION.

# CHAPTER 5.1

## Cardiovascular risk profile of patients included in stent trials: A meta-analysis of individual patient data from randomized clinical trials. Insights from 31 prospective stent trials in Europe

Vranckx P, Boersma E, Garg S, Goedhart D, Van Es GA, Serruys P.W.J.C.

*EuroIntervention* 2011;**7**:859-71 [**original research paper**]

# Cardiovascular risk profile of patients included in stent trials; a pooled analysis of individual patient data from randomised clinical trials: insights from 33 prospective stent trials in Europe

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**KEYWORDS**

- coronary artery disease
- prognosis
- risk stratification
- percutaneous coronary intervention

## Abstract

**Aims:** Few data document trends in cardiovascular (CV) risk-factors in patients with or without previous symptomatic CV disease. We assessed the prevalence and trends in (non) modifiable CV risk-factors, and the use of cardioprotective therapies in patients enrolled in coronary stent trials.

**Methods and results:** This analysis included prospective data on 10,253 mainly European adults who were enrolled in 32 coronary stent studies between 1995 and 2006. Data was collected at the time of enrolment using a standardised patient clinical record form, and was analysed by considering three consecutive time periods: 1995-1997 (I), 1998-2002 (II) and 2003-2006 (III) rendering approximately equal numbers per period. Overall the proportion of active smokers remained constant (Period I to III: 28%, 27%, 21%, p=0.45), however the proportion increased in females below 50 years (about 2%/ year, R.RR: 1.20, P: 0.05 period III versus I). Prevalent diabetes increased (16%, 17%, 25%; p=0.029). The prevalence of a body-mass index (BMI) ≥25 kg/m² was high, but no trend was observed (69%, 68%, 70%; p=0.24). The proportion of patients with elevated blood pressure (i.e., ≥140/90 mmHg, in diabetes ≥130/80 mmHg) remained unchanged (55%, 50.%, 53%; p=0.22), despite an increase in the number of patients taking anti-hypertensive agents (84%, 89%, 90%; p=0.30). Conversely, the proportion of patients with elevated total cholesterol (i.e., ≥4.5 mmol/L) decreased (80%, 66%, 52%; p=0.002), which was consistent with the increase in patients taking lipid lowering drugs (32%, 62%, 69%; p=0.083). The portion of patients reaching therapeutic targets for blood lipids improved, but no improvement was seen in blood pressure control (p=0.29).

**Conclusions:** There is an unmet clinical need in primary and secondary CV prevention in Europe. Patients requiring PCI are an important target population in whom lifestyle changes and aggressive secondary preventative measures should be aimed. Ultimately PCI should open the door towards optimising secondary prevention.

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## Introduction

Atherosclerosis and coronary thrombosis are a major cause of premature death worldwide, and are an important source of loss of disability-adjusted life years.[1-3] As its clinical consequences are highly relevant for patients and society, so are the benefits of prevention. Effective prevention involves a strategy based on the knowledge of a population's attributable risk, which itself is prone to variation as the prevalence of several risk factors may fluctuate within a population over time.[4]

Patients with established atherosclerotic cardiovascular disease (CVD) (coronary artery disease [CAD], cerebrovascular disease, and peripheral arterial disease [PAD]) are at particular risk of recurrent nonfatal and fatal cardiovascular (CV) events.[5]

The EUROASPIRE study group applied a cross-sectional design to assess trends in modifiable cardiovascular risk factors and medical treatment in CVD patients from 1995-96, 1999-2000, and 2006-07 in selected geographical areas and hospitals in Europe. The results were discouraging, and revealed a continuing gap between the standards set by guidelines on secondary cardiovascular risk prevention, and the results achieved in clinical practice.[6] As per design, the EUROASPIRE surveys focussed on secondary prevention in routine clinical practice patients. We aimed to support the EUROASPIRE findings in the clinical trial setting, together with simultaneously addressing the aspect of primary prevention.

The prevalence of baseline demographics and the CV-risk profile of patients included in stent investigations is influenced by specific study inclusion and exclusion criteria, changes in the prevalence of CV-risk factors and related therapy, and may or may not mirror trends reported in routine clinical practice. This information is important when considering differences between trial results and extrapolations with routine clinical practice.

We conducted a retrospective analysis of prospectively collected data from stent trials conducted mainly in Europe by an Academic Research Organisation (ARO) over the last two decades focusing on modifiable CV-risk factors and medical treatment. The aim of the present investigation was to analyse apparent variations in overall CV-risk over time in this specific patient population.

## Methods

### STUDY POPULATION AND DATA COLLECTION

We analysed the baseline data sets of 10,253 patients, with angiographic proven obstructive atherosclerotic CAD, enrolled in one of 32 prospective, randomised native coronary stent trials conducted predominantly in Europe by a single independent ARO (Cardialysis, Rotterdam, The Netherlands) between 1995 and 2006 (last patient in 10/2006) All trials except two were registered in the ClinicalTrials.gov database [ClinicalTrials.gov]. A summary of all trials included in the current analysis, together with their inclusion and exclusion criteria are presented in Appendices 1 and 2, respectively. Detailed trial information and trial results are available elsewhere. Individual databases were managed by Cardialysis, Rotterdam, The Netherlands who conducted systematic audits and quality checks.

We addressed trends in the prevalence of diabetes and individual modifiable CV risk factors, together with the presence of established symptomatic atherosclerotic peripheral or cerebral arterial disease. Modifiable CV-risk factors considered in this analysis consisted of current smoking, systolic blood pressure (SBP), body mass index (BMI) and hypercholesterolaemia. Patients were classified as to their gender and age (men: 65 years or older; women 70 years or older). The cut-offs for age were arbitrary set considering the relation between age and cardiovascular disease in men and women with or without diabetes.[7] The standard case record form (CRF) did not record the participants' level of physical activity.

The use of cardioprotective drugs such as cholesterol lowering medications (statins, fibrates), antiplatelet drugs (clopidogrel, ticlopidine, aspirin), anti-hypertensive agents (beta-blockers, calcium antagonists, angiotensin-converting enzyme [ACE] inhibitors/angiotensin receptor blockers, diuretics) and any diabetic treatment prior to randomisation was systematically recorded. Information on contra-indications against the use or reasons for stopping or specific cardioprotective drugs could not be captured from the data base.

Each individual study was approved by the appropriate local regulatory and ethics committee of the participating trials. All participants provided informed consent before taking part in each of the individual studies.

### DEFINITIONS

Information about the patient's previous history of coronary or other atherosclerotic disease, reported medication, and baseline CV-risk factors were obtained via a standardised patient CRF used by the ARO in all stent trials, thus enabling the following definitions to be used in the current analysis:

Current smoking was defined as the consumption of an average of at least five cigarettes per day within the month prior to enrolment.

Prevalent diabetes mellitus was defined as a fasting serum glucose level ≥7.0 mmol/l (126mg/dl), non-fasting glucose level ≥11.1 mmol/l (200 mg/l), or a patient indicating a previous diagnosis of diabetes mellitus made by a physician, or the current use of diabetes medication. Diabetes treatment was specified: exercise/diet only, treatment with oral hypoglycaemic agents, or treatment with insulin.[8]

Prevalent hypertension was defined as a seated systolic (SBP) ≥140 mmHg and a diastolic (DBP) ≥90 mmHg, (except among patients with diabetes in whom this was defined as BP >130/80 mmHg). Patients were further stratified as "optimal" if mean SBP was <120 and diastolic pressure <80 mmHg, as "normal" if mean SBP was <130 mm Hg/DBP was 80-84 mm Hg and "high normal" if SBP 130-139 mmHg/DBP 85-89 mmHg.[9] If the systolic and diastolic pressure readings belonged to different categories, the higher of the two readings was used to assign the blood-pressure category.

Body mass index was calculated as weight in kilograms divided by the square of height in meters. Patients were considered to be of normal weight, overweight or obese if their respective BMI's were <25, 25≤ and <30, or ≥30.[10]

Established, symptomatic CVD[5] consisted of one or more of the following criteria: history of unstable angina with documented obstructive CAD, history of percutaneous coronary intervention (PCI), history of coronary artery bypass grafting, or previous myocardial infarction (MI).

Documented cerebrovascular disease consisted of a hospital or neurologist's report with the diagnosis of transient ischaemic attack or ischaemic stroke. Documented PAD consisted of a history of intermittent claudication together with a previous and related intervention, such as angioplasty, stenting, atherectomy, peripheral arterial bypass graft, or other vascular intervention including amputation.

Prior MI was defined as either a self-reported history of physician diagnosed MI, or a history of MI identified on the baseline electrocardiogram, which was characterised by the presence of a major Q-wave or a minor Q-wave with ischaemic ST-T changes.

### STATISTICS

We considered three consecutive study periods: 1995-1997 (Period I), 1998-2002 (Period II) and 2003-2006 (Period III), rendering approximately equal numbers of patients per study period. The time period refers to the starting date of the study. We respected the time periods used in the EUROASPIRE program.[6]

Analyses were done applying the method of Generalised Estimated Equations (GEE) with a Poisson distribution, a logarithmic link, modelling the study period either as factor or as a covariate.[11] By taking the study level as a random factor, using patients as replicates, nested within the study we acknowledge patients within a study form a more homogeneous group than between studies. This model also allowed to accommodate for "ignorable" missing data.[12] An exchangeable working correlation matrix was used to apply the GEE methodology. For the purpose of this analysis baseline values from stent investigations, recorded in the database, were grouped into higher level terms. In the case that a patient scored positively on one of the lower level terms, he or she became member of the higher level term, otherwise the existence of one variable that showed that the patient did not belong to the higher level term was sufficient to exclude him/her from membership, even in the presence of missing data on other lower level terms. This strategy was used to minimise the loss of data, however, this may have led to some underestimation when calculating the prevalence percentages of these high level terms (e.g., statins and fibrates were grouped into the class of lipid lowering drugs). Patients were classified into using lipid lowering drugs when they reported using at least one of the drugs. In the case that there was no information at all about any drug in this class they were classified as missing, in all other cases they were classified as using no lipid lowering drug at all. This strategy was used for all grouped variables.

With this approach, the estimated regression coefficients were identical to those obtained using ordinary logistic regression, but the standard errors were adjusted to account for the clustered data structure. All tests were 2-sided, p-values were not used to reject null hypotheses, and they are only shown to inform the reader on the probability level of a given outcome.

Results are summarised as relative risks for study periods 1998-2002 (RR1) and 2003-2006 (RR2) both with respect to the 1995-1997 period. Trends are calculated by using the time period as a covariate into the GEE model.

Statistical analyses and graphics were produced with assistance of a commercially available statistical software package (SAS version 8.2; SAS, Cary, NC, USA)

### ROLE OF THE FUNDING SOURCE

The sponsors of the individual trials had no role in this study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Between February 1995 and 2006, 10,253 patients (male: 76%) were pooled from 32 coronary stent trials in patients with obstructive CAD. The mean age of patients included in the analysis was respectively 60.1, 60.6 and 62.0 years for time Periods I, II, and III **(Table 1)**. **Tables 2-4** show the frequency and distribution of the modifiable CV-risk factors over the study periods in relation to patient age, gender, medical history of CV disease, and treatment. Relative changes between consecutive time periods, taking Period I as a reference, are expressed as relative risks, and are shown in **Table 5**, together with trends over the 12 year study period.

Overall the proportion current smokers did not differ between time periods (p trend: 0.45), not even in the subgroup of patients with known CVD (p trend: 0.43) **Tables 2 and 5**. There was a decrease in male smokers over time which was consistent in all age categories, however this trend was offset by an increase in the proportion of women smokers aged less than 50 years **(Figure 1)**.

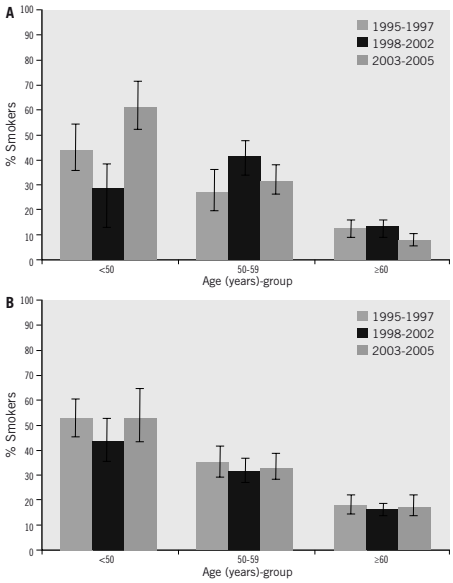


**Figure 1.** *A) Percentage current female smokers and 95% confidence interval by age and study period; B) Percentage current male smokers and 95% confidence interval by age and study period.*

**Table 1. Prevalence of cardiovascular risk factors expressed as counts and percentages***

| | | 1995-1997 | 1998-2002 | 2003-2006 | Total |
|---|---|---|---|---|---|
| Age | >70 (Women), >65 (Men) | 1287 (29%) | 684 (31%) | 998 (34%) | 2969 |
| | ≤70 (Women), ≤65 (Men) | 3189 (71%) | 1548 (69%) | 1920 (66%) | 6657 |
| Sex | Men | 3486 (78%) | 2162 (76%) | 2164 (74%) | 7812 |
| | Women | 1010 (22%) | 675(24%) | 754 (26%) | 2439 |
| SBP (mmHg) | SBP<120 | 798 (28%) | 909 (32%) | 893 (31%) | 2600 |
| | 120≤SBP<130 | 539 (19%) | 518 (18%) | 559 (19%) | 1616 |
| | 130≤SBP<140 | 495 (17%) | 544 (19%) | 550 (19%) | 1589 |
| | SBP≥140 | 1043 (36%) | 856 (30%) | 898 (31%) | 2797 |
| Total cholesterol | ≤4.5 mmol/L | 2852 (63%) | 1793 (63%) | 2458 (84%) | 7103 |
| | >4.5 mmol/L | 1645(37%) | 1045 (37%) | 460 (16%) | 3150 |
| BMI | <18 | 9 (3%) | 13 (5%) | 10 (4%) | 32 |
| | 18≤BMI<25 | 870 (31%) | 886 (32%) | 836 (29%) | 2592 |
| | 25≥BMI<30 | 1356 (48%) | 1290 (46%) | 1375 (48%) | 4021 |
| | BMI≥30 | 610 (21%) | 598 (21%) | 636 (22%) | 1844 |
| Diabetes mellitus | | 701 (16%) | 496 (17%) | 732 (25%) | 1929 |
| Current smokers | | 1103 (28%) | 769 (27%) | 650 (22%) | 2522 |

*Percentage relative to the study period; SBP: systolic blood pressure; BMI: body mass index

**Table 2. Prevalence of current smoking, overweight and/or obesity expressed as counts and percentages (percentages relative to the study period) by age, sex and history of established cardiovascular disease.**

| Subgroups | | Current smoker: >5 cigarettes per day | | | Overweight and obesity: BMI > 25 kg/m² | | | Obesity: BMI >30 kg/m² | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 1995-1997 | 1998-2002 | 2003-2006 | 1995-1997 | 1998-2002 | 2003-2006 | 1995-1997 | 1998-2002 | 2003-2006 |
| Age | >70 (Women), >65 (Men) | 151/1118 (13.5%) | 83/681 (12.2%) | 93/997 (9.3%) | 532/835 (63.7%) | 451/676 (66.7%) | 653/980 (66.6%) | 132/835 (15.8%) | 86/519 (19.1%) | 170/980 (17.3%) |
| | ≤70 (Women), ≤65 (Men) | 936/2794 (33.5%) | 515/1542 (33.4%) | 557/1918 (29.0%) | 1408/1970 (71.4%) | 1064/1524 (69.8%) | 1357/1876 (72.3%) | 466/1970 (23.7%) | 341/1524 (22.4%) | 465/1876 (24.7%) |
| Sex | Men | 920/3018 (30.5%) | 481/1695 (28.4%) | 530/2162 (24.5%) | 1523/2145 (71.0%) | 1176/1682 (69.9%) | 1517/2122 (71.5%) | 419/2145 (19.5%) | 327/1682 (19.4%) | 439/2122 (20.7%) |
| | Women | 167/894 (18.7%) | 117/528 (22.2%) | 120/753 (15.9%) | 417/660 (63.2%) | 339/518 (65.4%) | 493/734 (67.2%) | 179/660 (27.1%) | 143/518 (27.6%) | 196/734 (26.7%) |
| Established CVD | A Previous MI | 337/1261 (26.7%) | 275/907 (30.3%) | 296/1054 (28.1%) | 667/997 (68.3%) | 598/897 (66.7%) | 710/1032 (68.8%) | 186/977 (19.0%) | 187/897 (20.8%) | 220/1032 (21.3%) |
| | B Previous PCI or CABG | 39/193 (20.2%) | 18/100 (18%) | 16/132 (12.1%) | 85/172 (49.4%) | 63/99 (41.4%) | 92/127 (72.4%) | 24/172 (14.0%) | 22/99 (22.2%) | 34/127 (26.8%) |
| | C Previous peripheral vascular disease | 76/220 (34.5%) | 47/142 (33.1%) | 63/217 (29.0%) | 115/183 (62.8%) | 89/141 (63.1%) | 136/208 (65.4%) | 32/183 (17.5%) | 31/141 (22.0%) | 47/208 (22.6%) |
| | D Previous stroke | 3/49 (6.1%) | 7/54 (13.0%) | 17/84 (20.2%) | 38/49 (77.6%) | 42/54 (77.8%) | 54/80 (66.6%) | 8/49 (16.3%) | 14/54 (25.9%) | 22/80 (27.5%) |
| | Any of A, B, C, D | 419/1600 (26.2%) | 335/1168 (28.7%) | 358/1425 (25.1%) | 838/1233 (68.0%) | 776/1155 (67.2%) | 955/1390 (68.5%) | 235/1233 (19.1%) | 253/1155 (21.9%) | 307/1390 (22.1%) |

CVD: cardiovascular disease; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; Previous stroke (of any kind): cerebrovascular accident, transient ischaemic attack, reversible intermittent neurological deficit

Mean body weight respectively was 78.3, 78.8, and 78.7 kilogram for periods I, II and III. The overall proportion of obese and overweight patients did not show a trend over time, not even in the patient group with history of CV disease **(Table 5)**. There was a possible increase however, in the proportion of overweight women (p trend: 0.15), whilst the proportion of obese women remained much the same **(Table 2)**. The proportion of obese women was higher than obese men throughout the study period.

Only three fifth of patients in all three periods had their BP below target levels (respectively: 55%, 50%, 53%), and most compelling this occurred in only half of the patients with established CVD (respectively: 51%, 52%., 51%; p trend: 0.56 ) **Table 3, 3B, Appendix 2, and Table 5**. Of those patients taking BP lowering drugs, although not necessarily taken as anti-hypertensive treatment, the proportion that achieved the SBP target of <140/90 mm Hg (<130/80 mm Hg in patients with diabetes) did not differ over time (period I: 47%, period II:49%, period III: 47%; p=0.53; **Tables 3 and 5**). The proportion of hypertensive patients not taking blood-pressure-lowering treatment declined over time (respectively: 19%, 10%, 9.0%%; p=0.21). Overall, the proportion of patients with a raised total blood cholesterol

**Table 3A. Prevalence of hypertension, hypercholesterolaemia and diabetes expressed as counts and percentages (percentages relative to the study period) by age, sex, history of established cardiovascular disease and cardioprotective therapy.**

| Subgroups | | Raised blood pressure BP>140/90 mmHg non diabetes, >130/80 mmHg diabetes | | | Raised cholesterol concentration: >4.5 mmol/l (200 mg/dl) | | | Prevalent diabetes | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 1995-1997 | 1998-2002 | 2003-2006 | 1995-1997 | 1998-2002 | 2003-2006 | 1995-1997 | 1998-2002 | 2003-2006 |
| Age | >70 (Women), >65 (Men) | 503/847 (59.4%) | 389/682 (57.0%) | 600/993 (60.4%) | 433/560 (77.3%) | 199/332 (59.9%) | 135/278 (48.6.0%) | 230/1250 (18.4%) | 134/684 (19.6%) | 291/998 (29.2%) |
| | ≤70 (Women), ≤65 (Men) | 1057/1988 (53.2%) | 731/1540 (47.5%) | 922/1906 (48.4%) | 1207/1489( 81.1%) | 492/763 (64.5%) | 325/613 (53.0%) | 442/3084 (14.3%) | 253/1548 (16.3%) | 440/1919 (22.9%) |
| Sex | Men | 1139/2162 (52.7%) | 807/1698 (47.5%) | 1066/2153 (49.5%) | 1260/1591 (79.2%) | 495/821 (60.3%) | 320/660 (48.5%) | 477/3369 (14.2%) | 272/1703 (16.0%) | 486/2164 (22.5%) |
| | Women | 421/673 (62.6%) | 313/524 (59.7%) | 455/745 (61.1%) | 380/458 (83.0%) | 196/274 (71.5%) | 140/231 (60.6%) | 195/965 (20.2%) | 115/529 (21.7%) | 245/753 (32.5%) |
| Established CVD | Any of A,B,C,D | 608/1243 (48.9%) | 571/1168 (48.9%) | 692/1417 (48.8%) | 724/912 (79.4%) | 347/576 (60.2%) | 147/342 (43.0%) | 313/1861 (16.8%) | 224/1173 (19.1%) | 373/1426 (26.2%) |
| | A Previous MI, | 456/981 (46.5%) | 411/907 (45.3%) | 466/1050 (44.4%) | 596/757 (78.7%) | 262/441 (59.4%) | 113/272 (41.5%) | 237/1449 (16.4%) | 167/911 (18.3%) | 263/1055 (24.9%) |
| | B Previous PCI or CABG | 91/173 (52.6%) | 50/101 49.5%) | 71/131 (54.2%) | 82/96 (85.4%) | 25/52 (48.1%) | 5/13 (38.5%) | 46/235 (19.6%) | 25/101 (24.8%) | 43/132 (32.6%) |
| | C Previous peripheral vascular disease | 118/184 (64.1%) | 92/143 (64.3%) | 140/216 (64.8%) | 97/120 (80.8%) | 58/90 (64.4%) | 27/48 (56.3%) | 61/253 (24.1%) | 32/143 (22.4%) | 77/217 (35.5%) |
| | D Previous stroke | 37/48 (77.1%) | 37/54 (68.5%) | 46/81 (56.8%) | 14/18 (77.8%) | 20/30 (66.7%) | 4/13 (30.8%) | 17/49 (34.7%) | 18/54 (33.3%) | 33/84 (39.3%) |

CVD: cardiovascular disease; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; Previous stroke (of any kind): cerebrovascular accident, transient ischaemic attack, reversible intermittent neurological deficit

**Table 3B. Prevalence of blood pressure categories expressed as counts and percentages (percentages relative to the study period) by age, sex, history of established cardiovascular disease and cardioprotective therapy.**

| | | Systolic blood pressure (mmHg) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1995-1997 | | | | 1998-2002 | | | | 2003-2006 | | | |
| | | <120 | 120-129 | 130-139 | ≥140 | <120 | 120-129 | 130-139 | ≥140 | <120 | 120-129 | 130-139 | ≥140 |
| Age | >70 (Women), >65 (Men) | 186/847 (22.0%) | 146/847 (17.2%) | 153/847 (18.1%) | 362/847 (42.7%) | 165/682 (24..2%) | 117/682 (17.2%) | 141/682 (20.7%) | 259/682 (38.0%) | 240/993 (24.2%) | 178/993 (17.9%) | 187/993 (18.8%) | 338/993 (39.1%) |
| | ≤70 (Women), ≤65 (Men) | 602/1988 (30.3%) | 385/1988 (19.4%) | 336/1988 (16.9%) | 665/1988 (33.5%) | 538/1540 (34.9%) | 295/150 (19.2%) | 284/1540 (18.4%) | 423/1540 (27.5%) | 653/1906 (34.3%) | 381/1906 (20.0%) | 363/1906 (19.0) | 509/1906 (28.7%) |
| Sex | Men | 624/2162 (28.9%) | 434/2162 (20.1%) | 387/2162 (17.9%) | 717/2162 (33.2%) | 571/1698 (33.6%) | 323/1698 (19.0%) | 326/1698 19.2%) | 478/1698 (28.2%) | 711/2153 (33.0%) | 432/2153 (20.1%) | 407/2153 (18.9%) | 603/2153 (28.0%) |
| | Women | 164/673 (24.4%) | 97/673 (14.4%) | 102/673 (15.2%) | 310/673 (46.1%) | 132/524 (25.2%) | 89/524 (17%) | 99/524 (18.9%) | 204/524 (38.9%) | 182/746 (24.4%) | 127/746 (17.0%) | 143/294 (19.2%) | 294/746 (39.4%) |
| Established CVD | Any of A,B,C,D | 402/1243 (32.3%) | 266/1243 (21.4%) | 213/362 (17.1%) | 362/1243 (29.1%) | 405/1168 (34.7%) | 214/1168 (18.3%) | 203/1168 (17.4%) | 346/1168 (29.6%) | 484/1417 (34.2%) | 294/1417 (20.7%) | 243/1417 (17.1%) | 396/1417 (27.9%) |
| | A Previous MI | 349/981 (35.6%) | 214/981 (21.8%) | 161/981 (16.4%) | 257/981 (26.2%) | 340/907 (37.5%) | 165/907 (18.2%) | 162/907 (17.9%) | 240/907 (26.5%) | 401/1050 (38.2%) | 222/1050 (21.1%) | 165/1050 (15.7%) | 262/1050 (25.0%) |
| | B Previous PCI or CABG | 41/173 (23.7%) | 39/173 (22.5%) | 34/173 (19.7%) | 59/173 (34.1%) | 35/101 (34.7%) | 16/101 (15.8%) | 19/101 (18.8%) | 31/101 (30.7%) | 36/131 (27.5%) | 32/131 (24.4%) | 19/44 (14.5%) | 44/131 (33.6%) |
| | C Previous peripheral vascular disease | 37/184 (20.1%) | 27/184 (14.7%) | 39/81 (21.2%) | 81/184 (44.0%) | 28/143 (19.6%) | 30/143 (21.0%) | 18/143 (12.6%) | 67/143 (46.9%) | 42/216 (19.4%) | 46/216 (21.3%) | 41/216 (19.0%) | 87/216 (40.3%) |
| | D Previous stroke | 9/48 (18.8%) | 3/48 (6.3%) | 6/48 (12.5%) | 30/48 (62.5%) | 13/54 (24.1%) | 5/54 (9.3%) | 11/54 (20.4%) | 25/54 (46.3%) | 24/81 (29.6%) | 13/81 (16.0%) | 16/81 (19.8%) | 28/81 (34.6%) |

CVD: cardiovascular disease; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; Previous stroke of any kind: cerebrovascular accident, transient ischaemic attack, reversible intermittent neurological deficit

concentration decreased over the three time periods (p trend: 0.002) **Tables 3 and 5**, with a similar trend observed in the subgroup of patients with established CVD (p trend: <0.001). Although the proportion of patients taking lipid-lowering drugs (statins, fibrates) who achieved the cholesterol target of <4.5 mmol/L, was twice as high in period III than in Period I **(Tables 3 and 5)**, only 48% of patients receiving treatment in Period III achieved the target for optimal cholesterol control, a trend consistent with the increase in

statin use (**Table 4**; R.R= 9.7, p:0.02). Of note, statin use was absent, or not specifically asked about in the CRF in Period I, and therefore the relative risk was calculated comparing Period III to II, and consequently no trend could be calculated.

The frequency of prevalent diabetes increased over time (p trend: 0.03) and this increase was more prominent in men than in women **(Tables 3 and 5)**. There was a parallel, proportional increase in the concomitant use of lipid lowering and antihypertensive drugs in these patient groups. In the group of diabetics, the proportion of patients with hypertension increased, whilst those with a cholesterol level >4.5 mmol showed a reverse trend **(Figure 2)**.

The proportion of patients taking either statins, calcium channel blockers, β-blockers, diuretics and antiplatelet treatment increased over time and to the same extent considering age and gender, in secondary and primary prevention **(Tables 4 and 5)**.

## Discussion

The lack of improvement in modifiable behavioural risk factors in patients enrolled in stent investigations in Europe between 1995 and 2006 reflects similar evolutions in the general population.[6,13-15] Potential patient selection bias, reflecting the specific inclusion and exclusion criteria of the individual studies must be taken into account when putting the current results into perspective. This study emphasises the continuing gap between the standards set in guidelines on CV risk prevention, and the results achieved in clinical practice. Our results are the product of lifestyle, inadequate risk factor management, and the underuse of prophylactic drug therapies, even after the development of a potential life-threatening disease. Overall, these results call for action.

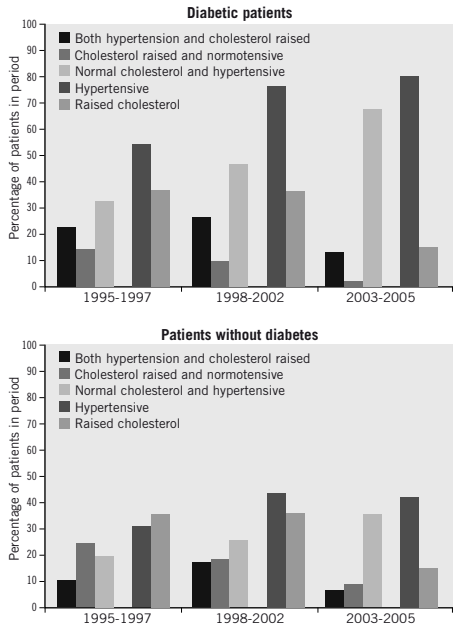


**Figure 2.** *Influence of hypertension and cholesterol in patients with or without diabetes.*

In our analysis the prevalence of smokers was systematically higher than in the corresponding time periods of the EUROASPIRE surveys, however similar trends appeared. Overall, there was a decrease in smoking over time in all age categories, although this trend was partially offset by an increase in the proportion of women smokers younger than 50 years. The high number of smokers in patients with previous symptomatic CV disease is worrisome. Promotion of smoking cessation is important at both a population and individual level, for both primary and secondary prevention.[16,17] The magnitude of the increase in CV-risk through smoking is closely, and linearly, related to the number of cigarettes smoked, with even low levels of smoking (e.g., five cigarettes per day) still being associated with an appreciable increased risk of acute MI.[18] A physician's advice to stop smoking is one of the most important first steps in the cessation process, but efforts need to be sustained over time, and more than likely will need to be complemented by pharmacological therapies to counteract nicotine dependence.[19,20]

The prevalence of obesity, systolic hypertension and to slightly lesser extent diabetes was lower in our analysis as compared to EUROASPIRE and a recent all-comers trial setting.[21] Most studies involved in our analysis only included patients with "simple" coronary lesion morphology. Consequently, we potentially excluded from our analysis a patient cohort with high arterial atherosclerotic burden and hence patients with a high prevalence of obesity, hypertension and diabetes.

The frequency of overweight and obese patients included in elective stent studies was slightly lower when compared to the general population for the three time periods considered.[6] In EUROASPIRE, but not in our analysis, the distribution of BMI shifted in a skewed fashion such that the proportion of the population with morbid obesity increased by a greater extent than the proportion who were overweight. Still in period III seven out of ten patients had a BMI ≥25 kg/m² and over one fifth were obese. The numbers of patients classified as overweight and/or obese has reached epidemic proportions, despite both being associated with numerous comorbidities. More than 70% of overweight patients were on anti-hypertensive or lipid lowering drugs in our analysis. The maladaptive effects of excessive body weight on various CV-risk factors, together with its adverse effects on CV structure and function, results in its propensity to reduce overall survival.[22,23] Weight reduction interventions, beyond bariatric surgery, involves lifestyle choices including dietary intervention and increased physical exercise.[24] In a stepwise approach approved prescription medications targeting the various systems that regulate eating behaviour and body weight can be a valid adjunct to behavioural changes. The long-term maintenance of weight reduction is difficult and needs sustained personal and family motivation, and long-term professional support.

**Table 4A. Prevalence of cardiovascular treatment per drug category as counts and percentages (percentages relative to the study period) by age, sex, history of established cardiovascular disease and cardioprotective therapy.**

| | | Cardioprotective drug treatment | | | | | |
|---|---|---|---|---|---|---|---|
| | | 1995-1997 | | 1998-2002 | | 2003-2006 | |
| | | Blood pressure lowering therapy | | | | | |
| | | No | Yes | No | Yes | No | Yes |
| Age | >70 (Women), > 65 (Men) | 228 (19.9%) | 919 (80.1%) | 73 (10.7%) | 611 (89.3%) | 86 (8.6%) | 912 (91.4%) |
| | ≤70 (Women), ≤ 65 (Men) | 404 (14.3%) | 2427 (85.7%) | 167 (10.8%) | 1381 (89.2%) | 198 (10.3%) | 1721 (89.7%) |
| Sex | Men | 490 (16.0%) | 2576 (84.0%) | 201 (11.8%) | 1502 (88.2%) | 222 (10.3%) | 1942 (89.7%) |
| | Women | 142 (15.6%) | 770 (84.4%) | 39 (7.4%) | 490 (92.6%) | 62 (8.2%) | 691 (91.8%) |
| Established CVD | Any of A,B,C,D | 192 (11.5%) | 1472 (88.5%) | 95 (8.1%) | 1078 (91.9%) | 94 (6.6%) | 1332 (93.4%) |
| | A Previous MI, | 131 (10.0%) | 1180 (90.0%) | 70 (7.7%) | 841 (92.3%) | 62 (5.9%) | 993 (94.1%) |
| | B Previous PCI or CABG | 87(17.6%) | 407 (82.4%) | 32 (8.0%) | 366 (92.0%) | 45 (8.1%) | 513 (91.9%) |
| | C Previous peripheral vascular disease | 36 (15.5%) | 197 (84.5%) | 13 (9.1%) | 130 (90.9%) | 9 (4.0%) | 214 (96.0%) |
| | D Previous stroke | 11 (24.4%) | 34 (75.6%) | 5 (9.3%) | 49 (90.7%) | 9 (10.7%) | 75 (89.3%) |
| | | Lipid lowering treatment | | | | | |
| Age | >70 (Women), >65 (Men) | 273 (72.8%) | 102 (27.2%) | 220 (45.4%) | 265 (54.6%) | 373 (37.4%) | 625 (62.6%) |
| | ≤70 (Women), ≤65 (Men) | 651 (66.5%) | 328 (33.5%) | 392 (35.5%) | 712 (64.5%) | 529 (27.6%) | 1390 (72.4%) |
| Sex | Men | 746 (71.6%) | 296 (28.4%) | 473 (38.5%) | 757 (61.5%) | 683 (31.6%) | 1481 (68.4%) |
| | Women | 178 (57.1%) | 134 (42.9%) | 139 (38.7%) | 220 (61.3%) | 219 (29.1%) | 534 (70.9%) |
| Established CVD | Any of A,B,C,D | 433 (66.8%) | 215 (33.2%) | 261 (31.3) | 573 (68.7%) | 323 (22.7%) | 1103 (77.3%) |
| | A Previous MI, | 383 (65.7%) | 200 (34.3%) | 202 (30.5%) | 461 (69.5%) | 211 (20.0%) | 844 (80.0%) |
| | B Previous PCI or CABG | 41 (80.4%) | 10 (19.6%) | 74 (27.9%) | 191 (72.1%) | 120 (21.5%) | 438 (78.5%) |
| | C Previous peripheral vascular disease | 58(68.2%) | 27 (31.8%) | 27 (29.3%) | 65 (70.7%) | 64 (28.7%) | 159 (71.3%) |
| | D Previous stroke | NI | NI | 11 (26.8%) | 30 (73.2%) | 26 (31.0%) | 58 (69.0%) |
| | | Antiplatelet therapy | | | | | |
| Age | >70 (Women), >65 (Men) | 128 (10.9%) | 1042 (89.1%) | 67 (9.8%) | 617(90.2%) | 80 (8.0%) | 918 (92.0%) |
| | ≤70 (Women), ≤65 (Men) | 243 (8.4%) | 2666 (91.6%) | 98 (6.3%) | 1450 (93.7%) | 126 (6.6%) | 1793 (93.4%) |
| Sex | Men | 276 (8.8%) | 2877 (91.2%) | 125 (7.3%) | 1578 (92.7%) | 143 (6.6%) | 2021 (93.4%) |
| | Women | 95 (10.3%) | 831 (89.7%) | 40 (7.6%) | 489 (92.4%) | 63 (8.4%) | 690 (91.6%) |
| Established CVD | Any of A,B,C,D | 130 (7.7%) | 1560 (92.3%) | 65 (5.5%) | 1108 (94.5%) | 57 (4.0%) | 1369 (96.0%) |
| | A Previous MI, | 90 (6.8%) | 1239 (93.2%) | 43 (4.7%) | 868 (95.3%) | 37 (3.5%) | 1018 (96.5%) |
| | B Previous PCI or CABG | 37 (7.4%) | 463 (92.6%) | 29 (7.3%) | 369 (92.7%) | 37 (7.4%) | 463 (92.6%) |
| | C Previous peripheral vascular disease | 31 (12.8%) | 211 (87.2%) | 14 (9.8%) | 129 (90.2%) | 9 (4.0%) | 214 (96.0%) |
| | D Previous stroke | 5 (10.2%) | 44 (89.8%) | 1 (1.9%) | 53 (98.1%) | 9 (10.7%) | 75 (89.3%) |

CVD: cardiovascular disease; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; Previous stroke (of any kind): cerebrovascular accident, transient ischaemic attack, reversible intermittent neurological deficit

**Table 4B. Prevalence of statin use expressed as counts and percentages (percentages relative to the study period) by age, sex, history of established cardiovascular disease and cardioprotective therapy.**

| | | Statin use | | |
|---|---|---|---|---|
| | | 1995-1997 | 1998-2002 | 2003-2006 |
| Age | >70 (Women), >65 (Men) | NI | 18/524 (3.4%) | 419/740 (56.6%) |
| | ≤70 (Women), ≤65 (Men) | NI | 52/1708 (3.0%) | 1459/2177 (67.0%) |
| Sex | Men | NI | 53/1701 (3.1%) | 1386/2164 (64.0%) |
| | Women | NI | 17/529 (3.2%) | 492/753 (65.3%) |
| Established CVD | Any of A, B, C, D | NI | 32/1059 (3.0%) | 1025/1426 (71.9%) |
| | A Previous MI, | NI | 29/911 (3.2%) | 1093/1862 (58.7%) |
| | B Previous PCI or CABG | NI | 4/101 (4.0%) | 98/132 (74.2%) |
| | C Previous peripheral vascular disease | NI | 11/143 (7.7%) | 144/217 (66.4%) |
| | D Previous stroke | NI | 2/54 (3.7%) | 51/84 (60.7%) |
| Antiplatelet treatment | | NI | 66/2067 (3.2%) | 1802/2711 (66.5%) |
| – Aspirin | | NI | 64/1995 (3.2%) | 1752/2625 (66.7%) |
| – Thienopyridine (ticlopidine or clopidogrel) | | NI | 32/879 (3.6%) | 1217/1778 (68.4%) |
| Any blood-pressure-lowering treatment | | NI | 63/1992 (3.2%) | 1766/2633 (67.1%) |
| – β blockers | | NI | 45/1536 (2.9%) | 1436/2056 (69.8%) |
| – ACE-inhibitors and ARBs | | NI | 30/742 (4.0%) | 1010/1455 (69.4%) |
| – Calcium channel blockers | | NI | 25/681 (3.7%) | 451/701 (64.3%) |
| – Diuretics | | NI | 9/294 (3.1%) | 329/532 (61.8%) |
| Any lipid lowering drugs | | NI | 70/977 (7.2%) | 1878/2015 (93.2%) |
| – Statins | | NI | 70/70 (100%) | 1878/1878 (100%) |
| – Fibrates | | NI | 70/977 (7.2%) | 1426/2328 (61.3%) |

**Table 5. Relative risks for study periods 1998-2002 and 2003-2006 both with respect to the 1995-1997 period for the individual risk factors studied, cardioprotective drugs by class and concomitant disease. Trends are calculated by using the time period as a covariate.**

| | 1998-2002 vs. <1997 | >2002 vs. <1997 | |
|---|---|---|---|
| | Relative risk (95% Confidence interval) | Relative risk (95% Confidence interval) | $\chi^2$1 trend (probability) |
| **Risk factor** | | | |
| Current smoking (>5 cigarettes/day) | 0.96 (0.80-1.15) | 0.89 (0.71-1.11) | 0.57 (p=0.45) |
| Obesity: BMI > 30kg/m$^2$ | 1.02 (0.86-1.21) | 1.06 (0.91-1.25) | 0.55 (p=0.45) |
| Overweight: BMI > 25kg/m$^2$ | 1.00 (0.94-1.07) | 1.04 (0.98-1.11) | 1.40 (p=0.24) |
| Hypertension[1] | 0.84 (0.68-1.04) | 0.86 (0.69-1.07)) | 1.48 (p=0.22) |
| Raised cholesterol concentration[2] | 0.78 (0.69-0.88) | 0.61(0.54-0.70) | 9.43 (p=0.002) |
| Diabetes mellitus[3] | 1.11 (0.96-1.28) | 1.43 (1.17-1.75) | 4.78 (p=0.03) |
| Blood pressure control treatment | 1.04 (0.95-1.15) | 1.06 (0.96-1.17) | 1.09 (p=0.30) |
| Lipid lowering treatment | 3.40 (0.86-13.44) | 3.80 (0.98-14.77) | 3.01 (p=0.08) |
| **Cardioprotective drugs by class** | | | |
| Antiplatelet treatment | 1.03 (0.99-1.06) | 1.04 (0.996-1.09) | 2.9 (p=0.09) |
| Aspirin | 1.02 (0.99-1.06) | 1.03 (0.98-1.09) | 1.46 (p=0.23) |
| Thienopyridine (clopidogrel, ticlopidine) | 1.24 (0.69-2.24) | 1.82 (1.05-3.16) | 4.43 (p=0.04) |
| β blockers | 1.11 (1.01-1.22) | 1.16 (1.06-1.27) | 6.88 (p=0.009) |
| ACE-inhibitors and ARBs | 0.77 (0.45-1.30) | 1.06 (0.60-1.77) | 0.3 (p=0.86) |
| Calcium-channel blockers | 0.74 (0.62-0.89) | 0.61 (0.54-0.67) | 11.30 (p<0.001) |
| Diuretics | 1.38 (1.07-1.78) | 1.85 (1.48-2.30) | 9.54 (p=0.002) |
| Statins | >2002 vs. 1998-2002: 0.92 (0.88-0.97) | | |
| Fibrates | 3.45 (0.86-13.91) | 1.14 (0.22-5.99) | 1.45 (p=0.23) |
| **Concomitant disease** | | | |
| Peripheral vascular disease | 0.84 (0.48-1.47) | 0.67 (0.38-1.19) | 0.37 (p=0.54) |
| Cerebrovascular disease | 0.48 (0.21-1.13) | 0.66 (0.27-1.61) | 0.62 (p=0.43) |
| Congestive heart failure | 0.40 (0.31-0.52) | 0.55 (0.30-1.02) | 0.36 (p=0.55) |

[1] Systolic blood pressure 140 mm Hg or more and/or diastolic blood pressure 90 mm Hg or more for patients without diabetes and systolic blood pressure 130 mm Hg or more and/or diastolic blood pressure 80 mm Hg or more for patients with diabetes; [2] Total cholesterol 4·5 mmol/L or more; [3] Prevalent diabetes: a fasting serum glucose level ≥7.0 mmol/l (126 mg/dl), non-fasting glucose level ≥11.1 mmol/l (200 mg/l), or participant report of a physician diagnosis of diabetes or current use of diabetes medication; ACE-inhibitors: angiotensin-converting enzyme inhibitors; ARB: angiotensin-receptor blockers

The prevalence of diabetes in the current study is less than reported in the real world,[6] though there was a possible trend towards an increase in the proportion of diabetics, especially in women (p trend: 0.19) and the elderly (p trend: 0.03) over time.

Also the prevalence of hypertension was relatively low, compared to the corresponding time periods in the EUROASPIRE surveys, and only showed a small time trend towards better blood pressure management in the subgroup of younger patients (p trend: 0.18). Despite the increased number of patients with systolic hypertension taking one or more BP lowering drugs, there was no corresponding improvement in overall BP control. Moreover, the proportion of patients taking one or more anti-hypertensives that lowered their systolic BP within the normal range did not change. This failure to manage BP effectively was higher than reported in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) at both one and two years follow-up.[25] Potential explanations for this are the sub-optimal dosing and titration of medication and/or poor patient compliance. BP lowering is essential for CV disease prevention; in a previous large meta-regression analysis within trial gradients in achieved systolic pressure almost completely accounted for the differences in cardiovascular outcomes, including stroke and MI.[26]

In contrast with BP, the management of blood lipid concentrations improved substantially, which is largely attributed to the increased use of statins from 1998 onwards. Despite this however, only about half of patients achieved the target cholesterol concentration of below 4.5 mmol/L, set by the 2003 joint European societies guidelines on CV disease prevention.[27] Lipid control in patients taking lipid lowering drugs has improved, however, reaching the 2007 total cholesterol target of 4.0 mmol/L or less may prove to be an important challenge for patients and physicians.[28] Systematic reviews indicate that a reduction of total (and LDL) cholesterol by statins is associated with marked reductions in both fatal and non-fatal CV events.[29] In the subgroup of patients with a history of CV disease we noticed a reduction in the portion of patients using concomitant cardioprotective drugs, that remarkably paralleled the

trend for those that did not reach the preset cut-off threshold target of total cholesterol (≤4.5 mmol/l) accepted for this analysis. Again, this might be an indication of lack of change in lifestyle, suboptimal prevention or both, in this subgroup of patients.

Even if drug treatment according to guidelines and blood lipid status substantially improved, the attainment of therapeutic targets for BP did not. Again this might, point to the fact that drug treatments alone are not sufficient, and must be combined with a professional lifestyle intervention. The recommendations for lifestyle management remain the foundation of preventive cardiology: to stop smoking, make healthy food choices, and become physically active. Moreover, the evidence for their effectiveness in cardiovascular disease prevention and rehabilitation programmes that address lifestyle is compelling.[30] The preset targets as recommended by clinical practice guidelines are not unrealistic. In the Clinical Outcomes Utilising Revascularisation and Aggressive Drug Evaluation (COURAGE) trial, patients had high rates of adherence to the regimen of diet, regular exercise, and smoking cessation.[31]

An important strength of this analysis is that all baseline data were collected using a standardised CRF in an established network of participating sites across Europe by a single ARO.

The findings of this analysis must be considered within the context of the studies' limitations. Our study results only apply to patients in the need for PCI for symptomatic CAD, extrapolations to the general populations may not be valid. A selection bias towards the sickest patients, not receiving effective CV prevention cannot be excluded. Patients included in stent investigations were recruited in specialist cardiac centres and may not be a representative sample of all patients with CV disease requiring PCI and stenting in Europe. The reality of preventive therapy and lifestyle changes in non-specialist centres may be considerably different. Our analysis included only those aged 25-84 year because of the limited data available in older patient groups. Moreover, elderly patients and women have been shown to be under-represented in many clinical trials and surveys in cardiovascular heart disease.[32]

Changes in the baseline characteristics of patients who were enrolled in these stent investigations between 1995-2005 most probably reflect the shift in the general patient population. However, we acknowledge the slight variation in individual inclusion and exclusion criteria among studies which may have had an impact on the results. On the other hand, our statistical analysis allows correction for a relatively large variation of some items between studies within (a) study period(s) with respect to the observed trend over time.

## Conclusion

Patients requiring PCI are an important target population in whom lifestyle changes and aggressive secondary preventative measures should be aimed. PCI should open the door towards optimising secondary prevention.

## Conflict of interest statement

G.E. Van Es and D. Goedhart are employees of Cardialysis. All other members of the analysis and writing committee have no conflict of interest to declare.

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# Appendix

**Table 1. Studies included in the Cardialysis stent database.**

| Study | Study name | Number of patients |
|---|---|---|
| ACS329[1] | ACS Multilink® Radiation Coronary Stent System Project | 31 |
| ADVANCE[2] | Additional Value of NIR Stents for Treatment of Long Coronary Lesions | 437 |
| ARTS-I[3] | Arterial Revascularisation Therapies Part I | 1205 |
| ARTS-II[4] | Arterial Revascularisation Therapies Part II | 607 |
| BENESTENT-2[5] | Belgian Netherlands Stent-2 | 827 |
| DIRECTOR[6] | DIRECT stenting with the ORBUS R Stent | 30 |
| DOMINO[7] | The Study to Compare Cypher Versus Cypher Select in Treating Coronary Artery Lesions | 102 |
| EUROSPAH[8] | European Sonotherapy Prevention of Arterial Hyperplasia | 403 |
| FINESS1[9] | First International New Intravascular Rigid-Flex Endovascular Stent Study | 255 |
| FINESS2[10] | First International New Intravascular Rigid-Flex Endovascular Stent Study-2 | 156 |
| GRANITE[1] | Gamma Radiation to Athermatous Neointima using Intra Coronary Therapy in Europe | 96 |
| HEALING-II[11] | Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth | 63 |
| JO-STENT[1] | | 115 |
| MAGIC 5-L[L12] | The relationship between Wallstent length and late clinical and angiographic results | 276 |
| MUST[13] | Multicentre Stents Ticlopidine | 260 |
| NIRTOP[14] | Comparison of the NIRFLEX and NIRFLEX Royal Stent Systems | 158 |
| NUGGET[15] | NIR ultra-gold gilded equivalency trial | 603 |
| NOBORI[16] | Nobori Stent Trial | 120 |
| PAIR[17] | Pullback Atherectomy for In-stent Restenosis Trial | 52 |
| PAMI[18] | Primary Angioplasty in Myocardial Infarction | 900 |
| STENT PAMI PILOT STUDY[19] | Primary Angioplasty in Myocardial Infarction – pilot study | 101 |
| RAVEL[20] | Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions | 238 |
| REALITY[21] | Comparison of the Cypher Sirolimus Eluting and the Taxus Paclitaxel Eluting Stent Systems Trial | 1386 |
| SCEPTER[22] | Study of the Controlled Elution of Paclitaxel for the Elimination of Restenosis | 271 |
| SICTO[23] | Sirolimus-eluting stent in chronic total occlusions | 25 |
| SIMPLE[24] | The safety and efficacy of the Infinnium paclitaxel eluting stent for the treatment of single de novo lesions | 103 |
| SPIRIT[25] | Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions | 60 |
| SOPHOS[26] | Study Of PHosphorylcholine coating On Stents | 425 |
| TAXUS III[27] | TAXUS stent trial | 28 |
| TESTER[28] | Terumo Stent Registry | 100 |
| VELVET-2[29] | Direct stenting with the Bx VELOCITY balloon-expandable stent mounted on the Raptor rapid exchange delivery system versus pre-dilatation in a European randomized Trial | 401 |
| WELLSTENT NATIVE STUDY[30] | The safety and efficacy of the self-expanding Wallstent | 105 |
| WEST-1[31] | West European Stent Trial | 102 |
| WEST-2[32] | West European Stent Trial | 165 |


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**Table appendix 2. Relevant clinical in-and exclusion criteria for trials included this analysis.**

| Inclusion criteria | Study acronym | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ADVANCE | ARTS-I | ARTS-II | BENESTENT_II | DIRECTOR | DOMINO | EUROSPAH | FINESS-1 | FINESS-2 | GRANITE | HEALING-II | JO-STENT | MAGIC 5-L | MUST | NIRTOP | NUGGET | NOBORI | PAIR | PAMI | STENT-PAMI PILOT | RAVEL | REALITY | SCEPTER | SICTO | SIMPLE | SPIRIT | SOPHOS | TAXUS-III | TESTER | VELVET-2 | WELLSTENT NATIVE STUDY | WEST-1 | WEST-2 |
| Age 18 to 85 years | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | | ■ |
| Stable and unstable angina.* | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | | | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| Myocardial infarction | | | | | | | | | | | | | | | | | | | ■ | ■ | | | | | | | | | | | | | | |
| Eligible for PCI | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | | | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| Informed consent | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| Not pregnant and protected against pregnancy during the study | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| Participating in an investigational drug or another device study | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| **Exclusion criteria** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| LV- EF ≤25% | | | | | | | | | | | | | | | ■ | ■ | | | | | | ■ | | | | | | | | | | | | |
| ≤30% | ■ | | | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | | | ■ | | | | ■ | | ■ | ■ | ■ | ■ | | ■ | | ■ | ■ | | |
| Heart failure or CS | | ■ | ■ | | | | | | | | | | | | | | | | ■ | ■ | | | | | | | | | | | | | | |
| Intolerance of aspirin, clopidogrel, ticlopidine, heparin, stainless steel, or contrast material. | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| Impaired renal function | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Creatinine >3.0 g/dl | | ■ | ■ | | | | | | | ■ | ■ | | | | | ■ | ■ | | | | ■ | ■ | ■ | ■ | ■ | ■ | | ■ | ■ | ■ | | | | |
| Creatinine clearance <50 ml/kg/min | | ■ | ■ | ■ | ■ | ■ | ■ | ■ | | ■ | ■ | | | | | | ■ | | | | ■ | ■ | | ■ | | | | | | ■ | | | |
| Any significant condition which in the investigators opinion could interfere with the patient's optimal participation in the study. | | ■ | ■ | ■ | ■ | ■ | ■ | | | ■ | ■ | | | | | ■ | ■ | ■ | | | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| Known malignancy or life expectancy of less than the duration of the trial | ■ | ■ | ■ | ■ | ■ | ■ | ■ | | | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | | | ■ | ■ | | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| Q-wave-MI in the territory supplied by the vessel to be stented and a large akinesia in the same region | | | | | | | | | | | ■ | ■ | ■ | ■ | ■ | ■ | ■ | | | | ■ | ■ | ■ | ■ | ■ | ■ | ■ | | ■ | ■ | ■ | | |
| MI <48 hours | | | | | | | ■ | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <72 hours | | | | | | | | | ■ | ■ | ■ | | | | ■ | ■ | | ■ | | | ■ | ■ | | | ■ | ■ | | | ■ | ■ | | | |
| <7 days | ■ | ■ | ■ | ■ | ■ | ■ | | | | | | | ■ | | | | | | | | | | | | | | ■ | ■ | | | ■ | | |
| <14 days | | | | | | | | | | | | | | ■ | | | | | | | | | | | | | | | | | | | |
| <30 days | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | ■ | ■ |
| Stroke <6 months | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | | ■ | | | ■ | ■ | ■ | ■ | | | | | ■ | | | ■ | ■ | ■ | ■ | | | ■ | | |
| GI bleed or peptic ulcer <6 months | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | | ■ | | | ■ | ■ | ■ | ■ | | Active bleed | | | ■ | | | ■ | ■ | ■ | ■ | | | ■ | | |
| Hepatic failure | | ■ | ■ | ■ | ■ | ■ | ■ | | | | ■ | | ■ | | ■ | | | | | | | | | | ■ | | | ■ | | | ■ | ■ | ■ |

CS: cardiogenic shock; GI: gastrointestinal; HF: heart failure; MI: myocardial infarction; PCI: percutaneous coronary intervention; LV-EF: left ventricular ejection fraction; H: hours; D: days; M: months; * Canadian Cardiology Society (I-IV) and Braunwald (B and C, I-III) classifications, or documented silent ischaemia.

# CHAPTER 5.2

## A Patient-Level Pooled Analysis Assessing the Impact of the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) Score on 1-Year Clinical Outcomes in 6,508 Patients Enrolled in Contemporary Coronary Stent Trials

Garg S, Sarno G, Girasis C, Vranckx P, de Vries T, Swart M, Bressers M, Garcia-Garcia HM, van Es GA, Räber L, Campo G, Valgimigli M, Dawkins KD, Windecker S, Serruys PW.

*JACC Cardiovasc Interv*. 2011;**4**: 645-53. [**original research paper**]

CLINICAL RESEARCH

# A Patient-Level Pooled Analysis Assessing the Impact of the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) Score on 1-Year Clinical Outcomes in 6,508 Patients Enrolled in Contemporary Coronary Stent Trials

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**Objectives** This study sought to assess the impact of the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score (SXscore) on clinical outcomes in patients undergoing percutaneous coronary intervention.

**Background** The SXscore has been demonstrated to have an ability to predict clinical outcomes in patients undergoing percutaneous revascularization. Current studies are limited by the relatively small number of patients in each SXscore group.

**Methods** Patient-level data from 7 contemporary coronary stent trials were pooled by an independent academic research organization (Cardialysis, Rotterdam, the Netherlands). Analysis was performed on a cohort of 6,508 patients treated with drug-eluting stents and who had calculated SXscores. Clinical outcomes in terms of death, myocardial infarction (MI), repeat revascularization, and major adverse cardiac events (MACE, a composite of death, MI, and repeat revascularization) were subsequently stratified according to SXscore quartiles: $SXscore_{Q1} \leq 8$ (n = 1,702); $8 < SXscore_{Q2} < 15$ (n = 1,528); $15 \leq SXscore_{Q3} < 23$ (n = 1,620); and $SXscore_{Q4} \geq 23$ (n = 1,658).

**Results** One-year outcomes were available in 6,496 patients (99.8%). At 1-year follow-up, all clinical outcomes including mortality, MI, repeat revascularization, MACE, and definite and any stent thrombosis were all significantly higher in patients in the highest SXscore quartile. Similar trends were observed in a subgroup of 2,093 patients (32.2%) who presented with an ST- or non–ST-segment elevation MI. The rate of MACE among patients with an SXscore >32 and ≤32 was 24.9% and 14.0%, respectively ($p < 0.001$). The SXscore was identified as an independent predictor of all clinical outcomes including mortality, MACE, and stent thrombosis ($p < 0.001$ for all).

**Conclusions** This study confirms the consistent ability of the SXscore to identify patients who are at highest risk of adverse events. (J Am Coll Cardiol Intv 2011;4:645–53) © 2011 by the American College of Cardiology Foundation

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The Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score (SXscore) is an angiographic scoring system that was developed to quantify the complexity of coronary artery disease (CAD) in patients undergoing coronary revascularization (1,2). The score was initially developed for use in the SYNTAX trial as a means of bringing together the cardiologist and cardiac surgeon to study, in great detail, the coronary angiogram of patients selected for enrollment (3). Subsequent analyses, however, have indicated that the SXscore can be used to assist in deciding the optimal revascularization strategy in patients with complex CAD (3,4), while also identifying those patients treated by percutaneous coronary intervention (PCI) who are at highest risk of adverse cardiac events (3–14). This ability to risk stratify patients has been evaluated in numerous studies, which include those with an all-comers design (8–10), and those more specifically enrolling patients with multivessel disease (5,6), complex CAD (triple-vessel and/or left main disease) (3,12–14), or those presenting with ST-segment elevation myocardial infarction (STEMI) (11). Importantly, the SXscore has consistently been identified as an independent predictor of major adverse cardiac events (MACE) and/or mortality at follow-up ranging between 1 and 5 years (5–13).

**Abbreviations and Acronyms**

**CABG** = **coronary artery bypass graft**

**CAD** = **coronary artery disease**

**MACE** = **major adverse cardiac event(s)**

**MI** = **myocardial infarction**

**PCI** = **percutaneous coronary intervention**

**ST** = **stent thrombosis**

**STEMI** = **ST-segment elevation myocardial infarction**

**SXscore** = **Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery score**

**TVR** = **target vessel revascularization**

These assessments of the SXscore are limited however by the relatively small number of patients in each SXscore tertile, which have ranged from approximately 200 to 700 patients (5,8). In an effort to overcome these limitations, the present study pooled patient-level data from 7 contemporary coronary stent trials (3,15–20) where the SXscore was available, thereby enabling a more precise evaluation of the benefit of calculating the SXscore in patients treated by PCI.

## Methods

**Study design and patient population.** We identified 7 contemporary coronary stent trials for which the SXscore was available (3,15–20): SIRTAX (Sirolimus-Eluting Stent Compared With Paclitaxel-Eluting Stent for Coronary Revascularization) trial, LEADERS (Limus Eluted From a Durable Versus Erodable Stent Coating) trial, RESOLUTE (Resolute All Comers) trial, ARTS II (Arterial Revascularization Therapies Study II), SYNTAX, STRATEGY (Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent Versus Abciximab and Bare-Metal Stent in Myocardial Infarction) trial, and MULTISTRATEGY (Multicenter Evaluation of Single High-Dose Bolus Tirofiban Versus Abciximab With Sirolimus-Eluting Stent or Bare-Metal Stent in Acute Myocardial Infarction) study. Detailed individual study design and trial results are available elsewhere (3,15–20). In brief, all studies included patients with obstructive CAD that was amendable to coronary stent implantation, with drug-eluting stents used exclusively in all but 2 studies. Study inclusion criteria were deliberately heterogeneous ranging from an all-comers design (15–17), to studies only recruiting patients with complex CAD (3,18), or only those with STEMI (19,20). A summary of all studies, including pertinent inclusion and exclusion criteria, study stents, study procedures, and dual antiplatelet therapy regimes are shown in Online Table 1. All studies complied with the Declaration of Helsinki and were approved by the ethical review board in each institution. All patients provided written, informed consent for participation in the individual studies.

After identification of appropriate studies, the principal investigators of each study were subsequently contacted and individual patient data were requested on a broad range of core baseline clinical variables, procedural results, and clinical outcomes at 1-year follow-up. Clinical outcomes included data on death, myocardial infarction (MI), any repeat revascularization (either PCI or coronary artery bypass graft [CABG]), and stent thrombosis (ST). Death and MI were available from all studies, whereas any repeat revascularization was only available from 4 studies: ARTS II, SYNTAX, RESOLUTE, and LEADERS. Of the remaining 3 studies, 2—STRATEGY and MULTISTRATEGY—reported only clinically indicated target vessel revascularization (TVR) (19,20), whereas 1—SIRTAX—reported clinically and nonclinically driven target lesion revascularization and TVR (16). Data for ST was available from all studies. A summary of individual trial endpoints is shown in Online Table 2.

Patient-level-based data were subsequently transferred to an independent academic research organization (Cardialysis, Rotterdam, the Netherlands), where they were merged

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Manuscript received September 27, 2010; revised manuscript received January 3, 2011, accepted February 23, 2011.

with a database containing the calculated SXscore and its components. Data from each trial were recoded by researchers (S.G., M.S., and T.d.V.), and finally, 2 researchers (S.G., P.W.S.) analyzed and interpreted the data.

**SYNTAX score.** The SXscore for each patient was calculated by scoring all coronary lesions with a diameter stenosis ≥50%, in vessels ≥1.5 mm, using the SXscore algorithm, which is described in full elsewhere (1,2) and is available on the SXscore Website (21). In the SYNTAX, LEADERS, and RESOLUTE studies, all angiographic variables required to calculate the SXscore were recorded prospectively by a team of 2 core laboratory analysts (Cardialysis) (3,15,17). In contrast, the SXscore in the SIRTAX, ARTS II, STRATEGY, and MULTISTRATEGY studies was calculated retrospectively by individual teams made up of 2 researchers (S.G., G.S., C.G., or M.V.) (16,18–20). Of note, at the time of the calculation, all investigators were blinded to clinical data, clinical presentation, and outcomes. In the event of disagreement, the opinion of a third analyst was sought, and the final decision was established by consensus. Core laboratory analysts and researchers have been shown on 2 occasions to have a similar degree of intraobserver variability (2,22).

The initial description of the SXscore calculation did not include patients presenting with STEMI or those with restenotic lesions. Patients with occluded infarct-related arteries were subsequently scored as occlusions of unknown duration in a similar manner as any chronically occluded artery. Similarly, patients with lesions due to restenosis or in-stent restenosis were scored in the same manner as if the lesion were a de novo lesion. Although this methodology was not described in the original description of the SXscore, it has previously been applied to other all-comers and STEMI populations (8–11).

**Clinical endpoints and definitions.** The primary endpoint of this pooled analysis was all-cause mortality at 1-year follow-up. The secondary endpoints included MACE, a composite of death, MI, and any repeat revascularization; a combined safety endpoint of death and MI; and the individual endpoints of MI, repeat revascularization (PCI or CABG), and stent thrombosis. In patients presenting with an MI, clinically indicated TVR is also reported.

Complete definitions are available in the individual study publications (3,15–20). Deaths from all causes are reported. As indicated in Online Table 3, there was a wide variation in the definition of MI between studies that reflects the heterogeneous study inclusion criteria, the variations in study design, and the different periods during which studies were performed. As all clinical events from each individual trial were adjudicated by independent clinical event committees, no attempt was made to readjudicate MI events in the different trials to compensate for the differences in individual definition of MI. Therefore, all MIs reported in the current study are as per individual protocol definitions. All repeat revascularization procedures were reported. The definitions of target lesion revascularization and TVR, and the criteria for a clinically driven revascularization used in the 5 studies reporting these outcomes (15–17,19,20) are provided in Online Table 2. All studies apart from the SYNTAX study reported ST defined according to the Academic Research Consortium definitions (23).

**Statistical analysis.** All patients with a calculated SXscore were included in the analysis. All variables were stratified according to SXscore quartiles. Discrete data were summarized as percent (frequencies), whereas continuous data were expressed as mean ± SD. Testing for (linear) trends was done by using generalized linear models with SYNTAX class as a covariable for continuous variables and the Cochran-Armitage test for trends in categorical data. The distribution of the SXscore was assessed for normality using the Kolmogorov-Smirnov test. Clinical outcomes are presented separately for all patients, those presenting with an MI (STEMI or non-STEMI), and those patients with an SXscore >32, which was the highest SXscore tertile in the SYNTAX study (3). Survival curves were constructed for time-to-event variables using Kaplan-Meier estimates and compared by the log-rank test. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. A Cox multivariate model

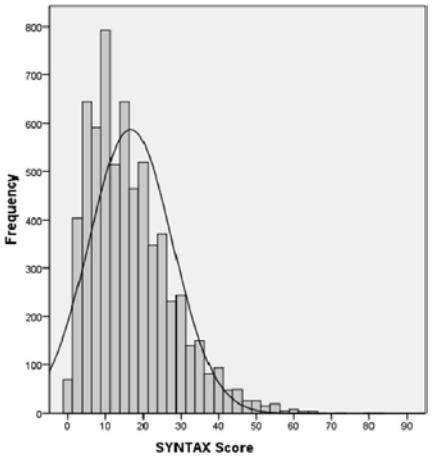


**Figure 1. Distribution of the SYNTAX Scores Among the 6,508 Patients Enrolled in the Study**

Histograms of the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score with a superimposed normal curve. The score distribution is skewed to the right, and not normally distributed.

**Table 1. Baseline Clinical Characteristics Stratified According to SYNTAX Score Quartile**

| Variable | SXscore ≤8 (n = 1,702) | 8 < SXscore <15 (n = 1,528) | 15 ≤ SXscore <23 (n = 1,620) | SXscore ≥23 (n = 1,658) | p Value |
|---|---|---|---|---|---|
| Baseline characteristics | | | | | |
| Male | 73.7 (1,254) | 74.3 (1,136) | 76.1 (1,233) | 77.0 (1,276) | 0.01 |
| Age, yrs | 62.2 ± 10.7 | 62.8 ± 10.8 | 63.7 ± 10.7 | 66.5 ± 10.3 | <0.001 |
| Body mass index, kg/m$^2$ | 27.6 ± 4.3 | 27.9 ± 4.4 | 27.5 ± 4.3 | 27.7 ± 4.6 | 0.78 |
| Risk factors | | | | | |
| Previous MI | 28.9 (423/1,464) | 29.3 (397/1,354) | 30.4 (447/1,471) | 33.3 (536/1,611) | 0.007 |
| Diabetes | 18.7 (316/1,689) | 20.4 (310/1,519) | 24.5 (395/1,611) | 29.2 (483/1,653) | <0.001 |
| Hypertension | 68.7 (1,159/1,686) | 68.1 (1,032/1,516) | 69.8 (1,120/1,605) | 71.4 (1,177/1,648) | 0.06 |
| Hypercholesterolemia | 65.4 (1,110/1,681) | 63.1 (954/1,511) | 65.8 (1,054/1,602) | 68.1 (1,119/1,642) | 0.04 |
| Family history of ischemic heart disease | 40.6 (396/976) | 35.8 (312/871) | 35.7 (353/988) | 28.5 (338/1,188) | <0.001 |
| Current smoker | 36.0 (510/1,417) | 33.6 (441/1,311) | 32.3 (448/1,385) | 22.9 (341/1,489) | <0.001 |
| Peripheral vascular disease | 5.9 (57/964) | 7.2 (62/865) | 7.0 (69/991) | 9.1 (111/1,221) | 0.007 |
| Previous PCI | 31.8 (468/1,470) | 24.8 (339/1,369) | 19.1 (285/1,492) | 12.8 (208/1,623) | <0.001 |
| Previous stroke | 3.9 (34/879) | 2.9 (24/830) | 4.4 (43/974) | 7.0 (87/1,240) | <0.001 |
| Creatinine clearance, ml/1.73 m$^2$ | 95.0 ± 42.4 | 94.0 ± 35.1 | 89.7 ± 32.9 | 84.9 ± 31.7 | <0.001 |
| Creatinine >200 μmol/l | 0.6 (8/1,392) | 1.0 (14/1,367) | 0.7 (11/1,487) | 1.8 (28/1,576) | 0.004 |
| Ejection fraction | 58.2 ± 11.0 | 56.2 ± 11.7 | 56.0 ± 12.6 | 55.5 ± 13.4 | <0.001 |
| SYNTAX score | 5.0 ± 2.2 | 11.4 ± 1.7 | 18.3 ± 2.3 | 31.8 ± 8.3 | <0.001 |
| Indication for treatment | | | | | |
| Stable angina | 38.5 (656) | 36.5 (558) | 35.6 (576) | 42.1 (698) | 0.07 |
| Unstable angina | 19.4 (330) | 17.1 (262) | 19.8 (321) | 24.5 (406) | <0.001 |
| ST-segment elevation MI | 18.4 (314) | 23.3 (356) | 22.3 (362) | 14.6 (242) | 0.005 |
| Non–ST-segment elevation MI | 15.3 (261) | 15.1 (231) | 12.1 (196) | 7.9 (131) | <0.001 |
| Silent ischemia | 9.9 (62/625) | 9.7 (61/630) | 9.8 (79/809) | 8.6 (100/1,157) | 0.37 |

Values are % (n), mean ± SD, or % (n/N).
MI = myocardial infarction; PCI = percutaneous coronary intervention; SXscore = SYNTAX score; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

was performed using the covariates sex, age greater than 65 years, diabetic status, urgency of procedure, SXscore, and use of a first-generation drug-eluting stent. A p value of $<0.05$ was considered significant, and all tests were 2-tailed. Data were analyzed with SAS (version 9.2, SAS Institute, Inc., Cary, North Carolina).

## Results

The SXscore was available in 6,508 of 7,639 patients (85.2%) enrolled in the 7 individual studies. The main reasons for absent SXscores were missing baseline angiograms, the presence of prior surgical revascularization, or treatment with bare-metal stents. In total, the SXscore ranged from 0 to 83, with a mean ± SD of 16.7 ± 11.1 and a median of 15 (interquartile range: 8 to 23). The distribution of the SXscore is shown in Figure 1; the score was not normally distributed (Kolmogorov-Smirnov test $p < 0.05$). In this analysis, the 6,508 patients were divided according to their SXscore into quartiles defined as: $SXscore_{Q1}$ ≤8 (n = 1,702), 8 < $SXscore_{Q2}$ <15 (n = 1,528); 15 ≤ $SXscore_{Q3}$ <23 (n = 1,620); $SXscore_{Q4}$ ≥23 (n = 1,658).

**Baseline angiographic and procedural characteristics.** Baseline clinical, angiographic, and procedural characteristics of the study population, stratified according to SXscore quartiles, are shown in Tables 1 and 2. Table 2 demonstrates that indicators of lesion complexity, such as an ostial lesion, a total occlusion, and the presence of a bifurcation, were all significantly more common in the highest SXscore quartile, reflecting the higher calculated SXscore for these lesions.

**Outcomes at 12 months.** Clinical outcomes at 12 months, which were available in 6,496 patients (99.8%) and a subset of 2,093 patients (32.2%) presenting with an STEMI or a non-STEMI, are shown in Table 3, whereas cumulative survival curves for all patients and those presenting with an MI are shown in Figure 2 and Online Figure 1, respectively. Overall, the primary endpoint of death was significantly higher in the highest SXscore quartile (1.6% vs. 1.2% vs. 3.2% vs. 4.6%, $p < 0.001$). A similar trend was noted for all other clinical endpoints, including the safety composite of death/MI and overall MACE, a composite of death/MI and repeat revascularization. All clinical outcomes in patients presenting with an MI, apart from death and cardiac death, were also significantly worse in those patients in the highest SXscore quartile.

**Table 2. Baseline Lesion and Procedural Characteristics Stratified According to SYNTAX Score Quartile**

| Variable | SXscore ≤8 (n = 1,702) | 8 < SXscore <15 (n = 1,528) | 15 ≤ SXscore <23 (n = 1,620) | SXscore ≥23 (n = 1,658) | p Value |
|---|---|---|---|---|---|
| Extent of disease | | | | | |
| Number of disease lesions | 1.4 ± 0.7 | 2.3 ± 1.0 | 3.0 ± 1.2 | 4.1 ± 1.6 | <0.001 |
| 1-vessel disease | 69.6 (1185) | 30.6 (467) | 15.4 (250) | 6.1 (101) | <0.001 |
| 2-vessel disease | 25.7 (437) | 49.6 (758) | 42.4 (687) | 24.9 (413) | 0.11 |
| 3-vessel disease | 2.7 (46) | 17.2 (263) | 40.4 (655) | 66.7 (1,106) | <0.001 |
| Lesion location | | | | | |
| Left main stem | 0.4 (7) | 3.8 (58) | 6.2 (100) | 21.1 (350) | <0.001 |
| Right coronary artery | 47.9 (816) | 58.5 (894) | 67.4 (1,092) | 80.5 (1,335) | <0.001 |
| Circumflex artery | 33.9 (577) | 49.3 (754) | 63.4 (1,027) | 81.7 (1,354) | <0.001 |
| LAD artery | 47.2 (803) | 72.6 (1,110) | 88.7 (1,437) | 93.8 (1,555) | <0.001 |
| Proximal LAD involvement | 8.0 (136) | 19.9 (304) | 34.8 (563) | 60.3 (1,000) | <0.001 |
| All de novo lesions | 92.7 (1,304/1,407) | 93.9 (1,303/1,388) | 95.3 (1,432/1,503) | 96.5 (1,547/1,603) | <0.001 |
| Lesion characteristics | | | | | |
| ≥1 bifurcation lesion | 18.9 (322) | 48.7 (744) | 60.9 (986) | 71.6 (1,187) | <0.001 |
| ≥1 trifurcation lesion | 0.5 (9) | 2.0 (31) | 3.2 (52) | 8.0 (132) | <0.001 |
| ≥1 ostial lesion | 1.8 (30) | 3.9 (60) | 4.2 (68) | 8.1 (134) | <0.001 |
| ≥1 occlusion | 7.9 (135) | 21.1 (323) | 33.1 (537) | 42.9 (712) | <0.001 |
| ≥1 tortuous lesion | 15.0 (256) | 29.1 (444) | 41.6 (674) | 62.7 (1,039) | <0.001 |
| ≥1 lesion ≥20 mm | 12.3 (209) | 28.1 (430) | 46.0 (745) | 66.9 (1,109) | <0.001 |
| ≥1 calcified lesion | 3.1 (52) | 11.8 (180) | 21.1 (342) | 43.6 (723) | <0.001 |
| ≥1 lesion with thrombus | 5.2 (88) | 6.3 (97) | 6.7 (108) | 6.2 (103) | 0.18 |
| Procedural characteristics | | | | | |
| Number of stents implanted | 1.7 ± 1.1 | 2.2 ± 1.5 | 2.9 ± 2.0 | 4.0 ± 2.3 | <0.001 |
| Total stent length, mm | 24.6 ± 15.3 | 36.3 ± 24.0 | 51.7 ± 35.0 | 75.7 ± 46.3 | <0.001 |
| ≥100 mm of stent implanted | 0.4 (4/1,086) | 2.1 (20/966) | 9.7 (104/1,075) | 24.9 (312/1,253) | <0.001 |
| Post-procedural hospital stay, days | 2.1 ± 2.8 | 2.5 ± 2.7 | 2.8 ± 3.3 | 3.8 ± 6.3 | <0.001 |

Values are mean ± SD, % (n), or % (n/N).
LAD = left anterior descending artery; other abbreviations as in Table 1.

The rate of ST followed the same trend as other clinical outcomes, with the highest rate noted in SXscore$_{Q4}$. Of note, rates of ST were higher in all quartiles for patients presenting with an MI compared with the full patient cohort.

**Clinical outcomes in patients with a SYNTAX score above and below 32.** In the current analysis, 9.3% of patients had an SXscore >32. The clinical outcomes of patients with an SXscore above and below 32 are shown in Table 4, whereas cumulative survival curves are shown in Online Figure 2. All events were at least 1.5× more common in patients with an SXscore >32 ($p < 0.001$ for all), and overall approximately one-quarter of patients in this high-risk group experienced an event (death, MI, or repeat revascularization) within 12 months.

**Multivariable analysis.** The results of the Cox multivariable analysis are shown in Table 5. Following adjusting of the confounding factors: age >65 years, sex, urgency of procedure, diabetic status, and use of a first-generation drug-eluting stent, the SXscore remained an independent predictor of clinical outcomes such as mortality, MACE, and ST (any and definite).

## Discussion

This study is the largest assessment of the SXscore in patients treated with PCI, and it confirms the ability of the SXscore to identify patients who are at highest risk of adverse events, irrespective of clinical presentation.

Several risk models have been developed for patients undergoing PCI; however, few, if any, have become embedded into regular clinical practice. Most of these risk models including the Mayo Clinic Risk Score, the EuroSCORE (European System for Cardiac Operative Risk Evaluation), and the National Cardiovascular Database Registry CathPCI risk score use a selection of clinical variables that have been identified as independent predictors of adverse outcome in those treated by PCI (24–30).

In contrast, the SXscore assesses the angiographic complexity of CAD and does not include any clinical variables in its calculation. The score was initially developed for the SYNTAX trial (3) to ensure the angiograms of patients selected for enrollment were appropriately scrutinized by members of the Heart Team, thereby ensuring patients

**Table 3. Clinical Outcomes at 1-Year Follow-Up Among All Patients and Those Presenting With an MI**

| Variable | SXscore ≤8 (n = 1,702) | 8 < SXscore <15 (n = 1,526) | 15 ≤ SXscore <23 (n = 1,617) | SXscore ≥23 (n = 1,651) | p Value |
|---|---|---|---|---|---|
| All patients | | | | | |
| Death | 1.6 (28) | 1.2 (19) | 3.2 (52) | 4.6 (76) | <0.001 |
| Cardiac death* | 0.8 (12/1,567) | 0.8 (11/1,412) | 2.3 (35/1,515) | 3.6 (57/1,599) | <0.001 |
| MI | 2.9 (50) | 3.2 (49) | 3.8 (61) | 6.1 (101) | <0.001 |
| Any repeat revascularization† | 7.7 (94/1,215) | 8.7 (102/1,167) | 11.4 (151/1,324) | 15.4 (236/1,529) | <0.001 |
| Death or MI | 4.3 (73) | 4.1 (62) | 6.5 (105) | 9.4 (156) | <0.001 |
| Death/MI or repeat revascularization† | 10.8 (131/1,215) | 11.4 (133/1,167) | 15.7 (209/1,324) | 21.1 (323/1,529) | <0.001 |
| ARC any stent thrombosis‡ | 1.3 (22/1,692) | 1.9 (28/1,448) | 3.1 (43/1,373) | 4.9 (45/920) | <0.001 |
| ARC definite stent thrombosis‡ | 0.6 (10/1,692) | 1.2 (17/1,448) | 1.5 (21/1,373) | 2.9 (27/920) | <0.001 |
| Patients presenting with MI§ | n = 575 | n = 587 | n = 558 | n = 373 | |
| Death | 2.4 (14) | 1.7 (10) | 5.6 (31) | 4.3 (16) | 0.006 |
| Cardiac death* | 0.9 (4/440) | 1.1 (5/473) | 3.9 (18/456) | 2.8 (9/321) | 0.005 |
| MI | 1.7 (10) | 2.9 (17) | 3.4 (19) | 6.4 (24) | <0.001 |
| Any repeat revascularization† | 7.3 (21/287) | 9.4 (33/351) | 12.3 (43/349) | 17.6 (50/284) | <0.001 |
| Clinically indicated target vessel revascularization | 2.8 (16) | 4.4 (26) | 6.5 (36) | 9.7 (36) | <0.001 |
| Death or MI | 4.0 (23) | 4.3 (25) | 8.2 (46) | 9.9 (37) | <0.001 |
| Death/MI or repeat revascularization† | 9.8 (28/287) | 12.3 (43/351) | 18.1 (63/349) | 22.5 (64/284) | <0.001 |
| ARC any stent thrombosis | 1.4 (8) | 2.2 (13) | 5.0 (28) | 5.9 (22) | <0.001 |
| ARC definite stent thrombosis | 0.7 (4) | 1.4 (8) | 2.7 (15) | 4.3 (16) | <0.001 |

Values are % (n) or % (n/N). *Cardiac death not available in the STRATEGY and MULTISTRATEGY studies. †Any repeat revascularization was not available in the SIRTAX, STRATEGY, or MULTISTRATEGY studies. ‡Any stent thrombosis or definite stent thrombosis defined according to ARC was not available in the SYNTAX study. §Includes ST-segment elevation MI and non–ST-segment elevation MI. Patients with acute MI were excluded from the SYNTAX and ARTS II studies.

ARC = Academic Research Consortium; ARTS II = Arterial Revascularization Therapies Study II; MULTISTRATEGY = Multicenter Evaluation of Single High-Dose Bolus Tirofiban Versus Abciximab With Sirolimus-Eluting Stent or Bare-Metal Stent in Acute Myocardial Infarction; SIRTAX = Sirolimus-Eluting Stent Compared With Paclitaxel-Eluting Stent for Coronary Revascularization; STRATEGY = Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent Versus Abciximab and Bare-Metal Stent in Myocardial Infarction; other abbreviations as in Table 1.

entered the appropriate arm of the trial. At the time of its development, it was hypothesized that the SXscore might help in identifying patients at highest risk of adverse events (1). Subsequent evaluations of the SXscore have confirmed this (3–14); however, studies have been hampered by relatively modest-sized patient cohorts, which for the purpose of analysis have been further subdivided into tertiles. Of note, the largest published assessment of the SXscore to date in patients treated with PCI, reported outcomes in 2,033 patients, with only 698 patients in the largest tertile (8). Importantly, the current pooled analysis has demonstrated findings consistent with previous evaluations of the SXscore, and to its strength, over 1,500 patients were present in each subgroup, alleviating some of the earlier concerns and ensuring robustness of the results. Furthermore, the identification of the SXscore as an independent predictor of clinical outcomes, including mortality MACE and ST, also provides further evidence to support the more routine use of the SXscore in the assessment of patients undergoing PCI.

This ability to identify patients at higher risk of adverse events has important clinical and research implications. From a clinical point of view, it enables physicians to more adequately inform or counsel their patients regarding the potential risk of adverse events and in the choice of revascularization procedure (CABG vs. PCI). Consequently, this should act as a trigger for more aggressive secondary preventive therapy, and lifestyle modification in those at highest risk, as well as close clinical monitoring of recurrent signs or symptoms of ischemia. Importantly, the present data also indicate that the SXscore is an independent predictor of ST, which speculatively might help identify those patients who would benefit most from assessment of platelet function together with more intensive, tailored and/or prolonged antiplatelet therapy. In clinical research, the ability to identify a population of patients with a particular anticipated event rate might help determine inclusion criteria for the design of more appropriately powered studies.

Previous studies that have assessed the SXscore and included a surgical treatment arm have concluded that SXscores >32/34 are the threshold above which patients fare better with CABG (3,4). In the present study, a one-tenth of the cohort had an SXscore over 32, and it is noteworthy that one-quarter of these patients experienced an event (death, MI, or repeat revascularization) within 12 months, confirming the poor outcomes associated with very high SXscores. In comparison, patients in the SYNTAX study with an SXscore >32, treated with CABG had a 1-year rate of major adverse cardiovascular and cerebrovas-

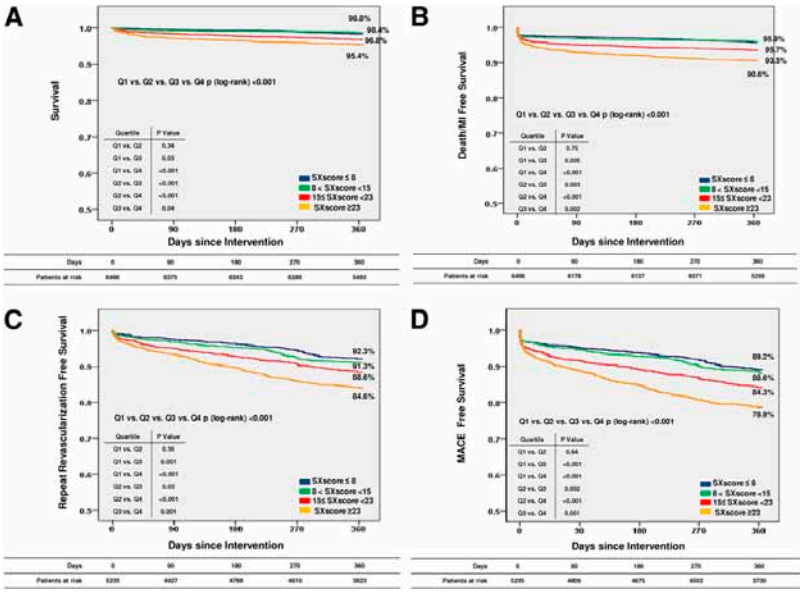


**Figure 2. Kaplan-Meier Cumulative Curves**

Kaplan-Meier cumulative curves for **(A)** death, **(B)** the composite of death and myocardial infarction, **(C)** repeat revascularization, and **(D)** major adverse cardiac events (MACE)—a composite of death, myocardial infarction, and repeat revascularization—at 1-year follow-up stratified according to SYNTAX score (SXscore) quartiles (Q). SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

cular events of 10.7% (3). This disparity reiterates the importance of discussing the most appropriate method of revascularization, which in this complex subgroup of patients should ideally be CABG.

The absence of clinical variables has been raised as a limitation of assessing risk using just the SXscore. Consequently, several modifications to the SXscore have been proposed by combining it with risk models using patient variables such as the ACEF (Value of Age, Creatinine, and Ejection Fraction) score and EuroSCORE (31,32). Evaluations of these combined scores have shown promising early results; however, data are limited to initial evalua-

**Table 4. Clinical Outcomes at 1-Year Follow-Up Among All Patients With SYNTAX Score Above and Below 32**

| Variable | SXscore ≤32 (n = 5,895) | SXscore >32 (n = 601) | RR (95% CI) | p Value |
|---|---|---|---|---|
| Death | 2.3 (135) | 6.7 (40) | 2.58 (1.94–3.42) | <0.001 |
| Cardiac death* | 1.5 (85/5,508) | 5.1 (30/585) | 2.81 (2.05–3.86) | <0.001 |
| MI | 3.8 (222) | 6.5 (39) | 1.66 (1.23–2.24) | 0.001 |
| Any repeat revascularization† | 10.3 (479/4,660) | 18.1 (104/575) | 1.76 (1.45–2.14) | <0.001 |
| Death or MI | 5.6 (330) | 11.0 (66) | 1.90 (1.50–2.40) | <0.001 |
| Death/MI or repeat revascularization† | 14.0 (652/4,660) | 24.9 (143/575) | 1.85 (1.55–2.20) | <0.001 |
| ARC any stent thrombosis‡ | 2.3 (122/5,199) | 6.8 (16/234) | 2.82 (1.75–4.55) | <0.001 |
| ARC definite stent thrombosis‡ | 1.3 (65/5,199) | 4.3 (10/234) | 3.19 (1.77–5.76) | <0.001 |

Values are % (n) or % (n/N). *Cardiac death not available in the STRATEGY and MULTISTRATEGY studies. †All repeat revascularization was not available in the SIRTAX, STRATEGY, or MULTISTRATEGY studies. ‡Any stent thrombosis or definite stent thrombosis defined according to ARC was not available in the SYNTAX study.

CI = confidence interval; RR= risk ratio; other abbreviations as in Tables 1 and 3.

**Table 5. Cox Multivariable Analysis**

| Clinical Outcome | Hazard Ratio for SYNTAX Score* (95% CI) | p Value |
|---|---|---|
| Death | 1.40 (1.21–1.62) | <0.001 |
| MI | 1.33 (1.19–1.49) | <0.001 |
| Any repeat revascularization | 1.29 (1.19–1.39) | <0.001 |
| Death or MI | 1.33 (1.21–1.46) | <0.001 |
| Death, MI, or repeat revascularization | 1.30 (1.21–1.40) | <0.001 |
| Definite stent thrombosis | 1.64 (1.31–2.05) | <0.001 |
| Any stent thrombosis | 1.51 (1.28–1.78) | <0.001 |

*After adjustment of confounding factors: age >65 years, sex, urgency of procedure, diabetic status, and use of a first-generation drug-eluting stent.
Abbreviations as in Tables 1 and 4.

tions in small patient populations, and examination in large robust populations is currently lacking. An extension to this concept has recently been reported by Chen et al. (33) who included not only clinical and angiographic variables, but also procedural variables such as the stenting technique employed. Although these additional variables were shown to improve the accuracy of risk prediction, these operator-dependent variables cannot be reliably predicted before undertaking revascularization, and therefore, unacceptably, their inclusion moves the ability to accurately calculate risk to a time point after the procedure has been completed.

**Study limitations.** This study is limited by the absence of a CABG comparator arm, and by the limited duration of follow-up. Unfortunately, comparisons of the SXscore with clinical models such as the EuroSCORE and ACEF score, and combined scores such as the clinical SYNTAX score were hindered by the respective absence of recorded EuroSCOREs, and the large number of missing quantitative values for the left ventricular ejection fraction and/or creatinine clearance, both of which are needed to calculate the ACEF and clinical SYNTAX scores.

## Conclusions

This study confirms the consistent ability of the SXscore to identify patients who are at highest risk of adverse events, irrespective of clinical presentation. These results provide important evidence to support the more routine use of the SXscore in any patient undergoing percutaneous coronary revascularization.

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**Key Words:** drug-eluting stent(s) ■ SYNTAX score.

## APPENDIX

**For supplementary information, tables, and figures, see the online version of this paper.**

# CHAPTER 5.3

## Combined Anatomical and Clinical Factors for the Long Term Risk Stratification of Patients Undergoing Percutaneous Coronary Intervention: The Logistic Clinical SYNTAX Score

*Euro Heart J* 2012 [**original research paper**]

# Combined anatomical and clinical factors for the long-term risk stratification of patients undergoing percutaneous coronary intervention: the Logistic Clinical SYNTAX score

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*Received 6 December 2011; revised 22 July 2012; accepted 9 August 2012*

**Background** The SYNTAX score (SXscore), an anatomical-based scoring tool reflecting the complexity of coronary anatomy, has established itself as an important long-term prognostic factor in patients undergoing percutaneous coronary intervention (PCI). The incorporation of clinical factors may further augment the utility of the SXscore to longer-term risk stratify the individual patient for clinical outcomes.

**Methods and results** Patient-level merged data from >6000 patients in seven contemporary coronary stent trials was used to develop a logistic regression model—the Logistic Clinical SXscore—to predict 1-year risk for all-cause death and major adverse cardiac events (MACE). A core model (composed of the SXscore, age, creatinine clearance, and left ventricular ejection fraction) and an extended model [incorporating the core model and six additional (best performing) clinical variables] were developed and validated in a cross-validation procedure. The core model demonstrated a substantial improvement in predictive ability for 1-year all-cause death compared with the SXscore in isolation [area under the receiver operator curve (AUC): core model: 0.753, SXscore: 0.660]. A minor incremental benefit of the extended model was shown (AUC: 0.791). Consequently the core model alone was retained in the final the Logistic Clinical SXscore model. Validation plots confirmed the model predictions to be well calibrated. For 1-year MACE, the addition of clinical variables did not improve the predictive ability of the SXscore, secondary to the SXscore being the predominant determinant of all-cause revascularization.

**Conclusion** The Logistic Clinical SXscore substantially enhances the prediction of 1-year mortality after PCI compared with the SXscore, and allows for an accurate personalized assessment of patient risk.

## Introduction

The SYNTAX score[1–4] (SXscore) has established itself as an important prognostic tool in risk stratifying patients in the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) pioneered Heart Team approach, and has since been validated in patients undergoing percutaneous coronary intervention (PCI) at a short and longer-term follow-up.[5–9] More recently the SXscore has been applied to contemporary 'All-Comers' coronary stent trials, and has consistently been

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shown to be an independent predictor of 1-year mortality and major adverse cardiac events (MACE).[10–12] In contrast, traditional risk scores for patients undergoing PCI principally allow for the estimation of procedural risk.[13–18]

The addition of clinical risk factors to the SXscore has been shown to potentially further augment its utility to objectively select the most appropriate revascularization strategy for patients planning to undergo surgical or percutaneous revascularization.[19–23] These approaches have involved the amalgamation of cardiac surgery-based summary risk scores to the SXscore to form the 'Global Risk' (SXscore and additive EuroSCORE)[23] and the 'clinical SXscore' (SXscore and the modified ACEF score).[19–22] As the individual clinical components of the cardiac surgery-based summary risk scores were not incorporated into the development of the combined risk models, and that these risk scores contained redundant information not relevant to the prediction of mortality after PCI—such as the chronic obstructive pulmonary disease and pulmonary hypertension in the EuroSCORE—this may have limited the predictive ability of the final risk models.[23] Furthermore, these approaches categorized patient risk without giving a more personalized risk assessment—with the Clinical SXscore[19–22] being able to identify a high-risk population only, and the Global Risk[23] a lower-risk population.

The aims of the present study are to combine the individual components of the Clinical SXscore—namely the continuous variables age, creatinine or creatinine clearance (CrCl), left ventricular ejection fraction (LVEF), and the SXscore—to form the Logistic Clinical SYNTAX score (Logistic Clinical SXscore). The underlying hypothesis being that the addition of these 'Core' clinical variables would provide the majority of the improvement to the 1-year predictive ability of the SXscore compared with the addition of further clinical variables. The second aim of this study was to allow for a more personalized approach to risk stratification, compared with the categorical approaches of previous risk models.[19–23]

# Methods

## Patients

Patient-level data from seven contemporary coronary stent trials[3,24–29] incorporating 6508 patients with a calculated SXscore were pooled for the present study and have previously been described.[19] An additional trial was excluded from the original database ($n = 187$)[30] due to permission being unobtainable from the study sponsor, and a further 12 patients excluded due to missing values for death, leading to a total of 6309 patients in the present analysis. The endpoints for the prognostic analyses were 1-year all-cause death and MACE [a composite of all-cause death, myocardial infarction (MI) and all-cause revascularization].

## Predictors and model development

During the development phase, two risk models were defined: (i) a core model that incorporated the SXscore and components of the ACEF and modified ACEF scores[31] (age, creatinine or CrCl and LVEF); (ii) an extended model that included the core model and the addition of best performing clinical variables that improved the performance of the core model. The CrCl was defined by the Cockcroft and Gault formula.[32] The left ventricular ejection fraction was defined as the percentage LVEF taken by transthoracic echocardiography or left ventriculography taken at the time of the diagnostic coronary angiogram.

As the Logistic Clinical SXscore was to be developed for predicting future longer-term (1-year) clinical outcomes, relatively weaker predictors (of borderline significance) were selected and retained in the extended model only if there was an appropriate increase in AUC when added to the core model in the multivariable logistic regression model, in line with work described by Harrell and others.[33,34]

Within all the coronary stent trials predictor values generally were >90% complete if the predictor was recorded. Multiple imputation of missing values in the trials with predictors recorded was undertaken using an advanced imputation strategy that takes the correlation between all potential predictors into account [method of chained equations (MICE algorithm in R software)].[35–37]

## Statistical analysis

Logistic regression analyses were performed to examine individual and joint relations between the core model, other clinical characteristics (extended model), and the binary outcome of 1-year all-cause death and MACE. Interaction terms between predictors were examined with likelihood ratio tests, but none was of sufficient relevance to extend the models beyond the main effects for each predictor. All analyses were stratified by the coronary stent trial.

Determining how the variables should be modelled was a vital step in identifying which variables were most strongly related to 1-year clinical outcomes. For the continuous predictors, possible non-linearity with clinical outcomes was assessed with restricted cubic spline functions. These are flexible functions that can accommodate curves in the form of the association to assess the assumption that patient characteristics are linearly related to the log odds of the outcome event.[33,34] To allow for a direct comparison of the prognostic value of predictors recorded in different units or scales, the odds ratios (ORs) for continuous predictors were scaled to correspond to a change from the 25th to 75th percentile of the predictor distribution.[37] Pooled ORs were estimated over the imputed data set, and repeated using only the complete data, which gave similar results (unpublished data). Statistical analyses were performed with R software[37] and SPSS Version 17.0 (SPSS, Inc., Chicago IL, USA).

## Validation

The predictive performance of the model was cross-validated by the omission of each of the coronary stent trials in turn, with the model fitted on the remaining pooled population, and the resulting fit tested on the omitted trial.[38–40] This methodology allowed for the estimation of the extent to which the predictive accuracy of the model (based on the entire sample) was affected by any differences between the seven coronary stent trials.[3,24–29] This form of cross-validation by trial was hence a stronger test of validity than if, for example, the study population had been divided at random into a development and validation cohort.[34,41,42]

The measure of predictive discrimination used to characterize the model performance in the original and the validation samples, was by the area under the receiver operating characteristic curve (AUC), and is equal to the *c*-statistic (the ability to distinguish a patient with and without a clinical outcome—and ranges from 0.50 (no better than flipping a coin) to 1.0 (model is 100% correct). Calibration—the agreement between observed and predicted risks—was assessed with the Hosmer–Lemeshow test and validation plots.[33,40]

### Model presentation

The final model is presented in a score chart with the scores based on the original logistic regression coefficients and can be used to obtain approximate predictions for individual patients.[34,40] Scores were based on rounding of the regression coefficients. A constant was subtracted or added to rescale the scores in positive integers. The sum scores were related to the risks of 1-year mortality with logistic regression. The score chart can be used to obtain approximate predictions for individual patients.

## Results

### Development of the model

Within the analysed data set 175 all-cause deaths (2.8%) and 797 MACE (15.8%) were observed. The univariate associations of the SXscore and clinical variables to 1-year all-cause death and MACE are shown in *Table 1*. Creatinine clearance was demonstrated to be a stronger univariate predictor of 1-year all-cause death compared with serum creatinine and was therefore incorporated into the core model (CrCl, OR: 2.2; 95% CI: 1.8–2.8; creatinine, OR: 1.4; 95% CI: 1.2–1.6). Linear relationships were a good approximation for the SXscore, age, CrCl, and LVEF with 1-year mortality, except that constant risk was evident at higher values for the LVEF (≥50%) and CrCl (≥90 mL/min) (Supplementary material online, Appendix). The four factors (SXscore, age, CrCl, and LVEF) were entered into a multivariable logistic regression model (*Table 2*) and confirmed to be strong independent predictors of 1-year mortality, thus forming the core model.

Similar analyses were repeated with the core model and the best performing clinical variables (six clinical variables: presentation, body mass index (BMI), peripheral vascular disease, diabetes, previous MI, smoking) for 1-year mortality to form the extended model.

**Table 1 Univariate associations between predictors of 1-year death and 1-year major adverse cardiac events in the pooled database of seven contemporary coronary stent trials**

| Characteristics | Coding | Death ($n$ = 6309) | | MACE ($n$ = 5048)[a] | |
|---|---|---|---|---|---|
| | | Number (%) | Univariate[b] | Number (%) | Univariate[b] |
| Core model | | | | | |
| SYNTAX score[c] | 23 vs. 8 | — | 1.7 (1.6–1.8) | — | 1.8 (1.7–1.8) |
| Age (years)[c] | 72 vs. 56 | — | 2.9 (2.7–3.1) | — | 1.2 (1.2–1.2) |
| CrCl[c] | 67 vs. 109 | — | 2.2 (1.8–2.6) | — | 1.2 (1.1–1.3) |
| Ejection fraction[d] | 40 vs. 50 | — | 2.2 (1.8–2.8) | — | 1.3 (1.1–1.5) |
| Extended model | | | | | |
| Presentation (%) | | | | | |
| Stable | | 72 (2.4) | 1.0 | 386 (15.1) | 1.0 |
| UA | | 32 (2.5) | 1.0 (0.7–1.6) | 185 (15.2) | 1.0 (0.8–1.2) |
| NSTEMI | | 25 (3.1) | 1.8 (1.1–2.9) | 102 (16.5) | 1.1 (0.8–1.4) |
| STEMI | | 46 (3.6) | 1.7 (1.1–2.9) | 97 (14.9) | 1.0 (0.8–1.3) |
| Female | | 58 (3.7) | 1.5 (1.1–2.1) | 215 (17.1) | 1.2 (1.0–1.4) |
| BMI[c] | 30 vs. 25 | — | 1.1 (1.0–1.1) | — | 1.0 (1.0–1.1) |
| PVD | | 20 (6.9) | 2.5 (1.5–4.1) | 49 (20.6) | 1.3 (0.9–1.8) |
| Diabetes (%) | | | | | |
| Non-insulin treated | | 32 (3.8) | 1.8 (1.2–2.8) | 146 (17.4) | 1.3 (1.1–1.6) |
| Insulin treated | | 27 (6.8) | 3.1 (2.0–4.8) | 101 (25.4) | 2.1 (1.6–2.6) |
| Hypertension (%) | | 134 (3.1) | 1.5 (1.1–2.2) | 579 (16.1) | 1.2 (1.0–1.5) |
| Hyperlipidaemia (%) | | 95 (2.3) | 0.6 (0.5–0.9) | 523 (15.3) | 1.0 (0.9–1.2) |
| Glycoprotein 2b3a use (%) | | 57 (3.3) | 1.2 (0.8–1.9) | 173 (16.3) | 1.1 (0.9–1.4) |
| Previous smoking (%) | | 48 (2.3) | 0.8 (0.6–1.2) | 259 (13.9) | 1.0 (0.8–1.2) |
| Current smoking (%) | | 37 (2.2) | 0.8 (0.5–1.1) | 178 (14.3) | 0.9 (0.7–1.1) |
| Previous MI (%) | | 68 (3.9) | 1.8 (1.3–2.4) | 250 (16.8) | 1.2 (1.0–1.4) |
| Previous PCI (%) | | 23 (1.9) | 0.7 (0.4–1.1) | 179 (16.9) | 1.2 (0.9–1.4) |
| TIA or CVA (%) | | 10 (5.5) | 1.5 (0.7–2.8) | 33 (22.8) | 1.4 (0.9–2.1) |
| Stent generation (%) | Newer generation | 58 (2.1) | 0.9 (0.5–1.6) | 382 (14.1) | 0.8 (0.6–1.1) |

CrCl, creatinine clearance; Yrs, years; UA, unstable angina; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; BMI, body mass index; PVD, peripheral vascular disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack; CVA, cerebrovascular accident.
[a]$n$ = 5048 without STRATEGY/MULTI-STRATEGY[24,28] and SIRTAX[26] trials secondary to all-cause revascularization not being recorded in the trials.
[b]Odds ratio (95% confidence interval).
[c]Odds ratios for continuous variables are given for the inter-quartile range.
[d]Odds ratio for a decrease in 10% for values below 50%.

**Table 2 Multivariable associations [odds ratio (95% CI)], between the individual components of the core model, for 1-year death and 1-year major adverse cardiac events in the pooled database of seven contemporary coronary stent trials**

| Characteristics | Coding | Death ($n$ = 6309) | MACE ($n$ = 5048)[a] |
|---|---|---|---|
| Core model | | | |
| SYNTAX Score[b] | 23 vs. 8 | 1.41 (1.15–1.73) | 1.72 (1.54–1.91) |
| Age (years)[b] | 72 vs. 56 | 2.06 (1.51–2.82) | 1.06 (0.92–1.22) |
| CrCl (ml/min)[b] | 67 vs. 109 | 1.53 (1.12–2.09) | 1.11 (0.94–1.31) |
| LVEF (%)[c] | 40 vs. 50 | 1.97 (1.61–2.41) | 1.10 (0.93–1.30) |

CrCl, creatinine clearance, LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events.
[a]$n$ = 5048 without STRATEGY/MULTI-STRATEGY[24,28] and SIRTAX[26] trials secondary to all-cause revascularization not being recorded in the trials.
[b]Odds ratios for continuous variables are given for the inter-quartile range (indicated in coding column).
[c]Odds ratio for a decrease in 10% for values <50%.

**Table 3 Performances of the Logistic Clinical SYNTAX score (core model) at cross-validation**

| Study | Death | | MACE | |
|---|---|---|---|---|
| | SYNTAX score | Core model | SYNTAX score | Core model |
| ARTS II[25] | 0.69 | 0.75 | 0.69 | 0.70 |
| LEADERS[27] | 0.63 | 0.74 | 0.62 | 0.61 |
| STRATEGY[24]/MULTI-STRATEGY[28] | 0.62 | 0.84 | — | — |
| RESOLUTE[29] | 0.57 | 0.77 | 0.63 | 0.63 |
| SIRTAX[26] | 0.64 | 0.71 | — | — |
| SYNTAX[3] | 0.67 | 0.73 | 0.58 | 0.59 |
| Overall[a] | 0.660 | 0.753 | 0.605[b] | 0.609[b] |

The core model was developed by omitting each study in turn, with the model fitted on the remaining pooled population, and validated by testing the resulting fit on the omitted trial.[38–40] Values shown are $c$-statistics for testing the resulting fit on the omitted trial (cross-validation).
LEADERS, biolimus-eluting stent with biodegradable polymer vs. sirolimus-eluting stent with durable polymer for coronary revascularization trial;[27] MACE, major adverse cardiac events; RESOLUTE, RESOLUTE all-comers trial;[29] SIRTAX, the sirolimus-eluting vs. paclitaxel-eluting stents for coronary revascularization trial;[26] SYNTAX, Synergy between PCI with Taxus and cardiac surgery trial;[3] ARTS II, the arterial revascularization therapies study part II trial;[25] STRATEGY, the single high-dose bolus tirofiban and sirolimus-eluting stent vs. abciximab and bare metal stent in myocardial infarction trial;[24] MULTISTRATEGY, comparison of angioplasty with infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarctiontrial.[28]
[a]Pooled population (combining all trials).
[b]$n$ = 5048 without STRATEGY/MULTI-STRATEGY and SIRTAX secondary to all-cause revascularization not being recorded in the trial.

## Model performances

### 1-Year all-cause death (death)

The core model (SXscore, age, CrCl, and LVEF) demonstrated a significantly better predictive ability for 1-year all-cause death compared with the SXscore in isolation (*Table 3*). Within the pooled population (combining all trials), the AUC was substantially higher for the core model compared with the SXscore in isolation (core model: 0.753, SXscore 0.660). A minor incremental benefit of the extended model (AUC: 0.791) compared with the core model was evident. Consequently, the core model was retained in the final Logistic Clinical SXscore, and the extended model excluded. The Hosmer–Lemeshow test confirmed that there was no evidence of poor calibration for the core model in pooled analyses of the seven trials ($P$ = 0.55). Validation plots of the core model indicated a good agreement between the observed and predicted risks in the three largest coronary stent trials ($n$ > 1000) (*Figure 1*). Within the SYNTAX trial recalibration of the validation plots was necessary to prevent generalized underestimation of predicted risk, and involved resetting the intercept of the calibration slope to zero.

### 1-Year major adverse cardiac events

For the outcome of 1-year MACE, the core and extended models added little incremental increase in predictive ability compared with the SXscore in isolation (AUC core model: 0.609, AUC extended model: 0.618, SXscore: 0.605) (*Tables 2 and 3*). Further analyses indicated that all-cause revascularization least benefited from the addition of clinical variables compared with death or MI (Supplementary material online, Appendix). Since the Logistic Clinical SXscore conferred no major additional benefit to the SXscore in predicting MACE, further analyses for this endpoint are not reported.

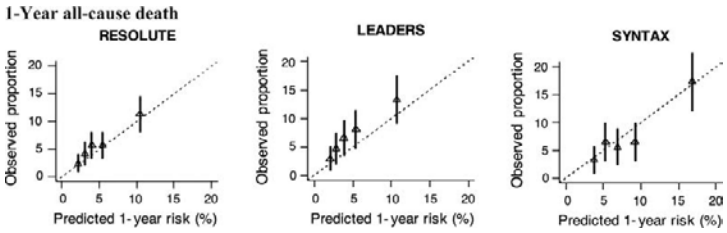


**Figure 1** Validation plots at cross-validation for the three largest coronary stent trials ($n > 1000$). Plots are shown for the core model predicting 1-year all-cause death. The triangles indicate the observed frequencies by quintile of predicted probabilities with a 95% confidence interval. Good agreement was evident between observed and predicted risks, indicating that the core model did not over or under-estimate 1-year mortality (i.e. good calibration).

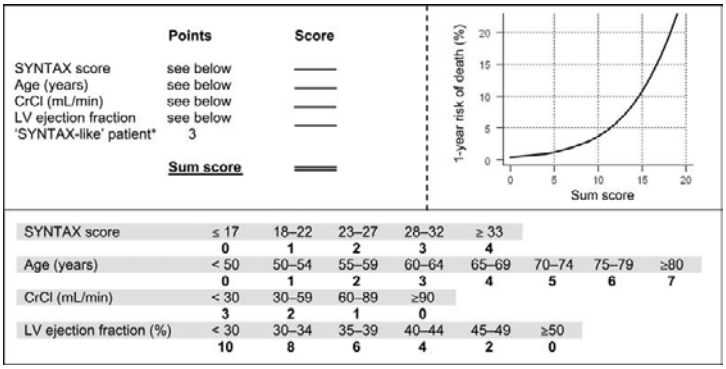


**Figure 2** The Logistic Clinical SYNTAX score for the prediction of 1-year death. *SYNTAX-like patient defined as fulfilling the enrolment criteria for the SYNTAX All-Comers trial, i.e. left main stem (isolated or associated with one-, two-, or three-vessel disease) or three-vessel disease alone. CrCl, creatinine clearance, LV ejection fraction, left ventricular ejection fraction.

### Score charts for 1-year all-cause death

A simple score chart for the bedside application of the final Logistic Clinical SXscore for predicting 1-year all-cause death after PCI is illustrated (*Figure 2*). An extra score is included for a "SYNTAX-like" patient, i.e. a patient presenting with left main disease (isolated or associated with 1, 2, or 3-vessel disease) or 3-vessel disease, due to the need to recalibrate risks to the SYNTAX trial patients as described previously. One-year mortality can be accurately estimated by the summation of scores. Similar charts for the extended model are enclosed in the Supplementary material online, Appendix.

## Discussion

The main findings from this study are that: (i) the Logistic Clinical SXscore—consisting of four continuous variables (SXscore, age, CrCl, LVEF)—substantially enhances the risk stratification of PCI patients for the outcome of 1-year all-cause death compared with the SXscore in isolation; (ii) the Logistic Clinical SXscore was able to accurately distinguish patients with or without a clinical outcome (discrimination) and could accurately predict individual patient risk (calibration) without under or over-estimating risk; (iii) the addition of further clinical variables to the four key predictors of the Logistic Clinical SXscore (SXscore, age, CrCl, and LVEF) did not substantially increase its predictive ability; (iv) an individualized approach to the longer-term (1-year) risk stratification of patients after PCI was achievable utilizing the SXscore and (v) the SXscore in isolation was the predominant determinant of 1-year MACE with little additional predictive benefit of clinical variables, predominantly secondary to the SXscore being the main determinant of all-cause revascularization.

## The logistic clinical SYNTAX score: predicting 1-year death

The findings of the Logistic Clinical SXscore, namely that a few strongly predictive clinical variables leading to the accurate prediction of 1-year all-cause death after PCI, are consistent with the concepts of the "law of parsimony" or "Occam's razor." Age, CrCl, and LVEF are objectively measured continuous clinical variables in line with the ACEF methodology, which has previously been shown to match or even surpass the EuroSCORE (consisting of 17 clinical variables) in predicting in-hospital mortality after elective coronary artery bypass graft surgery.[31,43,44] Explanations for this comparability have included that the clinical variables of the ACEF score were objectively defined and continuous.[31]

Notably the addition of a further six clinical variables to the Logistic Clinical SXscore to form the extended model lead to a minor incremental increase in its predictive ability. This is likely related to the inter correlation between the core model and the additional clinical variables. Clear correlations were evident (Pearson correlation coefficient 0.2 or greater, $P < 0.001$) for age and gender/hypertension; CrCl and gender/BMI; LVEF and MI; SXscore and prior PCI; BMI and diabetes mellitus. In addition the presence of diabetes has historically been associated with adverse outcomes after PCI.[45,46] It is however likely that patients with more severe diabetes were captured by the continuous variables in the Logistic Clinical SXscore, in particular a reduced CrCl. Both a reduced CrCl and proteinuria—a marker of diabetic nephropathy—have previously been shown to be significant determinants of adverse risk following PCI.[47–49] Furthermore diabetics without evidence of proteinuria have also previously been reported to have a similar survival compared with non-diabetics.[47]

## SYNTAX score

The SXscore calculation has previously been reported to have moderate inter-observer variability when performed by interventional cardiologists,[4,50] which may be perceived as a limitation of the Logistic Clinical SXscore. Appropriate training of SXscore reporting has, however, been shown to substantially reduce inter-observer variability.[1,2,50] It has previously been suggested that the SXscore is a reflection of the underlying co-morbidity of the patient,[23] for which the present study provides further supportive evidence. This notion is also supported by the 10-year predicted Framingham risk scores being recently shown to have a significant and direct relationship with the prevalence and magnitude of coronary artery calcium scores.[51]

## Comparisons with the clinical SYNTAX score

The Clinical SXscore, on which the Logistic Clinical SXscore is based, multiplied a variant of the surgical-based ACEF (age, creatinine, and ejection fraction) score (modified ACEF score) to the SXscore. In doing so the Clinical SXscore was shown to overestimate predicted risks (i.e. relatively poor calibration) despite modest increases in the discriminative ability of the Clinical SXscore being obtained.[20,23] The application of the Clinical SXscore to the present study (full data not shown) showed that it was able to identify a high-risk population only (mortality: 6.6% of the study population), compared with the intermediate- and low-risk groups (mortality: 2.3 and 1.1% of the study population, respectively) consistent with the previously reported literature.[19–23] Comparatively the Logistic Clinical SXscore within the present study was demonstrated to accurately predict risk across all risk groups (i.e. well calibrated) and importantly was able to provide an individualized risk assessment.

## Comparisons with other risk models

The recently reported Functional SXscore (FSS)—a fractional flow reserve (FFR)-guided SYNTAX scoring methodology—has been shown to potentially improve the predictive accuracy of the SXscore.[52] Within this study, the more objective assessment of coronary stenoses compared with visual assessment (to form the FSS) lead to incremental increases in the predictive accuracies for the outcomes of 1-year MACE (AUC: SXscore, 0.630; FSS, 0.677), 1-year death or MI (AUC: SXscore, 0.621; FSS, 0.676) and 1-year all-cause revascularization (AUC: SXscore, 0.627; FSS, 0.657).[52] Notably, improvements in the predictive accuracy for 1-year death were not reported with the FSS. Comparatively the Logistic Clinical SXscore in the present study demonstrated a substantial increase in the prediction of 1-year death (AUC: SXscore, 0.660; core model, 0.753), and improvements in the prediction of 1-year death or MI (AUC: SXscore, 0.594; core model, 0.657, extended model 0.666—Supplementary material online, Appendix) without the need for invasive pressure-wire coronary assessment.

The longer-term (1-year) mortality predictions provided by the Logistic Clinical SXscore are the principle differences compared with other reported risk scores, namely the National Cardiovascular Data Registry[16] score, the Mayo Clinical Risk score,[13,15] the EuroHeart PCI score,[18] and the New York PCI risk score,[14] in that they report in-hospital Death[14,16,18] or in-hospital MACE,[50,51] or at the most 30-day mortality[16] after PCI. Other risk scores that longer-term risk stratify patients include the New Risk Stratification score (NERS).[53] As previously described with the Clinical SXscore, NERS categorized patients into levels of risk (high and low risk) without giving an individualized assessment of patient risk, which was achievable with the Logistic Clinical SXscore. Furthermore NERS is a more complicated score that consists of 17 clinical variables, 33 anatomical factors, and 4 procedural details, and was developed for patients with left main coronary artery disease undergoing PCI.[53]

## Potential clinical application

Although the patient and clinician may wish to know the short-term risk of procedural complications associated with PCI, a longer-term perspective may also be beneficial. Not only would this appropriately inform the patient, but may also prove to be of benefit in determining whether surgical or percutaneous revascularization would be more appropriate as part of the Heart Team consensus. As recently reported, high co-morbidity patients may confer prognostic and morbidity benefits from undergoing surgical revascularization compared with PCI provided a certain threshold of operative risk is not exceeded.[23]

## Limitations

Although the Logistic Clinical SXscore was derived from 'All-Comers' types patients in contemporary stent trials, each trial still retained certain inclusion and exclusion criteria.[11] These criteria were, however, minimal which should legitimize the application of the Logistic Clinical SXscore to contemporary clinical practice. The authors recognize that further external validation of the Logistic Clinical SXscore in 'real-world' 'unrestricted' registry populations is necessary when these registries reporting the SXscore become available. This would further strengthen the results of this study, although the present analyses were already undertaken in a pooled analysis of seven different contemporary stent trials and internally validated with a cross-validation procedure. Comparisons of the Logistic Clinical SXscore with the Global Risk[23] were not possible since the EuroSCORE was not collected in the seven contemporary stent trials.

Cardiogenic shock is a risk variable that has consistently been shown to be a powerful predictor of in-hospital mortality.[13–18] This important subset of patients, although not an exclusion criteria in the 'All-Comers' trials, by practice lead to the under-recruitment of these patient types predominantly due to the inability to gain appropriate informed consent or refusal to participate.[54] Consequently, the Logistic Clinical SXscore should at present not be applied to these patients where other risk scores would be better suited.[13–18]

## Future directions

Potentially the integration of the Logistic Clinical SXscore into an online algorithm with the currently available SXscore[1] may serve to simultaneously allow for risk stratification of patients based on anatomical and clinical variables. In addition, the application of the Logistic Clinical SXscore in place of the SXscore to aid in determining the optimal revascularization modality in patients with complex coronary disease is a potential future application. The incorporation of the FSS as previously described,[52] to allow for a more objective assessment of the coronary anatomy, may enhance the predictive accuracy of the Logistic Clinical SXscore even further. Future direction with non-invasive imaging and FFR calculation[55]—utilizing computational fluid dynamics applied to coronary computed tomography angiography—may be feasible. The expansion of other risk variables to the Logistic Clinical SXscore such as the haemodynamic status as previously discussed may expand the use of this risk score to other patient types.

# Conclusion

Compared with the SXscore in isolation, the Logistic Clinical SXscore substantially enhances the risk stratification of PCI patients for death at 1-year and allows for an accurate individualized assessment of patient risk. The use of the Logistic Clinical SXscore may also further aid in the Heart Team consensus in determining the optimal revascularization modality.

# Supplementary material

Supplementary material is available at *European Heart Journal* online.

## Acknowledgements

The authors express their gratitude to all of the study participants and the principal investigators of the trials whose work made this study possible. V.F. thanks the Dickinson Trust Travelling Scholarship, Manchester Royal Infirmary, Manchester, England, UK. Y.V. was supported by The Netherlands Organization for Scientific Research (917.11.383).

## Funding

The SYNTAX Trial was funded by Boston Scientific Corporation.

**Conflict of interest:** M.V. reports research grants for lecturers and advisory boards: Iroko, Eli Lilly, Medtronic, and honoraria for lecturers and/or advisory boards: Cordis, Medtronic, Abbott, Eisai, Merck, AstraZeneca, Med Co, and Terumo. K.D.D. is a full-time employee of Boston Scientific and holds stock in Boston Scientific. S.W. received research grants from Abbott, Biosensors, Biotronik, Cordis, Boston Scientific, and Medtronic. The other authors report no conflicts of interest.

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# CHAPTER 5.4

## The global risk score

Serruys PW, Farooq V, Vranckx P, Brugaletta S, Girasis C; Garcia Garcia H, Holmes DR, Kappetein AP, Mack M, Feldman T, Morice MC; Ståhle E; James S, Colombo A, Pereda P; Huang J, Morel MA; Van Es GA; Dawkins KD, Mohr FW, Steyerberg EW.

*J Am Coll Cardiol Interventions 2012.* [**original research paper**]

CLINICAL RESEARCH

CME

# A Global Risk Approach to Identify Patients With Left Main or 3-Vessel Disease Who Could Safely and Efficaciously Be Treated With Percutaneous Coronary Intervention

## The SYNTAX Trial at 3 Years

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**CME Objective for This Article:** To understand the potential role of anatomical and clinical factors in the Heart Team consensus in determining the optimal revascularization modality in patients with complex coronary artery disease.

**CME Editor Disclosure:** *JACC: Cardiovascular Interventions* CME Editor Habib Samady, MB, ChB, FACC, has research grants from the Wallace H. Coulter Foundation, Volcano Corp., St. Jude Medical, Forrest Pharmaceuticals Inc., and Pfizer Inc.

**Author Disclosure:** The SYNTAX study was funded by Boston Scientific. Dr. Mack has served on the Speaker's Bureau of Boston Scientific, Cordis, and Medtronic. Dr. Feldman serves on the Speaker's Bureau of Boston Scientific; receives grant support from Abbott, Atritech, Boston Scientific, Edwards, and Evalve; and consults for Abbott, Coherex, Intervalve, Square One, and W.L. Gore. Dr. Morice reports that her institution received a research grant from Boston Scientific. Dr. Dawkins, Ms. Pereda, and Dr. Huang are all full-time employees of Boston Scientific. Dr. Dawkins holds stock in Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

**Medium of Participation:** Print (article only); online (article and quiz).

**CME Term of Approval:**

Issue Date: June 2012

Expiration Date: May 31, 2013

# A Global Risk Approach to Identify Patients With Left Main or 3-Vessel Disease Who Could Safely and Efficaciously Be Treated With Percutaneous Coronary Intervention

## The SYNTAX Trial at 3 Years

**Objectives** The aim of this study was to assess the additional value of the Global Risk—a combination of the SYNTAX Score (SXscore) and additive EuroSCORE—in the identification of a low-risk population, who could safely and efficaciously be treated with coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI).

**Background** PCI is increasingly acceptable in appropriately selected patients with left main stem or 3-vessel coronary artery disease.

**Methods** Within the SYNTAX Trial (Synergy between PCI with TAXUS and Cardiac Surgery Trial), all-cause death and major adverse cardiac and cerebrovascular events (MACCE) were analyzed at 36 months in low ($GRC_{LOW}$) to high Global Risk groups, with Kaplan-Meier, log-rank, and Cox regression analyses.

**Results** Within the randomized left main stem population (n = 701), comparisons between $GRC_{LOW}$ groups demonstrated a significantly lower mortality with PCI compared with CABG (CABG: 7.5%, PCI: 1.2%, hazard ratio [HR]: 0.16, 95% confidence interval [CI]: 0.03 to 0.70, p = 0.0054) and a trend toward reduced MACCE (CABG: 23.1%, PCI: 15.8%, HR: 0.64, 95% CI: 0.39 to 1.07, p = 0.088). Similar analyses within the randomized 3-vessel disease population (n = 1,088) demonstrated no statistically significant differences in mortality (CABG: 5.2%, PCI: 5.8%, HR: 1.14, 95% CI: 0.57 to 2.30, p = 0.71) or MACCE (CABG: 19.0%, PCI: 24.7%, HR: 1.35, 95% CI: 0.95 to 1.92, p = 0.10). Risk-model performance and reclassification analyses demonstrated that the EuroSCORE—with the added incremental benefit of the SXscore to form the Global Risk—enhanced the risk stratification of all PCI patients.

**Conclusions** In comparison with the SXscore, the Global Risk, with a simple treatment algorithm, substantially enhances the identification of low-risk patients who could safely and efficaciously be treated with CABG or PCI. (J Am Coll Cardiol Intv 2012;5:606–17) © 2012 by the American College of Cardiology Foundation

The SYNTAX score (SXscore) (1–4) has established itself as an important tool in the SYNTAX trial (The Synergy between PCI with TAXUS and Cardiac Surgery Trial) pioneered Heart Team approach, in which the cardiac surgeon and interventional cardiologist determined the optimal revascularization modality for patients with untreated left main stem (LMS) or 3-vessel (3VD) coronary artery disease (1,5–7). The SXscore has since been validated in the LMS percutaneous coronary intervention (PCI) population at short- and long-term follow-up (8–11); the 3VD PCI population at short-term (1-year) follow-up (12,13); and "All-Comers" patients undergoing PCI in contemporary stent trials at 1-year follow-up (14,15). In addition, both the current U.S. and European Guidelines on myocardial revascularization (16–18) advocate the use of the SXscore to determine the optimal revascularization modality in patients with unprotected left main or complex coronary disease, without the explicit use of clinical vari-

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Manuscript received February 7, 2012; revised manuscript received March 16, 2012, accepted March 22, 2012.

ables. Furthermore, the U.S. guidelines now gives surgical revascularization for unprotected left main coronary disease a Class 1B recommendation (16,17), compared with a Class 1A recommendation in previous guidelines (19).

Because the SXscore relies on the scoring of the coronary anatomy in isolation to objectively select the appropriate revascularization strategy for the individual patient, criticism has emerged, due to potentially important prognostic information being missing secondary to the absence of clinical factors (20,21). The EuroSCORE (22,23), a cardiac surgery-based clinical risk score, has been shown to have a reliable impact on prognosis and to be an independent predictor of major adverse cardiac events and mortality in surgical and percutaneously treated patients in the SYNTAX trial, thus confirming findings from previous studies (24–28).

Attempts have previously been made to combine the SXscore and additive EuroSCORE to form the Global Risk classification (29,30) and have been shown to potentially improve the risk stratification of patients undergoing surgical or percutaneous LMS intervention, compared with the SXscore alone. The Global Risk categorical approach reported in the present study, adapted from the previously reported Global Risk classification (29,30), uses the historically accepted cutoff levels for tertiles of the additive EuroSCORE (22,23)—of which a high EuroSCORE tertile has previously been shown to be an independent predictor of adverse outcomes after PCI (24,26–28)—and the now broadly accepted tertiles of the SXscore (Fig. 1) (1–4). Therefore the goal of the Global Risk is to improve in the identification of low-risk groups with LMS or 3VD, compared with the SXscore, who would achieve comparable surgical and percutaneous outcomes in terms of efficacy and safety at 3 years.

**Abbreviations and Acronyms**

**3VD** = 3-vessel disease
**BMS** = bare-metal stent(s)
**CABG** = coronary artery bypass graft surgery
**CI** = confidence interval
**$GRC_{LOW}$** = Low Global Risk
**$GRC_{INT}$** = Intermediate Global Risk
**$GRC_{HIGH}$** = High Global Risk
**HR** = hazard ratio
**LMS** = left main stem
**MACCE** = major adverse cardiac and cerebrovascular event(s)
**MI** = myocardial infarction
**PCI** = percutaneous coronary intervention
**SXscore** = SYNTAX Score

## Methods

The SYNTAX trial is a randomized, prospective, multicenter trial that incorporated an "All-Comers" design and consisted of pre-specified LMS (isolated or associated with 1-, 2-, or 3-vessel disease) and 3VD cohorts (1,6,7). Patients were randomized on a 1:1 basis to undergo either coronary artery bypass graft surgery (CABG) or PCI or placed in nested registries when considered unsuitable for randomization by the Heart Team (CABG nested registry for PCI-ineligible patients and PCI nested registry for CABG-ineligible patients). Exclusions were only limited to patients with prior coronary revascularization, the requirement of concomitant cardiac surgery, or ongoing acute myocardial infarction (MI). Recent MI with resolution of cardiac enzymes (<2× upper limit of normal) and unstable angina (no elevation in biomarkers) were not exclusion criteria.

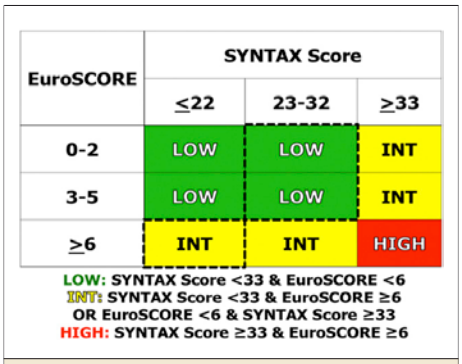


**Figure 1. The Proposed Global Risk**

The Global Risk demonstrating recategorization of established tertiles of risk for the SYNTAX Score and additive EuroSCORE to form low ($GRC_{LOW}$), intermediate ($GRC_{INT}$), and high ($GRC_{HIGH}$) Global Risk groups. **Highlighted (dashed) boxes** indicate patients moved (reclassified) into or out of the low SYNTAX Score group to form the low Global Risk group ($GRC_{LOW}$). Adapted from Capodanno et al. (29,30).

The PCI techniques between the randomized and nested registry populations were similar except that TAXUS Express (Boston Scientific Corporation, Natick, Massachusetts) paclitaxel-eluting stents were only permitted in the randomized population. Within the PCI nested registry the implantation of any type of drug-eluting stent or bare-metal stent (BMS) was permitted, although the use of TAXUS paclitaxel-eluting stents was encouraged. Of the 589 stents implanted within the PCI nested registry, 57% were TAXUS Express or Liberté (Boston Scientific Corporation), 19% were another drug-eluting stent, and 24% were BMS; 4 PCI nested registry patients did not receive a stent. Conversely CABG techniques between the randomized and nested registry were broadly similar, except that double left and right internal mammary artery grafts were more frequently performed in the randomized (27.6%) CABG population, compared with the CABG nested registry (16.1%).

The Global Risk was calculated by combining the SXscore (2–4)—calculated by an independent core laboratory (Cardialysis BV, Rotterdam, the Netherlands)—and the additive EuroSCORE, as assessed by the Heart Team before randomization (22,23). The additive EuroSCORE was used to form the Global Risk, because this was shown

**Table 1. Comparison of Anatomical Factors (SXscore) and Clinical Risk Scores for the CABG and PCI Populations**

| | CABG | | | | PCI | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Anatomical/Clinical Risk Score | Randomized (n = 897) | Nested Registry (n = 644) | All-Comers (n = 1,541) | p Value† | Randomized (n = 899) | Nested Registry (n = 195) | All-Comers (n = 1,094) | p Value† | p Value* |
| SXscore | 29.1 ± 11.4 | 37.8 ± 13.3 | 32.7 ± 12.9 | <0.001 | 28.4 ± 11.5 | 31.3 ± 12.5 | 28.9 ± 11.7 | 0.002 | <0.001 |
| Total Parsonnet score | 8.4 ± 6.8 | 9.0 ± 7.1 | 8.7 ± 6.9 | 0.15 | 8.5 ± 7.0 | 14.4 ± 9.5 | 9.6 ± 7.8 | <0.001 | 0.001 |
| Additive EuroSCORE | 3.8 ± 2.69 | 3.9 ± 2.7 | 3.8 ± 2.7 | 0.47 | 3.8 ± 2.6 | 5.8 ± 3.1 | 4.1 ± 2.8 | <0.001 | 0.008 |
| Logistic EuroSCORE, % | 3.9 ± 4.4 | 4.0 ± 4.4 | 3.9 ± 4.4 | 0.46 | 3.8 ± 4.5 | 7.7 ± 8.9 | 4.5 ± 5.8 | <0.001 | 0.009 |

Mean score ± 1 SD. *p value represents comparisons between the All-Comers (randomized and nested registry) coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) populations. †p value represents comparisons between the randomized and nested registry populations for the CABG and PCI populations.
SXscore = SYNTAX Score.

to be more predictive of clinical outcomes in the PCI population compared with the logistic EuroSCORE, findings consistent with a previous study (29). Patients were subsequently categorized into 3 classes of Global Risk, on the basis of predefined anatomical and clinical-risk categories (low, intermediate, and high) for the SXscore (2–4) and additive EuroSCORE, respectively (22,23) (Fig. 1).

**Statistical methods.** Comparisons of all-cause death and major adverse cardiac and cerebrovascular events (MACCE) (a composite of all-cause death, MI, stroke, and all-cause revascularization) (1,7) were performed (Kaplan-Meier curves) with the log-rank test and Cox proportional hazard ratios between the low Global Risk ($GRC_{LOW}$) groups for CABG and PCI. This prognostic model-based approach to identify a low subgroup of patients defined by prognostic factors is in contrast to the traditional approach to subgroup analysis (31–33). A logistic regression model that incorporated the SXscore and EuroSCORE as covariates was used to give each score proper relative weighting to each other within the Global Risk. This analysis allowed for the assessment of the predictive ability of the Global Risk: 1) the Hosmer–Lemeshow test for calibration—the assessment of the correctness of the prediction by the risk model, with poor fit indicated by a significant p value (<0.05); 2) receiver operator curves for discrimination (C-statistic)—the ability of the risk model to appropriately assign the correct risk prediction in patients who have the outcome, ranging from 0.50 (no discrimination) to 1.0 (perfect discrimination); 3) the Brier score—an overall risk model performance measure capturing both discrimination and calibration aspects of the risk model, ranging from 0 to 1, with a lower value (closer to 0) suggestive of a more predictive risk model (34–36). Comparisons were made with other risk models, namely, the SXscore (2,4); age, creatinine, and ejection fraction/modified age, creatinine, and ejection fraction scores (37,38); the Clinical SXscore (39,40); and the additive/logistic EuroSCOREs (22,23)—a brief description of which is enclosed in the Online Appendix.

Analyses on those groups that were reclassified according to the Global Risk compared with the SXscore alone were undertaken, following the principles of Net Reclassification Improvement (38,41) (Fig. 1). These reclassification analyses were to test whether the low Global Risk group ($GRC_{LOW}$) appropriately risk-stratified patients, compared with a low SXscore. Higher anatomical risk patients (i.e., intermediate SXscores with low-intermediate EuroSCOREs) would be appropriately reclassified as lower-risk ($GRC_{LOW}$) if they had comparable (or more favorable) PCI outcomes, compared with CABG. Conversely lower anatomical risk patients with a high clinical comorbidity (i.e., low SXscore with a high EuroSCORE) would only be appropriately reclassified to a higher risk group ($GRC_{INT}$) if they had more favorable surgical outcomes, compared with PCI. Further detailed methodology, including illustrative figures describing the reclassification concepts, is included in the Online Appendix. A 2-sided p value <0.05 was considered significant for all tests. All analyses were conducted with SAS System Software (version 8.0 or higher, SAS Institute, Cary, North Carolina) and SPSS (version 17.0, SPSS, Inc., Chicago, Illinois).

## Results

All randomized patients underwent planned follow-up. Within the nested registries, all PCI patients underwent planned follow-up, and 649 of the 1,077 CABG patients were randomly allocated for follow-up, on the basis of the original study protocol (1,7). Complete data, including clinical outcomes relating to the Global Risk, were available in 1,789 of 1,800 randomized patients (PCI, n = 899; CABG, n = 890), and 2,610 of 3,075 "All-Comers" patients (PCI, n = 1,088; CABG, n = 1,522) at 3-year follow-up.

Within the randomized SYNTAX population baseline demographic data and clinical characteristics for the treatment arms have previously been described and were well-balanced (1). Within the "All-Comers" population more complex coronary anatomy was present in the CABG population (mean SXscore ± 1 SD: CABG: 32.7 ± 12.9, PCI: 28.9 ± 11.7, p < 0.001) (Table 1). Conversely, significantly more comorbidity was present in the "All-

Comers" PCI population, as evidenced by significantly greater Parsonnet (42) and EuroSCOREs (Table 1).

**Clinical outcomes with PCI.** Within the randomized and "All-Comers" LMS (Fig. 2) and 3VD (Fig. 3) PCI populations, a low Global Risk group ($GRC_{LOW}$) could be differentiated from the higher risk groups ($GRC_{INT\text{-}HIGH}$) for All-Cause death and MACCE. Furthermore, within the LMS PCI population, the Global Risk demonstrated a clear incremental increase in predictive ability (C-statistics and overall risk model performance measures), compared with either the SXscore or the EuroSCORE in isolation (Fig. 4). Within the randomized and "All-Comers" 3VD PCI population, the additive EuroSCORE had a superior predictive ability for all-cause death and MACCE compared with the SXscore alone, with little or no additional improvements in the predictive ability of the Global Risk compared with the additive EuroSCORE (Fig. 4).

**Clinical outcomes with CABG.** At 36 months the Global Risk could differentiate between the $GRC_{INT-HIGH}$ groups only for all-cause death and MACCE in the randomized and "All-Comers" CABG populations (Figs. 2 and 3). The Global Risk added little or no improvement to the predictive ability, compared with the additive EuroSCORE used in isolation (Fig. 4).

**Comparison of CABG and PCI: low-risk LMS population.** Within the $GRC_{LOW}$ group of the randomized LMS population (n = 701), CABG resulted in significantly higher 3-year mortality compared with PCI (CABG: 7.5%, PCI: 1.2%, HR: 0.16, 95% CI: 0.03 to 0.70, p = 0.0054), with a trend toward a lower incidence of MACCE (CABG: 23.1%, PCI: 15.8%, HR: 0.64, 95% CI: 0.39 to 1.07, p = 0.088) and stroke (CABG: 3.5%, PCI: 0.6%, HR: 0.17, 95% CI: 0.02 to 1.46, p = 0.067). No statistically significant differences in MI or all-cause revascularization were found.

Within the $GRC_{LOW}$ group of the "All-Comers" LMS population (n = 1,079), no statistically significant differences in mortality (CABG: 5.3%, PCI: 2.7%, HR: 0.51, 95% CI: 0.18 to 1.44, p = 0.19) or MACCE (CABG: 18.0%, PCI: 18.5%, HR: 1.02, 95% CI: 0.65 to 1.60, p = 0.94) were observed. A significantly greater incidence of stroke was evident with CABG (CABG: 4.0%, PCI: 0.6%, HR: 0.13, 95% CI: 0.02 to 1.05, p = 0.025), and a significantly greater frequency of MI was evident with PCI (CABG: 0.9%, PCI: 3.9%, HR: 4.30, 95% CI: 0.89 to 20.70, p = 0.047). No statistically significant differences in all-cause revascularization were seen (CABG: 10.7%, PCI: 14.8%, HR: 1.40, 95% CI: 0.81 to 2.42, p = 0.23).

**Comparison of CABG and PCI: low-risk 3VD population.** Within the $GRC_{LOW}$ group of the randomized 3VD population (n = 1,088), no statistically significant differences in 3-year mortality (CABG: 5.2%, PCI: 5.8%, HR: 1.14, 95% CI: 0.57 to 2.30, p = 0.71) or MACCE (CABG: 19.0%, PCI: 24.7%, HR: 1.35, 95% CI: 0.95 to 1.92, p = 0.10) were observed. Percutaneous coronary intervention was associated with a significantly increased risk of all-cause revascularization (CABG: 10.5%, PCI: 18.5%, HR: 1.88, 95% CI: 1.19 to 2.96, p = 0.0055). No statistically significant differences in the risk of stroke were seen (CABG: 2.9%, PCI: 1.3%, HR: 0.45, 95% CI: 0.13 to 1.49, p = 0.18).

Within the "All-Comers" 3VD population (n = 1,531) no statistically significant differences in mortality were observed (CABG: 5.1%, PCI: 5.9%, HR: 1.16, 95% CI: 0.62 to 2.17, p = 0.65). A significantly higher incidence of MACCE was evident with PCI (CABG: 17.9%, PCI: 24.4%, HR: 1.42, 95% CI: 1.03 to 1.96, p = 0.031) secondary to predominantly greater all-cause revascularization (CABG: 9.1%, PCI: 18.5%, HR: 2.20, 95% CI: 1.44 to 3.35, p = 0.0002). No statistically significant differences in the incidences of stroke were seen (CABG: 3.2%, PCI: 1.5%, HR: 0.46, 95% CI: 0.16 to 1.30, p = 0.13).

**Analyses of reclassified patients.** Within the LMS population, patients (i.e., patients with an intermediate SXscore and low-moderate EuroSCOREs) were appropriately reclassified to the $GRC_{LOW}$ group (Fig. 1). More favorable outcomes were seen with PCI, compared with CABG (randomized population: 3-year all-cause death: CABG 10.8%, PCI 1.3%; 3-year MACCE: CABG 24.4%, PCI 15.6%). Conversely, patients reclassified to a higher-risk ($GRC_{INT}$) group (i.e., patients with a low SXscore and a high EuroSCORE) had more favorable surgical outcomes in the larger "All-Comers" population (Fig. 1), predominantly secondary to reduced MACCE with CABG (3-year MACCE: CABG 20.4%, PCI 27.0%).

Within the 3VD population more favorable surgical outcomes were evident in patients reclassified to the $GRC_{LOW}$ group. Further analyses indicated that a $GRC_{LOW}$ with an intermediate SXscore would remain better-managed by CABG, and a $GRC_{LOW}$ with a low SXscore would have comparable surgical and PCI outcomes. More favorable surgical outcomes were evident in patients (i.e., with a low SXscore and a high EuroSCORE) reclassified to the higher-risk ($GRC_{INT}$) group (randomized population: 3-year death: CABG 9.6%, PCI 21.3%; 3-year MACCE: CABG 22.5%, PCI 39.1%). Further detailed results of the reclassification analyses are included in the Online Appendix.

**Comparison of the Global Risk with other risk models.** The Global Risk was superior in predictive performance compared with other combined anatomical/clinical scores (derived from the SXscore) and their components. This included the Clinical SXscore (39) (Fig. 4).

## Discussion

The main findings of this study are: 1) clinical variables (EuroSCORE) per se are more predictive of clinical outcomes (all-cause death and MACCE), compared with anatomical variables (SXscore) in the PCI population; 2) within the LMS PCI population the Global Risk demonstrated a clear incre-

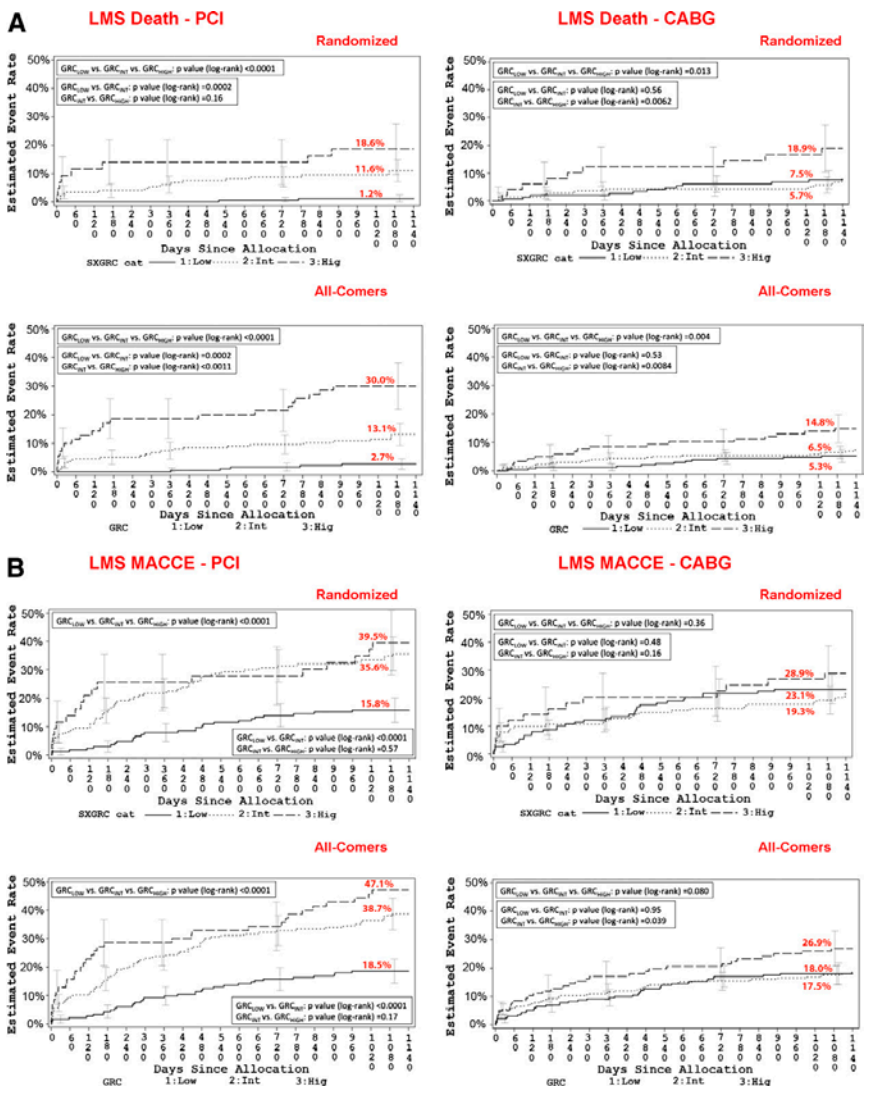


**Figure 2. Comparisons of Clinical Outcomes by Categories of Global Risk in the SYNTAX LMS Population**

Kaplan-Meier curves for cumulative rate of death **(A)** and MACCE **(B)** at 3-year follow-up stratified according to the Global Risk group; event rate ± 1.5 SE. CABG = coronary arty bypass grafting; GRCLOW = Low Global Risk; GRCINT = Intermediate Global Risk; GRCHIGH = High Global Risk; LMS = left main stem; MACCE = major adverse cardiac and cerebrovascular event(s); PCI = percutaneous coronary intervention.

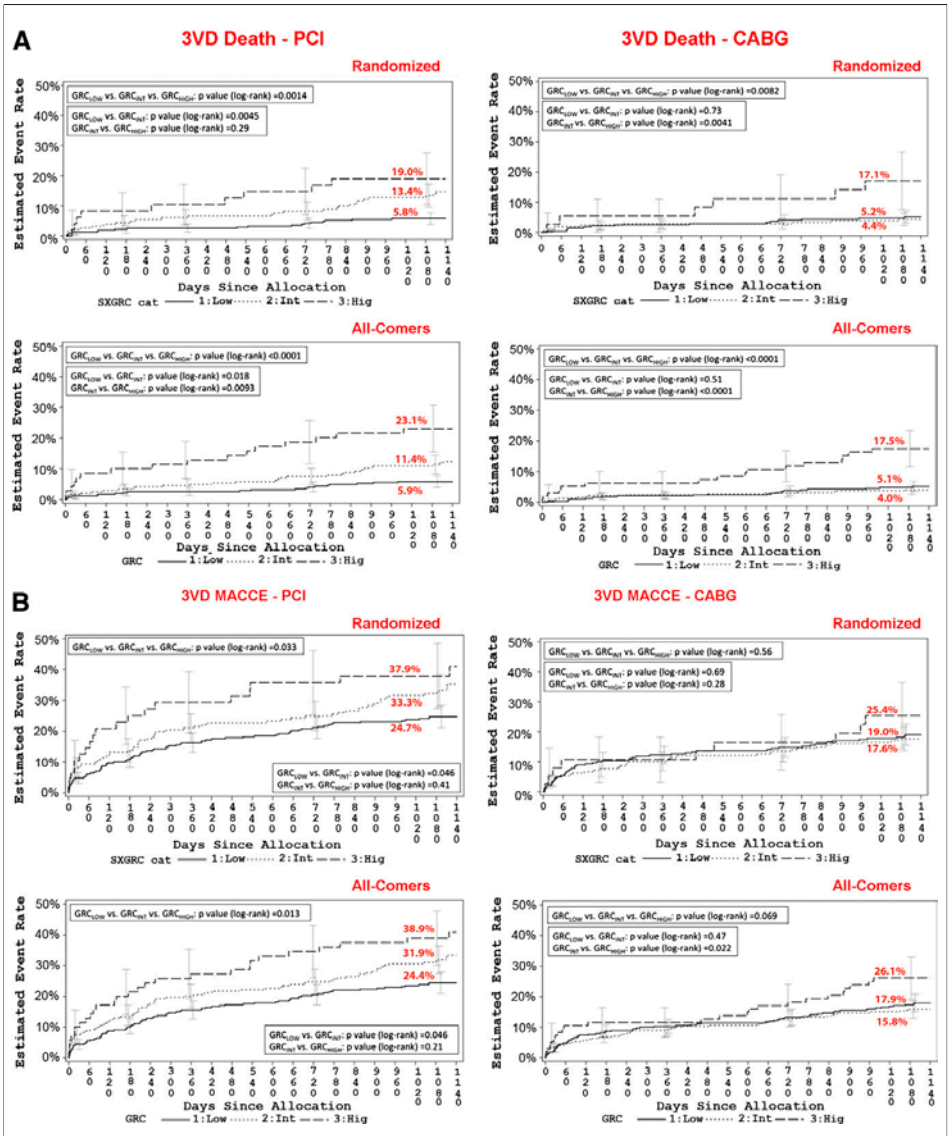


**Figure 3. Comparisons of Clinical Outcomes by Categories of Global Risk in the SYNTAX 3VD Population**

Kaplan-Meier curves for cumulative rate of death **(A)** and MACCE **(B)**, at 3-year follow-up stratified according to the Global Risk group; event rate ± 1.5 SE. 3VD = 3-vessel disease; other abbreviations as in Figure 2.

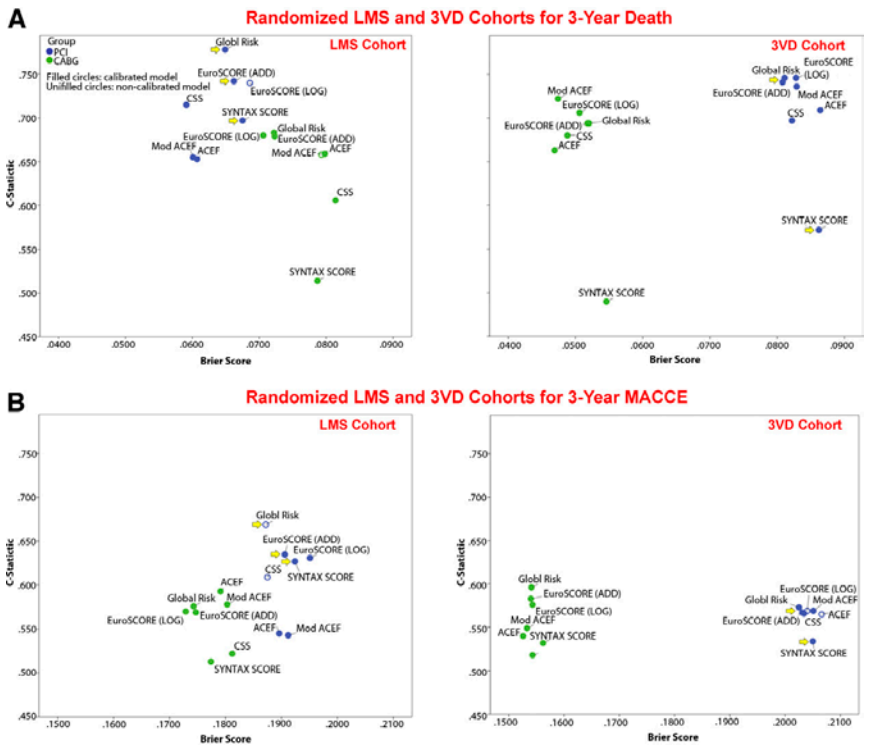


**Figure 4. Comparison of Different Risk Models for the Randomized LMS and 3VD Populations for Death and MACCE at 3 Years**

Comparison of different risk models for the randomized LMS and 3VD populations for death **(A)** and MACCE **(B)** at 3 years, with calibration (Hosmer–Lemeshow test), discrimination (C-statistic, y axes), and overall model performance measures (Brier score, x axes) (36). **Yellow arrows** in the LMS cohort demonstrate the incremental benefit, in terms of predictive ability, of the Global Risk compared with the additive EuroSCORE and SYNTAX Score as evidenced by a greater C-statistic and lower Brier score. **Yellow arrows** in the 3VD cohort demonstrate the incremental benefit of the additive EuroSCORE compared with the SYNTAX Score with little/no improvement of the predictive ability of the Global Risk compared with the additive EuroSCORE, as evidenced by comparable C-statistics and Brier scores. Note how even minor differences in the Brier score reflect overall improvements in the model performance and the different scales for the Brier scores for death and MACCE reflecting the findings that the risk models are superior in predicting death. ACEF = age, creatinine, and ejection fraction (score); CSS = clinical SYNTAX score; other abbreviations as in Figures 2 and 3.

mental benefit in its predictive ability, compared with the SXscore or EuroSCORE used in isolation; 3) within the 3VD PCI population, the Global Risk improved the risk stratification of patients, compared with the SXscore alone, by demonstrating that low SXscore patients with a high EuroSCORE to attain a mortality benefit in undergoing CABG compared to PCI; and 4) that the Global Risk substantially enhanced the identification of a low-risk population who could safely and efficaciously be treated with CABG or PCI at 3 years.

The application of the Global Risk to the SYNTAX population was complicated by the differing prognostic and morbidity outcomes between the LMS and 3VD populations. However, a low-risk population was identified with outcomes comparable to CABG and PCI at 3 years in terms of efficacy and safety, namely a $GRC_{LOW}$ group in the LMS population and a $GRC_{LOW}$ group with a low SXscore in the 3VD population. Ultimately reclassification analyses proved vital in ensuring the optimal revascularization modality in specific groups of patients. For example, high-EuroSCORE

patients with a low SXscore were shown to confer a clear mortality benefit from undergoing CABG in the 3VD population, and intermediate-SXscore patients with low-moderate EuroSCOREs were shown to confer a potential survival advantage in undergoing PCI in the LMS population. On the basis of these findings a treatment algorithm is proposed to simplify these concepts, which admittedly will require further validation in other unselected registries (Fig. 5).

The main strengths of the Global Risk are that the additive EuroSCORE is a simple bedside calculation and that the Global Risk can be applied across the entire spectrum of surgical and percutaneously treated patients. Within the "All-Comers" SYNTAX population the adoption of this treatment algorithm (Fig. 5) would potentially identify a smaller population of patients, compared with using the SXscore alone, who would have similar outcomes to CABG and PCI at 3 years in terms of efficacy and safety—namely, 39% of the LMS population (compared with 51% with low-moderate SXscores) and 21% of the 3VD population (compared with 26% with a low SXscore).

By identifying a low Global Risk ($GRC_{LOW}$) group within the randomized LMS population, a significant mortality benefit and trend toward a reduction in MACCE was evident for PCI at 3 years. This was not apparent in the "All-Comers" population. Several factors might explain this disparity in results. First, the "All-Comers" PCI population had significantly greater comorbidity (Table 1)—factors well known to be associated with in-hospital and long-term adverse outcomes after PCI (24,26–28). Second, a low EuroSCORE could not exclude nonadjustable characteristics, such as the judgment of the treating clinician in declining a patient for CABG and thus undergoing PCI instead, such as patients with a short-term survival—as were recruited within the "All-Comers" SYNTAX trial. Third, the CABG nested registry might potentially have been diluted with a proportion of lower-anatomical-risk patients who might have been suitable for PCI, because the concept of the clinical outcomes on the basis of tertiles of the SXscore were unknown at the time of the SYNTAX trial. Fourth, is the use of BMS in the nested PCI registries: although specific data pertaining to the indications for use of BMS were not collected, it is probable that a sizeable proportion of these patients might have had comorbidities that precluded the use of prolonged dual antiplatelet therapy. The adoption of the "All-Comers" approach is nonetheless more likely to mirror contemporary clinical practice and is perceived by many as the recommended approach (18,43).

**Adverse clinical comorbidity: CABG or PCI?** In both the LMS and 3VD populations the surgical benefit in the higher comorbidity patients (i.e., with a low SXscore and high EuroSCORE) was more pronounced, compared with PCI. In particular a substantial mortality benefit favoring CABG was evident in low-SXscore patients with a high EuroSCORE in the 3VD population. Although it has been previously demonstrated that a high EuroSCORE is a potential predictor of adverse outcomes after PCI (24,26–28), conventional clinical practice has suggested that high-comorbidity patients might be more suitable for PCI compared with CABG. In contrast to this accepted clinical practice, it seems that it is precisely these types of patients who would potentially stand to gain more from CABG on prognostic and morbidity grounds. These findings are probably related to PCI treating the individual lesion, whereas CABG would potentially protect the entire treated vessel from future cardiac events for the lifespan of the graft.

There is nevertheless a recognition that a certain threshold of operative risk would have to be acceptable for the cardiac surgeon and patient, and the latter of who may adamantly refuse a surgical approach due to the anticipated prohibitive risk of the proposed surgical intervention. It should, however,

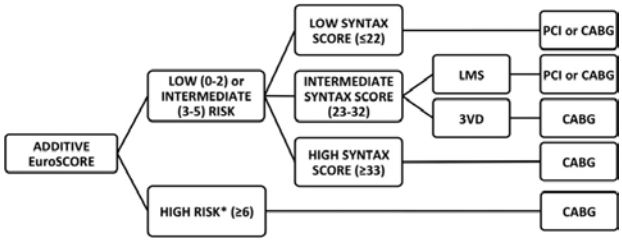


**Figure 5. Proposed Treatment Algorithm for the Management of LMS and 3VD Incorporating Clinical and Anatomical Variables**

Proposed treatment algorithm for the management of LMS and 3VD incorporating clinical (additive EuroSCORE) and anatomical (SYNTAX Score) variables. Although not explicitly stated PCI might be the preferred revascularization modality in low-risk patients subject to the Heart Team discussion. *If an acceptable threshold of operative risk is exceeded for the patient and cardiac surgeon, consideration of PCI should be considered—appropriate discussion concerning risk stratification should be undertaken. Abbreviations as in Figures 2 and 3.

be recognized that PCI may potentially be more hazardous for the patient with regard to long-term outcomes, compared with CABG. A greater understanding of this phenomenon may potentially reduce the threshold value for which surgical revascularization is declined during the Heart Team discussion.

**Anatomical and clinical variables in the LMS PCI population.** Before the introduction of the SXscore, heterogeneity of the LMS anatomical description and its impact on clinical outcomes were previously recognized by the use of classical terminology describing isolated LMS or LMS + 1-, 2-, or 3-vessel disease. The SXscore was an attempt to eliminate the historical and arbitrarily defined subdivisions of the coronary tree into LMS and 3VD and to create a common anatomical denominator (2,3). It now seems that the LMS outcomes are largely a reflection of the presence of distal LMS bifurcation disease, clinical comorbidity, and importantly, the increasing prevalence of 3VD and its association with clinical comorbidities (as discussed in the following) and anatomical complexities, such as multiple bifurcations and the presence of total occlusions leading to higher SXscores.

**Anatomical and clinical variables in the 3VD PCI population.** Within the 3VD PCI population the SXscore added very little incremental benefit to the additive EuroSCORE in predicting death and MACCE (Fig. 4). It might be hypothesized that the severity of 3VD (as evidenced by a higher SXscore) might be representative of patients with a more adverse risk profile who have evidence of systemic atherosclerosis and therefore are at greater longer-term cardiovascular and cerebrovascular risk. Consequently these patients might potentially benefit from CABG on prognostic and morbidity grounds due to the bypass grafts protecting the coronary vessel as discussed. This might also be an explanation for the comparability in long-term stroke outcomes between CABG and PCI for the 3VD SYNTAX population (6).

This hypothesis is supported by the significant and direct relationship of the 10-year predicted Framingham risk scores with the prevalence and magnitude of coronary artery calcium scores (44). Furthermore, the ankle-brachial pressure index (45–49) and common carotid intima-media thickness (50–53), both markers of peripheral vascular disease, have been correlated with the severity of coronary artery disease and clinical events.

**Implications of the Global Risk for future trials.** Given the heterogeneity of the outcomes between LMS and 3VD, the strategy for the future is to construct separate trials for the LMS and 3VD populations that should incorporate anatomical and clinical variables. Left main stem disease is currently subject to the ongoing EXCEL (Evaluation of Xience Prime or Xience V versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial, recruiting patients on anatomical entry criteria only—namely low-moderate SXscores—and does not directly take into account clinical variables except within the Heart Team discussion.

Within the 3VD population perhaps a more targeted identification of patients by other markers of atherosclerotic burden, such as ankle-brachial pressure index and common carotid intima-media thickness as discussed, in conjunction with the SXscore or Global Risk might prove beneficial. Another recently described approach is the "Functional SYNTAX Score"—utilizing the functional assessment of coronary lesions—and has potentially been shown to improve the identification of low and higher risk patients (54). In addition, the potential noninvasive calculation of the Functional SYNTAX Score, with computational fluid dynamics applied to coronary computed tomography angiography, has shown significant promise (55,56).

**Summary of the potential clinical implications of the Global Risk.** The practical clinical application of the Global Risk is summarized in a treatment algorithm in Figure 5. Although validation of the Global Risk concept is required, the practicalities are that not only high-anatomical-risk patients but also patients with significant comorbidity are best served by undergoing surgical revascularization, because they seem to be one of the patient groups that stand to potentially gain more from surgical revascularization on prognostic and morbidity grounds, particularly if they have 3VD. Clearly a threshold of operative risk for surgical revascularization should not be exceeded; therefore these issues are vital in the Heart Team discussion in selecting the most appropriate revascularization modality.

**Study limitations.** This study represents a post hoc analysis of the original SYNTAX Trial, and the predictive models were developed retrospectively at 3-year follow-up. The further analyses undertaken in the LMS and 3VD cohorts (1,7) should be considered as hypothesis-generating. Furthermore, the focus of this study was on low Global risk ($GRC_{LOW}$) groups, because CABG is the standard of care in the management of patients in the higher-Global Risk groups (1,5,6). Comparisons between the higher-Global Risk groups are nevertheless provided in the Online Appendix. In addition there was limited statistical power for the comparison between CABG and PCI for events such as stroke and MI and analyses of reclassified patients. Consequently external validation of the proposed Global Risk is required in unselected registries, with numbers greater than the SYNTAX "All-Comers" population. The "All-Comers" concept of the SYNTAX trial, although more representative of contemporary clinical practice compared with the randomized approach (18,43), has been reported to potentially not result in the inclusion of consecutive patients, predominantly due to the inability to gain appropriate informed consent and refusal to participate (57).

It is not possible to judge and account for the decisions made by the Heart Team in selecting a patient for randomization. However, this approach is representative of contemporary practice. It should also be acknowledged that, although the SYNTAX Trial was based on contemporary revascularization practice at the time, improvements in technology in both CABG and PCI might yield differences in clinical outcomes in future trials. Noninvasive or invasive carotid imaging to screen

for the presence of significant carotid disease was undertaken by the clinical consensus of the Heart Team to calculate the EuroSCORE. The possibility of a small minority of patients with clinically silent carotid disease cannot be excluded. The cardiac-related comorbidities within the EuroSCORE are more likely to reflect outcomes after PCI, whereas extracardiac factors (e.g., the presence of chronic obstructive pulmonary disease and poor neurological status) are unlikely to reflect outcomes (24–28)—this point should be borne in mind when interpreting the Global Risk. Furthermore, the use of the EuroSCORE with a continuous approach might have affected the results of the analysis. However, the categorical approach was adopted from the outset to allow application of the same risk model in CABG and PCI patients, given that a high SXscore tertile has consistently been shown to be an independent predictor of adverse outcomes after PCI (24,26–28). The newly developed EuroSCORE II (58) cannot be applied to the concept of the Global Risk, because this information was not collected during the original SYNTAX trial.

## Conclusions

In comparison with the SXscore, the Global Risk—with a simplified treatment algorithm—substantially enhances the identification of low-risk patients who could safely and efficaciously be treated with CABG or PCI.

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**Key Words:** 3-vessel disease ■ Global Risk ■ left main disease ■ SYNTAX Score.

## APPENDIX

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

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# CHAPTER 5.5

## Clinical Outcomes of Patients With Stable Coronary Artery Disease As Compared With Acute Coronary Syndromes After Percutaneous Coronary Interventions

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Submitted for Publication [**original research paper**]

## ABSTRACT

**Context:** Patients with acute coronary syndromes (ACS) are considered at increased risk of adverse events after percutaneous coronary interventions (PCI) compared with patients with stable coronary artery disease (SCAD). However, SCAD includes a broad spectrum of anatomic disease complexity, which has been shown to be predictive of outcomes.

**Objective:** To compare clinical outcomes after PCI between patients with ACS and those with SCAD stratified by the angiographic SYNTAX-score.

**Design, Setting and Patients:** Patient-level data were pooled from SIRTAX (n=1,012) LEADERS (n=1,707) RESOLUTE-AC (n=2,292) randomized trials. Out of 5,011 patients, 4,204 (84%) with calculated SYNTAX-score completed 2-year follow-up.

**Intervention(s):** Patients were stratified by clinical presentation (ie, ACS or SCAD) and angiographic disease complexity (ie, SYNTAX-score higher or lower tertile). Clinical outcomes of patients with low-risk SCAD (SLR, n= 531) and high-risk SCAD (SHR, n= 1,066) were compared with ACS patients (n= 2,607), respectively.

**Main outcome measure(s):** Major adverse cardiac events (MACE), a composite of cardiac death, myocardial infarction (MI) and ischemia-driven target lesion revascularization (TLR).

**Results:** At 2 years, the risk of MACE was higher for SHR patients (OR 1.34, 95%CI 1.08-1.66) and lower for SLR patients (OR 0.61, 95%CI 0.43-0.87) compared with ACS patients, respectively. Differences in disfavor of SHR compared with ACS patients were primarily driven by a higher risk of MI (OR 1.64, 95%CI 1.21-2.21), whereas no differences were observed for cardiac death (OR 0.77, 95%CI 0.49-1.21) and TLR (OR 1.21, 95%CI 0.91-1.62). Landmark analyses showed that SHR compared with ACS patients had a higher risk of MI during the first 30 days (OR 1.89, 95%CI 1.35-2.66) without differences beyond 30 days up to 2 years (OR 1.00, 95%CI 0.54 to 1.88). In addition, stratification by gender showed that differences between SHR and ACS patients with respect to MI were mainly present among female patients (female: OR 2.80, 95%CI 1.64-4.79; male: OR 1.25 , 95%CI 0.86-1.82; P-interaction =0.012).

**Conclusions:** In this pooled analysis, the majority of patients undergoing PCI for stable CAD (ie, with SYNTAX-score >8) had a higher risk of MACE than patients with ACS. This

was primarily due to a higher risk of MI among SHR patients during the first 30 days and among female patients.

**Trial registration:** URL:http://www.ClinicalTrials.gov; Unique identifier: NCT00297661 (Sirtax), NCT00389220 (Leaders), NCT00389220 (Resolute-AC).

## INTRODUCTION

Treatment of obstructive coronary lesions causing ischemia by means of percutaneous coronary intervention (PCI) with stent implantation improves functional status and clinical outcomes.[1-4] The expanding indications of PCI coupled with refinements in technology including the introduction of drug-eluting stents (DES) and more intensive adjunctive pharmacological treatment, resulted in treatment of increasingly complex lesions and patients with a history of established cardiovascular disease, coexisting morbidities, and complex coronary anatomy in recent years.[5-7] Complex lesions and patient subsets were excluded from the initial coronary stent studies. However, more recently large-scale investigations of stent technology have been performed in the context of so called 'all-comers' patient populations allowing the unrestricted use of DES.[8-11]

All-comers studies provide an unique opportunity to compare clinical outcomes among patients presenting with and without acute coronary syndromes (ACS) in the context of a randomized trial. Noteworthy, careful risk assessment based on clinical and angiographic characteristics is used to guide decision-making regarding type of therapeutic intervention, triage among hospital care levels, and allocation of clinical resources.[12-14] Therefore, identification of higher-risk patients remains of paramount importance. Patients presenting with ACS are currently considered to be at high risk of major adverse cardiac events (MACE) during short- and long-term follow-up, and therefore receive aggressive pharmacotherapy.[15] However, patients with stable coronary artery disease (SCAD) include a broad spectrum of anatomic disease complexity, which – as assessed by the SYNTAX-score – has been shown to be predictive of outcomes.[16-18] To date, no data are available comparing outcomes after PCI between patients with ACS and stable CAD stratified by anatomic disease complexity. Against this background, we compared clinical outcomes between patients with ACS and those with SCAD stratified into high and low risk cohorts according to the angiographic SYNTAX-score.

## METHODS

### Study Population

Individual data were pooled for 5,011 patients from 3 large randomized clinical trials investigating the unrestricted use of DES for coronary revascularization: the Sirolimus-Eluting and Paclitaxel-Eluting Stent for Coronary Revascularization (SIRTAX, n=1012) trial,[9] the Biolimus-Eluting Stent with Biodegradable Polymer versus Sirolimus-Eluting Stent with Durable Polymer for Coronary Revascularisation (LEADERS, n=1707) trial,[10] and the Comparison of Zotarolimus-Eluting and Everolimus-Eluting Coronary Stents (RESOLUTE AC, n=2292) trial.[11] All trials were conducted between 2004 and 2009 at European institutions, with the unrestricted use of DES and an all-comers study design. Inclusion criteria were broad in order to reflect routine clinical practice. Patients with either stable coronary artery disease or acute coronary syndrome (including patients with unstable angina, Non-ST segment elevation and ST-segment elevation myocardial infarction) were eligible, if they had at least one lesion with diameter stenosis of 50% or more in a vessel with reference diameter of 2.25 to 4.0 mm (SIRTAX and RESOLUTE All Comers) and 2.25 to 3.5 mm (LEADERS). None of the trials had any restriction with respect to number of treated lesions, treated vessels, lesion length, or number of stents implanted. Exclusion criteria were few and included known intolerance to the study drugs, metal alloys or contrast media, planned surgery within 6 months after the index procedure, and participation in another study. Angiographic follow-up was planned at 8 months among patients included in SIRTAX, at 9 months among 25% of patients included in LEADERS, and at 13 months among 20% of patients in RESOLUTE All Comers. The angiographic SYNTAX score at baseline was determined in each of the trials. The trials complied with the provisions of the Declaration of Helsinki, and the study protocols were approved by the institutional review board at each study center. All patients provided written informed consent for participation in the study.

### Procedures

Randomization was done after diagnostic angiography and before PCI in all 3 trials. In the SIRTAX trial patients were randomly allocated to receive sirolimus-eluting stents (Cypher, Cordis, Johnson & Johnson, Miami Lakes, FL) or paclitaxel-eluting stents (Taxus, Boston Scientific, Natick, MA), in the LEADERS trial patients were randomly allocated to receive biolimus-eluting stents (BioMatrix, Biosensors Inc, Newport Beach, CA) or sirolimus-eluting stents (Cypher, Cordis, Johnson & Jonhson, Miami Lakes, FL), and in the RESOLUTE All Comers trial patients were randomly allocated to receive zotarolimus-eluting stents (Resolute Endeavor, Medtronic Inc., Santa Rosa, CA) or everolimus-eluting stents (Xience V, Abbott Vascular, Santa Clara, CA). Balloon angioplasty and stent implan-

tation were performed according to standard techniques and in accordance with guidelines; direct stenting was allowed. Full lesion coverage was attempted by implanting one or several stents. No mixture of type of stents was permitted for a given patient unless the operator was unable to insert the study stent, in which case crossover to another device of the operator's choice was possible. In case of unplanned revascularization procedures requiring stent implantation, it was recommended that physicians use the same type as the initially allocated study stent. Procedural anticoagulation was achieved with unfractionated heparin at a dose of 5,000 IU or 70 to 100 IU per kilogram of body weight; the use of glycoprotein IIb/IIIa inhibitors was left to the operator's discretion. Dual antiplatelet therapy consisting of acetylsalicylic acid of at least 75 mg once daily and the thienopyridine clopidogrel 75 mg daily was prescribed for at least 12 months in SIRTAX and LEADERS, and for at least 6 months in the RESOLUTE All Comers trial.

### Definitions

The main outcome measure of the present study was the risk of MACE, defined as a composite of cardiac death, myocardial infarction (MI), and ischemia-driven target lesion revascularization (TLR). Secondary outcomes were the individual components of MACE as well as all-cause death, target-vessel revascularization, as well as definite and definite or probable stent thrombosis according to the Academic Research Consortium criteria.[19]

For each trial, a blinded clinical events committee independently adjudicated all adverse events. Endpoint definitions were comparable across the 3 trials. Cardiac death was defined as death from cardiac causes or any death from unknown causes in SIRTAX and LEADERS, and as any death unless an undisputed non-cardiac cause was present in RESOLUTE All Comers. MI was defined – in SIRTAX and LEADERS trials – as the presence of new Q waves in at least two contiguous leads and an elevated creatine kinase MB fraction, or – in the absence of significant Q waves – as an increase in the creatine kinase level to more than twice the upper limit of the normal range with an elevated level of creatine kinase MB or troponin.[9,10] In the RESOLUTE All Comers trial MI was defined according to an "extended historical" definition[20] consistent with the one used in SIRTAX and LEADERS. Target-lesion revascularization was defined as any revascularization for a stenosis within the stent or within a 5 mm border proximal and distal to the stent in all 3 trials. A revascularization was considered ischemia-driven in the presence of angiographic diameter stenosis of at least 50% and ischemic signs or symptoms, or with angiographic diameter stenosis of at least 70% regardless of ischemic signs or symptoms.[9-11]

Secondary angiographic endpoints were late lumen loss (i.e. difference between the post-procedure and follow-up minimal lumen diameter), rate of binary restenosis (i.e. % diameter stenosis of at least 50%), percent diameter stenosis (i.e. reference vessel diameter - minimal lumen diameter/reference vessel diameter x 100), and minimal lu-

men diameter. Angiographic endpoints were considered for both the in-stent (i.e. within the stent) and in-segment (i.e. within the stent and a 5 mm border proximal and distal) analysis. For a detailed description of quantitative coronary angiography methods we refer to the principal publications of the 3 trials.[9-11] The SYNTAX-score for each patient was calculated prospectively by scoring all coronary lesions with a DS≥50%, in vessels ≥1.5 mm, using the SYNTAX-score algorithm which is described in full elsewhere,[16,21] and available at www.syntaxscore.com. All angiographic variables pertinent to SYNTAX-score calculation were computed by two core laboratory analysts (Cardialysis B.V., Rotterdam, The Netherlands), blinded to clinical presentation and outcomes. In the event of disagreement, the opinion of a third analyst was sought, and the final decision was established by consensus. As previously described,[18,23-26] 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 were scored in the same manner as *de novo* lesion.

### Statistical analysis

Out of 5,011 randomized patients, 4,204 (84%) patients with calculated pre-procedural SYNTAX-score completed 2 years follow-up and were included in the present analysis. Patients were stratified according to baseline clinical presentation (ie, ACS or SCAD). Patients with SCAD where further stratified by SYNTAX-score (ie, higher tertiles [SYNTAX-Score >8] or lower tertile [SYNTAX-Score ≤8]). Clinical outcomes of patients with SCAD at low-risk (SLR) and at high-risk (SHR) were compared with patients with ACS, respectively. Clinical outcomes were compared overall, as well as according to a landmark analyses at 30 days and after stratification by gender. Mixed regression models were used with type of randomized clinical trial as the random intercept and treatment arms as random co-efficient. Percentages were predicted probabilities derived from mixed maximum logistic regression models for the categorical variables, whereas mean and standard deviations (SD) were predicted from the mixed likelihood regression models for the continuous covariates. All the odds ratios (OR) and 95% confidence intervals (CI) were adjusted for stent type. Cumulative incidence curves were constructed using the Kaplan-Meier methodology and compared using log-rank test. A sensitivity analysis was performed by excluding peri-procedural MI, defined as any non-Q-wave MI occurring within 48 hours after PCI not associated with definite stent thrombosis. All analyses are by intention to treat, performed using STATA 11.2 (StataCorp LP).

## RESULTS

Out of 4,204 patients 2,607 (62%) patients presented with ACS, 1,066 (25%) patients with stable, high-risk coronary artery disease (SHR), and 531 (13%) patients with stable, low-risk coronary artery disease (SLR). Baseline clinical characteristics of the three groups are summarized in **Table 1**. SLR patients were older (p<0.0001), more likely to be female (p=0.014), had more frequently hypertension (p<0.0001), hypercholesterolemia, and previous PCI (p<0.0001), and less frequently smoking habits (p<0.0001), previous coronary artery bypass grafting (p=0.028), multivessel disease (p<0.0001), and impaired left ventricular systolic function (p<0.0001) compared with ACS patients. SHR patients were older (p<0.0001), had more frequently diabetes mellitus (p<0.0001), hypertension (p<0.0001), hypercholesterolemia (p<0.0001), previous MI (p<0.0001), previous PCI (p<0.0001), multivessel disease (p<0.0001), and had less frequently smoking habits (p<0.0001), previous coronary artery bypass grafting (p<0.0001) and impaired left ventricular systolic function (p<0.0001) compared with ACS patients.

Angiographic and procedural characteristics are summarized in **Table 2**. SLR patients had more frequently the right coronary artery and less frequently a bypass graft as target lesion (p<0.0001), and had less frequently de-novo lesions (p=0.006), moderately or severely calcified lesions (p=0.033), and total occlusions (p<0.0001) compared with ACS patients. Conversely, SHR patients had more frequently the left anterior descending and less frequently a bypass graft as target vessel (p<0.0001), had more frequently moderate or severe calcified lesions (p<0.0001), and less frequently de-novo lesions (p=0.01) and total occlusions (p<0.0001) compared with ACS patients.

Clinical outcomes through 2 years are reported in **Table 3**, overall and according to a landmark analysis at 30 days. Cumulative incidence curves for MACE through 2 years are shown in **Figure 1**. At 2 years, the risk of MACE was lower for SLR patients (OR 0.61, 95%CI 0.43-0.87) and higher for SHR patients (OR 1.34, 95%CI 1.08-1.66) compared with ACS patients, respectively. SLR patients had a markedly reduced risk of cardiac death (OR 0.22, 95%CI 0.08-0.59) and similar risks of MI (OR 0.85, 95%CI 0.52-1.38) and TLR (OR 0.66, 95%CI 0.42-1.03) compared with ACS patients.

Differences in disfavor of SHR compared with ACS patients were primarily driven by a higher risk of MI (OR 1.64, 95%CI 1.21-2.21), whereas no differences were observed for cardiac death (OR 0.77, 95%CI 0.49-1.21) and TLR (OR 1.21, 95%CI 0.91-1.62). Landmark analyses showed that SHR patients compared with ACS patients had an increased risk of MI during the first 30 days (OR 1.89, 95%CI 1.35-2.66) without differences beyond 30 days up to 2 years (OR 1.00, 95%CI 0.54 to 1.88). No differences between groups were observed with respect to stent thrombosis through 2 years, as summarized in **Table 4**.

Risks of MACE and its individual components at 2 years stratified by gender are summarized in **Figures 2 and 3**. Female SHR patients had a higher risk of MACE compared with female ACS patients at 2 years, whereas the risk of MACE was similar among male SHR and ACS patients. However, formal tests for interaction were negative (p-interaction=0.22). Noteworthy, female SHR patients had a higher risk of MI compared with female ACS patients (OR 2.80, 95%CI 1.64-4.79) whereas no differences were noted among male patients (OR 1.25, 95%CI 0.86-1.82) with formal tests for interaction resulting positive (p-interaction=0.012).

Sensitivity analyses showed that differences in disfavor of SHR compared with ACS with respect to MACE (OR 1.23, 95%CI 0.97-1.55) and MI (OR 0.85, 95%CI 0.51-1.43) at 2 years were no longer evident by excluding periprocedural MI.

## COMMENT

This individual patient data pooled analysis of 3 large contemporary trials including all-comer patients undergoing PCI with the unrestricted use of drug-eluting stents has the following findings:

1) Patients with SCAD had a high baseline angiographic risk estimate in up to two thirds of cases
2) SHR patients showed a higher risk of MACE compared with ACS patients up to 2 years of follow-up, mainly due to a higher risk of MI occurring within the first 30 days after PCI
3) The increased risk of MI was particularly pronounced among female SHR patients
4) Excluding peri-procedural MI, the risk of MI was similar among SHR and ACS patients through 2 years

Patients undergoing PCI for ACS are regarded as a group at increased risk of further cardiac ischemic events[15,27] and have been excluded from early trials investigating DES. More recent randomized studies investigating the unrestricted use of DES applied an all-comers design, therefore extending recruitment also to ACS patients (including non-ST-elevation and ST-elevation ACS).[8-11] The SIRTAX, LEADERS, and RESOLUTE-AC trials, pooled in this individual patient data analysis are 3 large all-comers trials more closely representing treatment in routine clinical practice.[9-11] Noteworthy, rates of death of ACS patients included in this pooled analysis (4.3%) were comparable with those observed in contemporary ACS trials such as TRITON-TIMI 38[15] (3.0%) and PLATO[27] (4.5%), underscoring the representative nature of the present patient population.

Our findings indicate that a substantial proportion of patients with SCAD undergoing elective PCI have a higher risk of MACE compared with ACS patients at 30 days and 2 years of follow-up. Although the difference was mainly due to peri-procedural MI, it is interesting that by excluding the latter SHR patients maintained a similar risk of MACE compared with ACS patients. This result points to the fact that SHR patients need to be considered at least at similar risk as ACS patients, and might benefit from more intense pharmacotherapy and secondary prevention currently reserved to ACS patients. SHR patients have not been investigated in dedicated randomized clinical trials, and therefore there are limited grounds for evidence-based treatment guidelines, and the potential for undertreatment.

In our study, SHR patients and ACS patients differed in baseline clinical and angiographic characteristics underlying a different coronary atherosclerotic burden. Therefore, the pathophysiologic mechanisms leading to the increased risk of MACE in SHR patients and ACS patients might differ. While the importance of an aggressive risk factor management is expected to be critical for both groups, the therapeutic impact of adjunctive and preventive pharmacotherapy remains speculative and needs to be addressed in future studies.

The key difference in MACE as it relates to peri-procedural MI observed in our analysis raises two relevant issues. First, the adjudication of peri-procedural MI is difficult in ACS patients due to the elevated pre-procedural cardiac biomarkers. The critical challenge is to distinguish whether a new cardiac biomarkers elevation is induced by the PCI procedure (e.g., extension of ischemia, new procedural flow limiting complications, etc.) or if the cardiac biomarker release is the tail of the ongoing initial insult. [28] Second, the clinical relevance of peri-procedural MI remains problematic. In the 3 trials pooled in this analysis the MI definition was based on CK-MB, which is less sensitive than troponins, however the threshold used for MI definition was relatively low. Post-procedural cardiac biomarker elevation is more debated. To date there is no evidence of impaired long-term clinical outcomes among SCAD patients with post-procedural cardiac biomarker elevation without symptoms or electrocardiographic signs of ischemia.[28] Noteworthy, the recently released revised version of universal definition of MI document recommend a post-procedural threshold higher than the one used in our study (ie, 5x upper reference limit).[29]

Noteworthy, the excessive risk of MI was particularly pronounced among female SHR patients compared with female ACS patients, whereas no significant difference among male patients was noted. The observed positive interaction suggests that this difference is above what expected by chance alone. A sex-related difference in response to procedural triggers of myocardial injury may be possible. Nevertheless, this finding needs

to be cautiously interpreted in light of its observational nature as well as the debated clinical relevance of post-procedural cardiac biomarkers elevation.[30]

This analysis has a number of limitations. First, it is a post-hoc analysis of trials not primarily intended to investigate differences based on clinical indication for PCI. However, the large size, the all-comer nature of the study population, and the core-lab assessment of baseline characteristics provide an unique opportunity to compare outcomes of ACS patients with that of SCAD patients. Second, the relatively low event rates make our findings prone to chance. However, these rates are consistent with real-world contemporary clinical practice. Moreover, the observation that the cumulative risk of MACE and its individual components among the different groups point into the same direction support the robustness of our findings. Third, this post-hoc analysis was not powered for multiple effects modification. Therefore, our findings must be regarded as exploratory and hypothesis generating until confirmed by evidence from rigorously conducted prospective randomized trials.

## CONCLUSIONS

In this pooled analysis of 3 large contemporary trials the majority of patients undergoing elective PCI for SCAD had a higher risk of MACE than patients with ACS during long-term follow-up. This was primarily due to a higher risk of MI among SHR patients during the first 30 days, and was particularly pronounced among female SHR patients.

## AUTHOR CONTRIBUTIONS

Prof. P. Juni, Prof. P.W. Serruys and Prof. S. Windecker had full access to all of the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design : Prof. P.W. Serruys, Dr. P. Vranckx and Prof. S. Windecker.

Acquisition of data/study supervision: Prof. P.W. Serruys, Prof. S. Silber and Prof. S. Windecker.

Analysis and interpretation of data : Prof. P. Jüni, Dr. B. Kalesan, Dr. G.G. Stefanini, Prof. P.W. Serruys, Dr. P. Vranckx and Prof. S. Windecker.

Manuscript: First draft by Dr. P. Vranckx and Dr. G.G. Stefanini. Manuscript : critical revision of the manuscript for important intellectual content : Dr. V. Farooq, Prof. P. Juni, Dr. B. Kalesan, Dr. Y. Onuma, Prof. P.W. Serruys, and Prof. S. Windecker.

## FINANCIAL DISCLOSURES

CTU Bern, which is part of the university of Bern, has a staff policy of not accepting honoraria or consultancy fees. Prof. Juni: is an unpaid steering committee or statistical executive member of trials funded by Abbott Vascular, Biosensors, Medtronic and Cordis. Prof. Windecker: has received research contracts to the institution from Abbott Vascular, Boston Scientific, Biosensors, Cordis and Medtronic. All other author report no conflicts.

## FUNDING/SUPPORT

The SIRTAX trial was supported by research grants from Bern University Hospital (757) and University Hospital Zurich (33-03), respectively. The LEADERS trial was supported by Biosensors Europe SA, Switzerland. The RESOLUTE AC trial was supported by Medtronic CardioVascular, Santa Rosa, California, USA. The statistical analysis was funded by intramural grants provided by CTU Bern, Bern University Hospital, the Institute of Social and Preventive Medicine, University of Bern, and the Swiss National Science Foundation (SPUM, grant 33CM30-140336).

## ROLE OF THE SPONSORS

The individual trial sponsors had no role in the design, data analysis, data interpretation, and writing of this report.

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Table 1. Baseline Clinical Characteristics

| | SLR | SHR | ACS | SLR vs. ACS | | SHR vs. ACS | |
|---|---|---|---|---|---|---|---|
| | | | | Difference (95% CI) | p | Difference (95% CI) | p |
| *No. of patients* | *531* | *1066* | *2607* | | | | |
| Age | 64.6 (9.9) | 65.3 (10.4) | 62.8 (11.3) | 1.9 (0.9 to 3.0) | <.0001 | 2.5 (1.8 to 3.3) | <.0001 |
| Female | 154 (29.0) | 261 (24.5) | 624 (23.9) | 5.1 (1.0 to 9.1) | 0.014 | 0.5 (-2.5 to 3.6) | 0.724 |
| Diabetes | 120 (22.6) | 285 (26.7) | 516 (19.8) | 2.8 (-0.8 to 6.4) | 0.125 | 6.9 (4.0 to 9.9) | <.0001 |
| Insulin-requiring diabetes | 45 (37.5) | 84 (29.5) | 179 (34.7) | 2.8 (-6.7 to 12.3) | 0.562 | -5.2 (-12.0 to 1.6) | 0.133 |
| Obese | 157 (29.6) | 257 (24.2) | 663 (25.6) | 4.0 (0.1 to 8.0) | 0.046 | -1.4 (-4.6 to 1.7) | 0.375 |
| Renal impairment (eGFR<60) | 76 (14.3) | 167 (15.7) | 354 (13.6) | 0.7 (-1.9 to 3.3) | 0.579 | 2.1 (-0.4 to 4.5) | 0.095 |
| Hypertension | 395 (74.4) | 799 (75.0) | 1719 (65.9) | 8.5 (4.6 to 12.3) | <.0001 | 9.0 (5.8 to 12.3) | <.0001 |
| Hypercholesterolemia | 381 (71.8) | 757 (71.0) | 1505 (57.7) | 14.0 (9.7 to 18.4) | <.0001 | 13.3 (9.8 to 16.7) | <.0001 |
| Current smoking | 123 (23.2) | 212 (19.9) | 884 (33.9) | -10.8 (-14.8 to -6.7) | <.0001 | -14.0 (-17.3 to -10.8) | <.0001 |
| Previous MI | 149 (28.2) | 343 (32.6) | 691 (26.7) | 1.5 (-2.9 to 6.0) | 0.501 | 5.9 (2.7 to 9.2) | <.0001 |
| Previous PCI | 199 (37.5) | 402 (37.7) | 602 (23.1) | 14.4 (10.6 to 18.2) | <.0001 | 14.6 (11.5 to 17.8) | <.0001 |
| Previous CABG | 22 (4.1) | 16 (1.5) | 182 (7.0) | -2.8 (-5.4 to -0.3) | 0.028 | -5.5 (-7.3 to -3.7) | <.0001 |
| LVEF <0.50 | 55 (13.0) | 109 (14.5) | 479 (27.2) | -14.2 (-18.9 to -9.5) | <.0001 | -12.7 (-16.4 to -8.9) | <.0001 |
| Multi-vessel disease, | 31 (5.8) | 278 (26.1) | 491 (18.8) | -13.0 (-17.1 to -8.9) | <.0001 | 7.3 (4.6 to 10.0) | <.0001 |

Values are n (%). ACS= acute coronary syndromes; CABG= coronary artery bypass grafting; eGFR= estimated glomerular filtration rate; PCI=percutaneous coronary interventions; LVEF=left ventricular ejection fraction; SLR= stable low-risk; SHR= stable high-risk.

Table 2. Baseline Angiographic Characteristics

| | SLR | SHR | ACS | SLR vs. ACS | | SHR vs. ACS | |
|---|---|---|---|---|---|---|---|
| | | | | Difference (95% CI) | p | Difference (95% CI) | p |
| *No. of lesions* | 843 | 1469 | 3777 | | | | |
| Target vessel | | | | | <.0001 | | <.0001 |
| Left main | 2 (0.2) | 15 (1.0) | 52 (1.4) | -1.1 (-2.5 to 0.3) | | -0.4 (-1.7 to 1.0) | |
| Left anterior descending | 303 (35.9) | 683 (46.5) | 1535 (40.6) | -4.7 (-5.0 to -4.4) | | 5.9 (5.6 to 6.2) | |
| Left circumflex | 193 (22.9) | 344 (23.4) | 889 (23.5) | -0.6 (-0.9 to -0.4) | | -0.1 (-0.4 to 0.2) | |
| Right coronary artery | 335 (39.7) | 426 (29.0) | 1227 (32.5) | 7.3 (7.0 to 7.5) | | -3.5 (-3.7 to -3.2) | |
| Bypass graft | 10 (1.2) | 0 (0.0) | 74 (2.0) | -0.8 (-1.3 to -0.3) | | -2.0 (-2.5 to -1.5) | |
| De novo lesions | 772 (92.0) | 1349 (92.6) | 3556 (94.5) | -2.5 (-2.6 to -2.4) | 0.006 | -1.9 (-2.0 to -1.8) | 0.01 |
| Total occlusion | 15 (1.8) | 111 (7.7) | 716 (19.1) | -17.3 (-18.3 to -16.3) | <.0001 | -11.5 (-12.1 to -10.8) | <.0001 |
| Moderate or severe calcification | 132 (15.8) | 379 (26.1) | 707 (18.9) | -3.2 (-3.3 to -3.0) | 0.033 | 7.2 (6.8 to 7.6) | <.0001 |

Values are n (%). ACS= acute coronary syndromes; SLR= stable low-risk; SHR= stable high-risk.

Table 3. Clinical Outcomes Through 2 Years

| | SLR (N=531) | SHR (N=1066) | ACS (N=2607) | SLR vs. ACS | | SHR vs. ACS | |
|---|---|---|---|---|---|---|---|
| | | | | OR (95% CI) | p | OR (95% CI) | p |
| **Overall** | | | | | | | |
| Death | 12 (2.3) | 33 (3.1) | 112 (4.3) | 0.47 (0.26 to 0.87) | 0.0152 | 0.70 (0.47 to 1.04) | 0.0812 |
| Cardiac death | 4 (0.8) | 26 (2.4) | 81 (3.1) | 0.22 (0.08 to 0.59) | 0.003 | 0.77 (0.49 to 1.21) | 0.2612 |
| MI | 20 (3.8) | 75 (7.0) | 115 (4.4) | 0.85 (0.52 to 1.38) | 0.5148 | 1.64 (1.21 to 2.21) | 0.0013 |
| Ischemia-driven TVR | 29 (5.5) | 91 (8.5) | 183 (7.0) | 0.68 (0.45 to 1.02) | 0.0619 | 1.23 (0.95 to 1.61) | 0.1185 |
| Ischemia-driven TLR | 24 (4.5) | 75 (7.0) | 153 (5.9) | 0.66 (0.42 to 1.03) | 0.0696 | 1.21 (0.91 to 1.62) | 0.1917 |
| Cardiac death or MI | 21 (4.0) | 94 (8.8) | 179 (6.9) | 0.54 (0.34 to 0.86) | 0.0092 | 1.31 (1.01 to 1.70) | 0.0431 |
| MACE | 39 (7.3) | 148 (13.9) | 280 (10.7) | 0.61 (0.43 to 0.87) | 0.0057 | 1.34 (1.08 to 1.66) | 0.0077 |
| **0 to 30 days** | | | | | | | |
| Death | 0 (0.0) | 5 (0.5) | 25 (1.0) | 0.00 (0.00 to .) | 0.9936 | 0.48 (0.18 to 1.25) | 0.1321 |
| Cardiac death | 0 (0.0) | 5 (0.5) | 20 (0.8) | 0.00 (0.00 to .) | 0.9784 | 0.60 (0.22 to 1.60) | 0.3056 |
| MI | 15 (2.8) | 61 (5.7) | 81 (3.1) | 0.94 (0.54 to 1.65) | 0.8387 | 1.89 (1.35 to 2.66) | 0.0002 |
| Ischemia-driven TVR | 5 (0.9) | 19 (1.8) | 48 (1.8) | 0.48 (0.19 to 1.21) | 0.1206 | 0.97 (0.57 to 1.66) | 0.9199 |
| Ischemia-driven TLR | 4 (0.8) | 17 (1.6) | 45 (1.7) | 0.40 (0.14 to 1.13) | 0.0834 | 0.93 (0.53 to 1.63) | 0.7917 |
| Cardiac death or MI | 15 (2.8) | 64 (6.0) | 98 (3.8) | 0.76 (0.44 to 1.32) | 0.3323 | 1.63 (1.18 to 2.26) | 0.003 |
| MACE | 16 (3.0) | 71 (6.7) | 113 (4.3) | 0.70 (0.41 to 1.19) | 0.1817 | 1.57 (1.16 to 2.14) | 0.0037 |
| **31 days to 2 years** | | | | | | | |
| Death | 12 (2.3) | 28 (2.6) | 87 (3.3) | 0.61 (0.33 to 1.13) | 0.1186 | 0.77 (0.50 to 1.19) | 0.2471 |
| Cardiac death | 4 (0.8) | 21 (2.0) | 61 (2.3) | 0.29 (0.10 to 0.80) | 0.017 | 0.84 (0.51 to 1.38) | 0.4817 |
| MI | 5 (0.9) | 14 (1.3) | 34 (1.3) | 0.65 (0.25 to 1.68) | 0.3762 | 1.00 (0.54 to 1.88) | 0.9878 |
| Ischemia-driven TVR | 24 (4.5) | 72 (6.8) | 135 (5.2) | 0.76 (0.48 to 1.19) | 0.2265 | 1.32 (0.98 to 1.78) | 0.0666 |
| Ischemia-driven TLR | 20 (3.8) | 58 (5.4) | 108 (4.1) | 0.78 (0.48 to 1.27) | 0.3161 | 1.33 (0.95 to 1.85) | 0.0934 |
| Cardiac death or MI | 6 (1.1) | 30 (2.8) | 81 (3.1) | 0.32 (0.14 to 0.74) | 0.0074 | 0.90 (0.59 to 1.38) | 0.6278 |
| MACE | 23 (4.3) | 77 (7.2) | 167 (6.4) | 0.58 (0.37 to 0.90) | 0.0165 | 1.13 (0.86 to 1.50) | 0.3822 |

Values are n (%). ACS= acute coronary syndromes; CI= confidence interval; MACE= major adverse cardiac events; MI= myocardial infarction; OR= odds ratio ; SLR= stable low-risk; SHR= stable high-risk; TLR= target-lesion revascularization; TVR= target-vessel revascularization.

Table 4 Stent Thrombosis Through 2 Years

| | SLR (N=531) | SHR (N=1066) | ACS (N=2607) | SLR vs. ACS | | SHR vs. ACS | |
|---|---|---|---|---|---|---|---|
| | | | | OR (95% CI) | p | OR (95% CI) | p |
| Definite | | | | | | | |
| Early | 3 (0.5) | 9 (0.9) | 35 (1.3) | 1.89 (0.51 to 7.03) | 0.342 | 0.66 (0.32 to 1.38) | 0.273 |
| Late | 1 (0.2) | 2 (0.2) | 7 (0.3) | 1.21 (0.11 to 13.46) | 0.876 | 0.73 (0.15 to 3.51) | 0.693 |
| Very late | 0 (0) | 5 (0.5) | 10 (0.4) | - | - | 1.28 (0.43 to 3.75) | 0.656 |
| Overall | 4 (0.7) | 16 (1.6) | 52 (2.0) | 2.56 (0.85 to 7.70) | 0.095 | 0.79 (0.45 to 1.39) | 0.411 |
| Definite or probable | | | | | | | |
| Early | 3 (0.5) | 12 (1.2) | 47 (1.8) | 2.52 (0.71 to 8.98) | 0.154 | 0.65 (0.34 to 1.24) | 0.191 |
| Late | 2 (0.3) | 3 (0.3) | 9 (0.3) | 0.86 (0.14 to 5.16) | 0.865 | 0.86 (0.23 to 3.17) | 0.815 |
| Very late | 0 (0) | 5 (0.5) | 11 (0.4) | - | - | 1.17 (0.40 to 3.37) | 0.775 |
| Overall | 5 (0.9) | 20 (2.0) | 67 (2.6) | 2.52 (0.94 to 6.76) | 0.067 | 0.76 (0.46 to 1.26) | 0.293 |

Values are n (%).ACS= acute coronary syndromes; CI= confidence interval; OR= odds ratio; SLR= stable low-risk; SHR= stable high-risk.

**Figure 1. Major Adverse Cardiac Events Through 2 Years.**
Cumulative incidence curves of the main outcome measure MACE through 2 years follow-up. ACS= acute coronary syndromes; SLR= stable low-risk; SHR= stable high-risk; OR= odds ratio; CI= confidence interval.

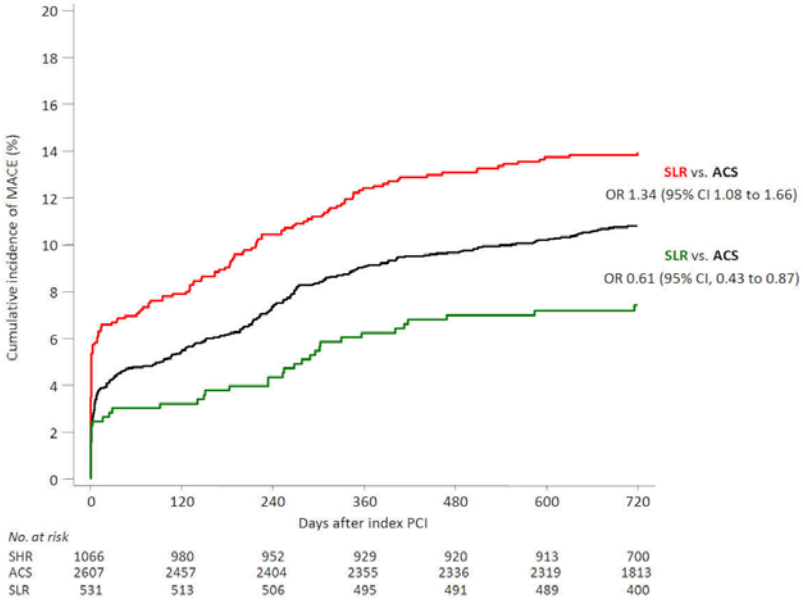



**Figure 2. Major Adverse Cardiac Events Through 2 Years.**
Cumulative incidence curves of the main outcome measure MACE through 2 years follow-up. ACS= acute coronary syndromes; SLR= stable low-risk; SHR= stable high-risk; OR= odds ratio; CI= confidence interval.

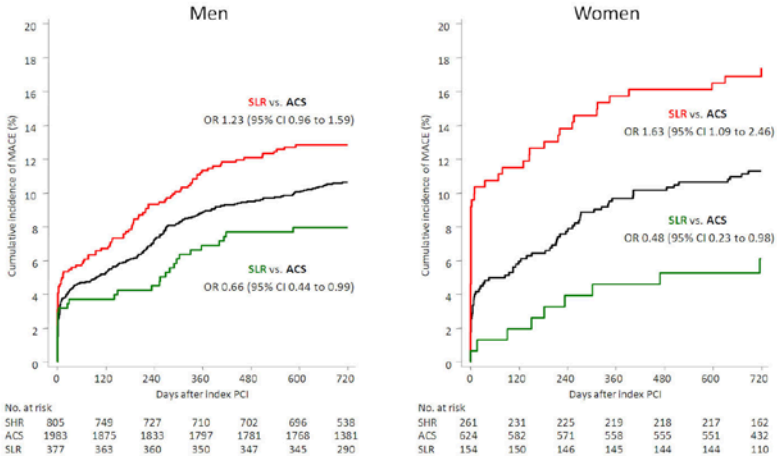
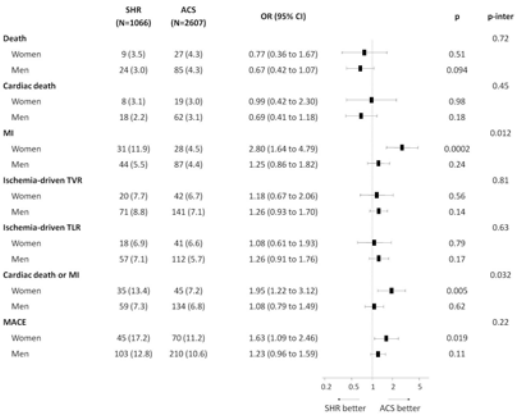


**Figure 3.**


SHR (N=1066)
ACS (N=2607)
OR (95% CI)
p
p-inter
Death
0.72
Women 9 (3.5) 27 (4.3) 0.77 (0.36 to 1.67) 0.51
Men 24 (3.0) 85 (4.3) 0.67 (0.42 to 1.07) 0.094
Cardiac death
0.45
Women 8 (3.1) 19 (3.0) 0.99 (0.42 to 2.30) 0.98
Men 18 (2.2) 62 (3.1) 0.69 (0.41 to 1.18) 0.18
MI
0.012
Women 31 (11.9) 28 (4.5) 2.80 (1.64 to 4.79) 0.0002
Men 44 (5.5) 87 (4.4) 1.25 (0.86 to 1.82) 0.24
Ischemia-driven TVR
0.81
Women 20 (7.7) 42 (6.7) 1.18 (0.67 to 2.06) 0.56
Men 71 (8.8) 141 (7.1) 1.26 (0.93 to 1.70) 0.14
Ischemia-driven TLR
0.63
Women 18 (6.9) 41 (6.6) 1.08 (0.61 to 1.93) 0.79
Men 57 (7.1) 112 (5.7) 1.26 (0.91 to 1.76) 0.17
Cardiac death or MI
0.032
Women 35 (13.4) 45 (7.2) 1.95 (1.22 to 3.12) 0.005
Men 59 (7.3) 134 (6.8) 1.08 (0.79 to 1.49) 0.62
MACE
0.22
Women 45 (17.2) 70 (11.2) 1.63 (1.09 to 2.46) 0.019
Men 103 (12.8) 210 (10.6) 1.23 (0.96 to 1.59) 0.11
0.2
0.5
1
2
5
SHR better
ACS better

# APPENDIX 5.1

## A Guide To Interpreting and Assessing the Performance of Prediction Models

Farooq V, Brugaletta S, Vranckx P, Serruys PW.

EuroIntervention. 2011;**6**:909-12 [**technical report**]

EuroIntervention

# A guide to interpreting and assessing the performance of prediction models

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*The authors have no conflict of interest to declare.*

Risk stratification is an integral and increasingly important aspect of the assessment of patients who are candidates for coronary revascularisation. Careful risk assessment for each patient, based on both clinical and angiographic characteristics, informs decisions regarding aggressive therapeutic interventions, triage among alternative hospital care levels and allocation of clinical resources.

Capodanno et al recently raised the interest within the interventional community on the importance of the assessment of performance of a prognostic score or prediction models.[1,2] The performance of a risk model or prognostic score had however been well established within statistical literature, with up to four different assessments being previously described (Table 1). An understanding of the basic concepts of the assessment of the prediction models are therefore essential, especially since this is currently subject to an intense area of research and new methods to refine these traditional concepts have and are still being developed.[3]

Steyerberg et al[3] recently eloquently summarised these concepts. Traditional measures for binary and survival outcomes include the Brier score to indicate overall model performance, the concordance (or c) statistic for discriminative ability (or area under the receiver operating characteristic ROC curve), and goodness-of-fit statistics for calibration. Consequently, it has been suggested and recommended that, as a minimum, the reporting of discrimination and calibration are essential for understanding the importance of a prediction model, with a recommendation against relying on the c-statistic alone.[3,4]

**Table 1. Assessment of the performance of a prognostic score.**

| |
|---|
| 1) How accurate is the score as a whole? |
| i.e., overall performance score |
| 2) How well can the score discriminate between those who do and do not experience the event? |
| i.e., discrimination measure (e.g., C-statistics) |
| 3) Is the score correctly calibrated? |
| i.e., goodness-of-fit (e.g., Hosmer-Lemeshow) |
| 4) Is the score transportable or generalisable? |

## The overall performance of the score

The scale of agreement (or lack of) between the predicted and actual outcomes (i.e., "goodness-of-fit" of the model) are central in allowing the assessment of the overall model performance. The overall model performance essentially captures both calibration and discrimination aspects as discussed below. The distances between observed and predicted outcomes are related to this concept, with better models having smaller distances between predicted and observed outcomes.

One such measure used widely to assess these concepts is the Brier score; this being initially proposed in the 1950s by Glenn Brier as a means to verify weather forecasts in terms of probability.[9] The Brier score is a quadratic scoring rule based on the average squared deviation between predicted probabilities for a set of events and their observed outcomes (Figure 1). Consequently, the score consists of only positive values ranging from 0 (perfect prediction) to 1 (worst possible prediction), with lower scores representing a higher accuracy and no rule-of-thumb, *per se*, on what constitutes an acceptable value. This would potentially allow comparison across different prediction models. [3,5-8]

## Discrimination and calibration

Accurate predictions discriminate between those with without the outcome. Individuals are categorised into different outcome groups on the basis of their risk model score in order to allow the physician

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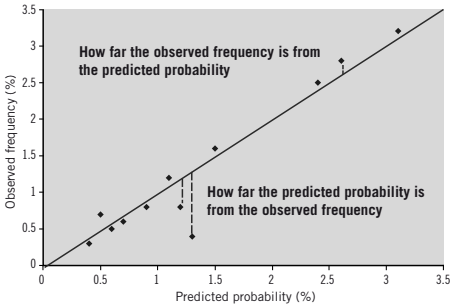


*Figure 1. The concept of the Brier Score.*

to assess the outcomes of each group. A well-discriminated model should therefore be able to discriminate between a trend towards a significantly different event rate within each respective category. For example, higher, intermediate and lower event rates should be discernible by their respective scores from the prediction models. Receiver operator characteristic (ROC) curves are commonly used to assess discrimination and are essentially a plot of true positive rate (sensitivity) of the score against false positive rate (1-specificity or 1-true negative rate). The area under the ROC curve (AUROC) gives an indication of the ability of the score to discriminate between those who do and do not experience the event with 0.5 being no better than chance and 1.0 a perfectly discriminated model.[3,5-8]

Conversely, calibration assesses how closely the predicted probabilities from the risk model agree with the actual outcomes (i.e., detecting a lack of goodness-of-fit). In keeping with the weather forecast analogy, this gives a probability of the forecast event and how close this prediction would be to the actual forecast event if and when it occurs. With the risk model however, this would be the agreement of all the predicted probabilities against their respective observed outcomes, which would give an indication as to how well calibrated our model was.

The Hosmer-Lemeshow goodness-of-fit test is frequently used to assess for calibration by assessing for the presence or absence of goodness-of-fit (based on chi-squared analysis and the subsequent significance of the *p*-value) for logistic regression models. A significant *p*-value means the overall model fit is NOT good, it however gives no indication of the nature of the goodness-of-fit. Within this test, observed outcomes are plotted by deciles of predictions, with a good discriminating model having more spread between such deciles compared to a poorly discriminating model. Good calibration and good discrimination are therefore usually inconsistent for predictive models, with a necessary trade-off between the two being required.[5-8]

Lastly is the proposition of potentially assessing whether the score will work in different populations from the population from which the score was derived. This can be performed with internal validation; i.e., performed on two separate samples within the study population, with the score derived in one sample and tested on the other as performed by Ito et al[11] in this issue of EuroIntervention.

Conversely, external validation is where the score is assessed on a separate population from the study group. The former would perhaps lead to a more optimistic assessment, and the latter, a potentially more accurate assessment of the validity of the score model. Other ways to cross-validate the models include methods such as "boot-strapping" and methods analogous to "jack-knifing," the former is described by Baran et al[10] in this issue of EuroIntervention they are however, outside the scope of this editorial.

Within this issue of EuroIntervention, three articles using these models are included.

Ito et al[11] developed a risk model to predict 30-day MACCE from the STENT Group Registry. The strengths of this study are that c-statistics, Hosmer-Lemeshow test of goodness-of-fit and an internal validation of the data were all performed. The latter was feasible given the large cohort of patients (>10,000 patients) investigated. The final c-statistic value was moderate (0.653 and 0.692 in the study and validation set) and was used by the authors to compare this model against other previously investigated models, despite the limitations of using c-statistics alone in comparing models as previously discussed.

Baran et al[10] developed a risk model for the VLST risk score for the second year post-DES implantation. Once again c-statistics and Hosmer-Lemeshow tests were performed; in this case a bootstrap method was used as a validation tool. Given the expected low event rate associated with stent thrombosis and moderate population size (approximately 7,500 patients), which is essentially underpowered to fully investigate stent thrombosis, it is noteworthy to see that a risk model could still be developed and does hold out the intriguing possibility of developing a model with a better discriminatory value within a larger patient group. The limitations, such as only being performed with one DES type and not comparing with BMS are obvious. However, the potential clinical utility with regards to this model are yet to be explored, and does potentially open the door with regards to perhaps better advising patients with respect to dual antiplatelet therapy regimes and even possibly the selection of PCI techniques, despite the studies limitations.

Federspiel et al[12] describe the fascinating concept of risk-benefit trade-off in the choice of coronary revascularisation modality: essentially trading the long-term risk of repeat revascularisation in exchange for short-term morbidity benefits. This issue is particularly pertinent in this present age, where the need for some individuals to remain active in their professional/personal lives are vital, and they are thus prepared to accept the longer term risks of coronary revascularisation in order to remain at their present functional state. Although this study was performed on the original ARTS study[13] data, which in itself was undertaken over ten years previously, the results are nevertheless supportive of this concept, and do allow a quantification of a level of risk that a patient would be able to accept in order to maintain their present state. Clearly, and as to what the authors elude to in their discussion, in order to better calculate the risk, data from SYNTAX[14] and FREEDOM trials, will be able to explore this concept to match modern day practice. This present study, however, is a welcome addition to the data in helping to explain these complex concepts to patients, and gives a taste of the quality of the

data due to come from further studies investigating this issue. In closing, it will be interesting to see how far we should go in allowing assessment of risk scores and importantly, allowing comparison of different types of risk models, within cardiology based trials. Undoubtedly, a greater collaboration with statisticians with expertise in these fields and cardiologists would aid in developing, refining and simplifying the assessment of these performance models.

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# APPENDIX 5.2

# 5-Year Follow-Up of Coronary Revascularization in Diabetic Patients With Multivessel Coronary Artery Disease Insights From ARTS (Arterial Revascularization Therapy Study)-II and ARTS-I Trials

Onuma Y, Wykrzykowska JJ, Garg S, Vranckx P, Serruys PW;
ARTS I and II Investigators.

*JACC Cardiovasc Interv.* 2011;**4**:317-23. [**original research paper, only provided as a reference** ]

**OBJECTIVES:** We compared the 5-year outcomes of diabetic patients with multivessel disease treated with sirolimus-eluting stents (SES), bare-metal stents (BMS), and coronary artery bypass graft surgery (CABG) enrolled in the ARTS (Arterial Revascularization Therapy Study) I and II studies.

**BACKGROUND:** Diabetes is an established risk factor for major adverse cardiac events after revascularization. Recent trials suggest that revascularization with drug-eluting stents has equivalent safety to CABG up to 2 years.

**METHODS:** The ARTS I and II studies included 367 diabetic patients (SES: 159, CABG: 96, and BMS: 112) compared with respect to 5-year clinical outcomes.

**RESULTS:** The rate of major adverse cardiovascular and cerebrovascular events was significantly higher in patients treated with BMS (BMS 53.6% vs. CABG 23.4% vs. SES 40.5%; log-rank, $p < 0.01$ for SES vs. BMS and SES vs. CABG). There was no significant difference in mortality among all 3 groups. There was, however, a statistically significant difference in the myocardial infarction rate between BMS and CABG arms (BMS 11.0%, CABG 5.2%, SES 4.8%, $p = 0.04$ for SES vs. BMS and $p = 0.76$ for SES vs. CABG). The rate of repeat revascularization was significantly lower in patients treated with CABG compared with SES (SES 33.2% vs. CABG 10.7%, $p < 0.001$). Revascularization rate of patients treated with SES at 5 years approached that of patients treated with BMS although remained significantly lower. This "catch-up" phenomenon was not apparent in the nondiabetic population.

**CONCLUSIONS:** At 5-year follow-up, CABG has comparable safety and superior efficacy compared with BMS and SES in the treatment of diabetic patients with multivessel disease.

# [ PART 6 ]

# APPENDIX 6.1

## Consensus on Definitions of Clinical End Points in Percutaneous Cardiovascular Intervention and Valvular Trials

Vranckx P, Cutlip DE, Mehran R, Leon MB, Serruys P .

In the PCR-EAPCI textbook on Percutaneous Interventional Cardiovascular Medicine Vol. IV Chapt. 4.4. [**technical report, only provided as a reference** ]

**OBJECTIVES:** To propose standardized consensus definitions for important clinical endpoints in transcatheter aortic valve implantation (TAVI), investigations in an effort to improve the quality of clinical research and to enable meaningful comparisons between clinical trials. To make these consensus definitions accessible to all stakeholders in TAVI clinical research through a peer reviewed publication, on behalf of the public health.

**BACKGROUND:** Transcatheter aortic valve implantation may provide a worthwhile less invasive treatment in many patients with severe aortic stenosis and since its introduction to the medical community in 2002, there has been an explosive growth in procedures. The integration of TAVI into daily clinical practice should be guided by academic activities, which requires a harmonized and structured process for data collection, interpretation, and reporting during well-conducted clinical trials.

**METHODS AND RESULTS:** The Valve Academic Research Consortium established an independent collaboration between Academic Research organizations and specialty societies (cardiology and cardiac surgery) in the USA and Europe. Two meetings, in San Francisco, California (September 2009) and in Amsterdam, the Netherlands (December 2009), including key physician experts, and representatives from the US Food and Drug Administration (FDA) and device manufacturers, were focused on creating consistent endpoint definitions and consensus recommendations for implementation in TAVI clinical research programs. Important considerations in developing endpoint definitions included (i) respect for the historical legacy of surgical valve guidelines; (ii) identification of pathophysiological mechanisms associated with clinical events; (iii) emphasis on clinical relevance. Consensus criteria were developed for the following endpoints: mortality, myocardial infarction, stroke, bleeding, acute kidney injury, vascular complications, and prosthetic valve performance. Composite endpoints for TAVI safety and effectiveness were also recommended.

**CONCLUSION:** Although consensus criteria will invariably include certain arbitrary features, an organized multidisciplinary process to develop specific definitions for TAVI clinical research should provide consistency across studies that can facilitate the evaluation of this new important catheter-based therapy. The broadly based consensus endpoint definitions described in this document may be useful for regulatory and clinical trial purposes.

# APPENDIX 6.2

## Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium

Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, Krucoff MW, Mack M, Mehran R, Miller C, Morel MA, Petersen J, Popma JJ, Takkenberg JJ, Vahanian A, van Es GA, Vranckx P, Webb JG, Windecker S, Serruys PW J

*Am Coll Cardiol. 2011 18;57:253-69.* **[technical report]**

**OBJECTIVES:** To propose standardized consensus definitions for important clinical endpoints in transcatheter aortic valve implantation (TAVI), investigations in an effort to improve the quality of clinical research and to enable meaningful comparisons between clinical trials. To make these consensus definitions accessible to all stakeholders in TAVI clinical research through a peer reviewed publication, on behalf of the public health.

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**CONCLUSION:** Although consensus criteria will invariably include certain arbitrary features, an organized multidisciplinary process to develop specific definitions for TAVI clinical research should provide consistency across studies that can facilitate the evaluation of this new important catheter-based therapy. The broadly based consensus endpoint definitions described in this document may be useful for regulatory and clinical trial purposes.

# APPENDIX 6.3

## Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document

Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, **Vranckx P**, Webb JG, Windecker S, Serruys PW, Leon MB.

*Eur Heart J. 2012 Oct;33(19):2403-18.* **[technical report]**

**OBJECTIVES:** The aim of the current Valve Academic Research Consortium (VARC)-2 initiative was to revisit the selection and definitions of transcatheter aortic valve implantation (TAVI) clinical endpoints to make them more suitable to the present and future needs of clinical trials. In addition, this document is intended to expand the understanding of patient risk stratification and case selection.

**BACKGROUND:** A recent study confirmed that VARC definitions have already been incorporated into clinical and research practice and represent a new standard for consistency in reporting clinical outcomes of patients with symptomatic severe aortic stenosis (AS) undergoing TAVI. However, as the clinical experience with this technology has matured and expanded, certain definitions have become unsuitable or ambiguous.

**METHODS AND RESULTS:** Two in-person meetings (held in September 2011 in Washington, DC, USA, and in February 2012 in Rotterdam, the Netherlands) involving VARC study group members, independent experts (including surgeons, interventional and non-interventional cardiologists, imaging specialists, neurologists, geriatric specialists, and clinical trialists), the US Food and Drug Administration (FDA), and industry representatives, provided much of the substantive discussion from which this VARC-2 consensus manuscript was derived. This document provides an overview of risk assessment and patient stratification that need to be considered for accurate patient inclusion in studies. Working groups were assigned to define the following clinical endpoints: mortality, stroke, myocardial infarction, bleeding complications, acute kidney injury, vascular complications, conduction disturbances and arrhythmias, and a miscellaneous category including relevant complications not previously categorized. Furthermore, comprehensive echocardiographic recommendations are provided for the evaluation of prosthetic valve (dys)function. Definitions for the quality of life assessments are also reported These endpoints formed the basis for several recommended composite endpoints.

# PART 7

**Summary and conclusions**

**Samenvatting en conclusies**

**Acknowledgements**

**Curriculum Vitae**

**List of publications0**

## SUMMARY AND CONCLUSIONS

Controlled safety and efficacy endpoint trials are a cornerstone in the search for medical therapeutic advances, their approval by regulatory bodies, and their adoption for clinical use by the medical communities. The concern about how the effects of pharmacologic as well as device therapies are understood in clinical practice requires attention to the methods of randomized clinical trials, including the selection of meaningful clinical endpoints.

The process by which clinical trials in cardiovascular medicine, and coronary stent devices in particular, are designed, conducted, analysed, presented, and published has evolved dramatically over the last decade. (THIS THESIS) Large, truly global studies with relatively long-term clinical endpoints are conducted to evaluate the effects of a particular treatment strategy on mortality and major morbidity within a disease entity. Unrestricted study populations, including more complex patients, have become the norm. (CHAPTER 1.2)

Globalisation in coronary stent research calls for uniform endpoint definitions and the harmonisation of clinical event adjudication. (APPENDIX 1.1, 2.1, 6.1) An important challenge is to maintain accuracy and consistency in the interpretation of clinical endpoints across geographic areas and over the course of the study. (CHAPTER 1.8)

### Globalisation in percutaneous cardiovascular intervention research:

CHAPTER-1.1 of this thesis introduces the interested reader to the Infinnium™ (Sahajanand Medical Technologies PvT.Ltd, India) Paclitaxel Dug Eluting Stent (DES) with biodegradable polymer surface coating. The Infinnium™ was the first indigenously designed and evaluated Drug-eluting-stent from India to have obtained a Conformité Européenne (CE) certificate for commercialization in Europe and may stand symbol for the Globalisation in percutaneous cardiovascular intervention research. Moreover, the application of a biodegradable polymer technology on stents remains scientifically appealing. Use of biodegradable polymers on stents means that, once completely degraded, the stent will be polymer-free and drug-free like a bare-metal stent.

### Outcome measures in contemporary all-comer trials allowing the unrestricted use of DES

CHAPTER 1.2 contains the 2-year follow up data of the first randomised controlled coronary stent trial in all-comers allowing the unrestricted use of 2nd generation DES. In RESOLUTE-AC there were no significant differences in patient-level (death from all-cause, non-fatal myocardial infarction, all coronary artery revascularization) or stent level (death from a cardiac cause, non-fatal target vessel myocardial infarction, ischemia driven target-lesion revascularization) composite event rates between the tested devices and the

patient-level event rate was almost double that of the reported stent-related composite event rate. Thus, during long-term follow-up, the optimization of secondary prevention and overall medical management of the patients remains at least as important as the selection of which stent to use. (See also CHAPTER 5.1) A challenge in THE RESOLUTE-AC (ALL-COMERS) trial conduct was to adapt the 2007 Academic Research Consortium (ARC) consensus endpoint definitions (APPENDIX 1.3), while maintaining accuracy and consistency across geographic areas and over the long course of the study. (CHAPTER 1.8) This was important while addressing minimally selected populations, including complex patients and/or lesions. (CHAPTER 1.6) In the Resolute-AC trial 60% of patients had stable coronary artery disease while 40% presented with ACS. (CHAPTER-1.2) The importance of complete capture of required source documentation and the use of core laboratories was emphasised. (CHAPTER 1.8) The differential implications of cardiac biomarker type on peri-procedural myocardial infarction (MI) following PCI were investigated. The adjudication of peri-procedural MI (Type-IVa according to the 2007 Universal definition of MI) was problematic and suffered from 'definition instability'. (CHAPTER 1.6-1.7) Peri-procedural MI should not be a component of the primary composite endpoints in coronary stent trials, which recruit patients with an evolving MI at the time of the index procedure. Finally, with new generation DES, late and very late stent thrombosis proved an infrequent, though still worrying, issue. However, it should no(t) (longer) be considered an independent endpoint in DES-versus-DES trials outside the clinical context. (CHAPTER 1.3-1.5)

**Weighting the benefits and the risks of anticoagulation regimen following DES implantation.**

Modulation of thrombotic and coagulation potential is a key factor in clinical outcomes and in preventing complications in patients undergoing PCI. There is clear evidence that anticoagulation in addition to platelet inhibition is effective and the combination of the two therapies is more effective than either treatment alone. The choice of the concomitant pharmacological environment is critical, as is the dosage of the drugs. Bleeding has become a critical factor in therapeutic decision making in cardiac patients, especially in those undergoing PCI for acute coronary syndromes.

To minimise the risk of ischaemic complications during and shortly after PCI, many adjunctive antithrombotic regimens targeting thrombin generation and/or activity have been investigated and are currently in use. (CHAPTER 2.1-2.2). Dabigatran etexilate is a novel, orally available, potent, direct thrombin inhibitor. Dabigatran etexilate given at a dose of 150mg twice daily is more effective than warfarin in prevention of stroke and systemic embolism in patients with atrial fibrillation. However, the D-FINE study suggested that a short course of dabigatran etexilate 150mg given twice daily prior to the procedure, without intra-procedural heparin, may not be sufficient to suppress

thrombin activation compared to intra-procedural heparin. The D-FINE study provides a precedent for the study of new oral anticoagulants in patients in the need of a PCI. (CHAPTER 2.4) The optimal concomitant anticoagulation regimen during PCI in patients receiving long-term anticoagulant treatment remains to be established in the future.

Post-percutaneous coronary intervention (PCI) bleeding has been strongly associated with subsequent case fatality. Yet, post-percutaneous coronary intervention (PCI) bleeding is not created equal. Vascular access-site related bleeding, while substantially contributing to the total of bleeding events, did not contribute to 12-month mortality and myocardial infarction to the same extent as non-access-site related bleeding. (CHAPTER 2.1)(1) Several different definitions for bleeding exist, and are used variably in clinical trials; all have specific limitations, all account for transfusions. Red blood cell transfusion is an independent predictor of mortality, NO-scavenging by free hemoglobin may have a role. (PART 3) The prognostic impact of bleeding may vary across definitions. Again, the lack of a common definition hampers comparison across studies. In 2010 a consensus Bleeding Academic Research Consortium grading scale was proposed. (APPENDIX 2.1)

Platelets are vital components of normal haemostasis and key participants in atherothrombosis by virtue of their capacity to adhere to injured blood vessels and to accumulate at sites of injury. The optimal duration of dual antiplatelet therapy and the risk–benefit ratio for long-term dual antiplatelet therapy remain uncertain for patients receiving drug-eluting stents. The PRODIGY trial (CHAPTER 2.2) challenged the current treatment guidelines for a 12-month dual antiplatelet regimen, including aspirin and clopidogrel, for patients receiving DES. The PRODIGY trial showed a clear increase in BARC-bleeding (APPENDIX 2.1), transfusion and net adverse clinical events with a DAPT regimen beyond 6 months. PRODIGY represents one more victory against the greatest enemy of drug-eluting stents – the wrongly assumed need for endless dual anti-platelet therapy

Evidence has emerged, regarding the inherent limitations of clopidogrel. The pharmacokinetic and pharmacodynamic effects of clopidogrel are highly variable and may be influenced by genetic polymorphisms, which translate into differential pharmacodynamic and therapeutic responses, leading to the notion of clopidogrel "non-responders". A personalized anti-platelet regimen tailored towards the individual residual platelet reactivity as assessed by the VerifyNow Aspirin and P2Y12 point-of-care assays reduced major adverse events at 30 days. (CHAPTER 2.6)

**PCI should open the door towards opening secondary prevention.**

There is an unmet need in primary and secondary prevention in Europe. (CHAPTER 5.1) Ultimately PCI should open the door towards optimising secondary prevention. The SYNTAX (SX-) score, based on simple baseline angiographic criteria, predicts procedural risk and annual rates of major adverse cardiovascular events (MACE) among patients undergoing percutane-

ous coronary intervention (PCI). (CHAPTER 5.2-3) The SX-score may, beyond the clinical presentation, may assist in decision making regarding the prognosis of therapeutic interventions. Up to two-thirds of patients undergoing PCI for stable CAD (SX-score >8) in routine clinical practice have a higher risk of MACE than ACS patients. It remains to be determined whether they would benefit from more intensive anti-platelet therapy. (CHAPTER 5.5)

**If anything can go wrong, fix it!**

The invasive management of the complex cardiac patient with advanced heart failure, cardiogenic shock and/or potential hemodynamic compromise during and beyond percutaneous coronary intervention (PCI) has become a special dimension for specialized Myocardial Intervention Centres providing state-of-the-art facilities for PCI including experienced senior operators and critical care physicians available on a 24 hours:7 days basis, and immediate access to cardiac surgery and mechanical circulatory support systems. However, at all times the benefits of a specific (percutaneous) procedures should be weighed against the risk involved: Pre-warned is pre-armed! (APPENDIX 4.1) In very high risk PCI, assisted circulation using the Tandemheart® percutaneous trans-septal left ventricular assist system may contribute to reduced procedural risk and improved survival (CHAPTER 4.2-4.3) Vascular access can be performed in a true percutaneous fashion in the majority of patients. (CHAPTER 4.4) The rate of device related cardiac and vascular complications was acceptable. (CHAPTER 4.2-4.4) The experience with these systems continuous to grow, with leading centres and investigators contributing meaningful information toward the application and development of the latest technologies. The time is now to advance to meaningful clinical investigations adequately powered to examine hard clinical endpoints. Procedure related safety endpoints may be similar to the ones proposed for trans-catheter aortic valve implantation clinical trials. (APPENDIX 6.2)

**Conclusions:**

This thesis has several main findings. The critical challenge in the conduct of large, truly global endpoint trials with long-term follow-up relates to the definition, collection and accurate assessment of endpoint data in a consistent timely manner. The few endpoints encountered with the new drug-eluting-stents and the need for large sample sizes further shifted the design from superiority trials to non-inferiority trials. During long-term follow-up, the optimization of secondary prevention and overall medical management of the patients remains at least as important as the selection of which stent to use. The majority of patients undergoing PCI for stable CAD in routine clinical practice have a higher risk of MACE than ACS patients. It remains to be determined whether they would benefit from more intensive anti-platelet therapy. Non vascular-access-site bleeding should be accounted for.

## SAMENVATTING EN CONCLUSIES:

Prospectief, gerandomiseerd klinisch onderzoek vormt de hoeksteen voor de medische vooruitgang. Het is een noodzakelijke voorwaarde voor de erkenning en financiering van een bepaalde behandeling door de overheid, en biedt de basis voor klinische behandel richtlijnen door professionele organisaties. Een goed inzicht in de studie methodiek is cruciaal voor een goed begrip van studieresultaten. De keuze van betekenisvolle klinische eindpunten, met een rechtstreekse link naar pathofysiologie, is essentieel.

Het proces waarbij toegepast klinisch onderzoek in de cardiologie , en voor coronaire stents in het bijzonder, wordt opgezet, geanalyseerd en gepubliceerd is wezenlijk geevolueerd over de laatste decade. (Dit proefschrift) Grote, mondiale studies, met relatief lange termijn eindpunten, worden opgezet om het effect van een bepaalde behandeling op een goed omschreven ziektetoestand te evalueren. Er gelden minimale selectie criteria voor deelname van patiënten aan de studies waardoor ze nauw komen aan te sluiten bij de routine klinische praktijk. (hoofdstuk 1.2)

Deze mondialisering in onderzoek met coronaire stents is enkel mogelijk middels éénduidige eindpunten definities en een consistente interpretatie van deze definities over het ganse verloop een studie (Appendix 1.1, 2.1, 6.1)(hoofdstuk 1.8)

### Mondialisering binnen het coronaire stent onderzoek

Hoofdstuk 1.1 van dit proefschrift introduceert de InfinniumTM stent (Sahajanand Medical Technologies Pvt.Ltd, India) Paclitaxel drug-eluting-stent (DES) met een biologisch afbreekbaar polymeer bedekking. De InfinniumTM is de eerste volledig in India ontworpen en geteste actieve stent, welke een CE-markering (Conformite Europeenne, CE) verwierf. De InfinniumTM stent staat hierbij symbool voor de mondialisering binnen het coronaire interventie en stent onderzoek. Bovendien blijft de toepassing van een biologisch afbreekbaar polymeer technologie op coronaire stents wetenschappelijk erg interessant. Gebruik van biologisch afbreekbare polymeren maakt dat, eenmaal de polymeer volledig is afgebroken, en het medicijn van de stent is vrijgezet, de stent zich zal gedragen zoals een niet-actieve stent.

### Klinische eindpunten in niet geselecteerde patienten-groepen met een ongelimiteerd gebruik van actieve-stents.

Hoofdstuk 1.2 toont de twee jaar resultaten van de Resolute-AC studie. De resolute-AC studie is de eerste prospectief opgezette, gerandomiseerde, stent studie waarbij twee verschillende actieve stents van de tweede generatie met mekaar worden vergeleken. In de resolute-AC was er geen verschil tussen de studie stents noch inzake het op de

patiënt gerichte, noch inzake het op de stent gerichte, samengesteld eindpunt. Het aantal patiënt gerichte eindpunten lag dubbel zo hoog dan het aantal stent gerichte eindpunten, dit doet besluiten dat secundaire cardiale preventie na het plaatsen van een stent minstens zo belangrijk is als het type stent dat wordt gekozen. (zie eveneens HOOFDSTUK 5.1)

De ARC (Academic Research Consortium)-consensus definities voor een uniform gebruik in coronaire stent studies zijn bedacht voor onderzoek bij stabiele patiënten met eenvoudige ('de novo') letsels van de kransslagaders.(BIJLAGE 1,1 ) Zoals reeds hoger aangegeven ligt de uitdaging in patiënt gebonden onderzoek in het nauwkeurig en uniform gebruik van de ARC-definities over het totale verloop van de studie en over alle deelnemende onderzoekscentra met vaak elk hun eigen gewoonten en protocollen. Dit blijkt zeker belangrijk wanneer een on-geselecteerde patiëntengroep wordt bestudeerd met inbegrip van meer complexe patiënten en letsels. (HOOFDSTUK 1.5) In de Resolute-AC studie presenteerden 60% van de patiënten met een stabiele coronaire hartziekte, terwijl 40% zich evenwel presenteerden met een acuut syndroom. (HOOFDSTUK1.2) De impact van ontbrekende patiëntengegevens bij de boordeling van eindpunten en ook de waarde van een onafhankelijk angiografisch referentie laboratorium ('core laboratory') kan niet voldoende worden benadrukt. (HOOFDSTUK 1.5) Voor de RESOLUTE-AC studie onderzochten we de invloed van het type cardiale biomarker type voor het opsporen van hartspierschade en de rapportering van myocard infarcten ten gevolge van percutane coronaire interventie (PCI). Het beoordelen van myocardinfarcten ten gevolge van PCI (Type-IVa op basis van de 2007 universele definitie van MI) bleek problematisch en  was onderhevig aan definitie-instabiliteit .(HOOFDSTUK 1.5, BIJLAGE 1.4, 6.1) Myocard infarcten ten gevolge van PCI dient op deze basis te worden geweerd als onderdeel van het primaire eindpunt in onderzoek naar coronaire stents wanneer ook acute patiënten worden toegelaten. Tot slot, blijft late en zeer late stent trombose een zeldzame, weliswaar nog steeds zorgwekkende, verwikkeling na plaatsen van een 2°generatie DES. Gezien deze lage aantallen wordt ook stent thrombose best niet langer beschouwd als een onafhankelijk eindpunt in onderzoek waarbij meerdere actieve stents met elkaar worden vergeleken. (HOOFDSTUK 1.3, BIJLAGE 1.2-1.3)

**Voordelen en/of risico's van antistolling behandeling na het plaatsen van een actieve stent (DES).**

Ballondilatatie met of zonder stent (PCI, percutane coronaire interventie) plaatsing vergt een intensieve antistolling om de procedure veilig te kunnen uit voeren. De keuze is de keuze van de farmacologische omgeving (dubbele of zelfs drievoudige bloedplaatjes remmende behandeling en anticoagulantia), net als de dosering van deze geneesmid-

delen is cruciaal. Bloeding is hierbij een belangrijk eindpunt en heeft om deze reden een impact op de therapiekeuze.

Meerdere intraveneuze anticoagulatie schema's gericht tegen thrombine activatie bij ballondilatatie en stenting in de kransslagaders werden getest en zijn momenteel geïmplementeerd in de klinische praktijk. Dabigatran etexilate is een nieuwe, krachtige, directe trombine-inhibitor welke via de mond kan worden ingenomen. Dabigatran etexilate in een dosis van 150mg tweemaal daags biedt een betere bescherming tegen het emboliseren van bloedklonters naar het hoofd en het lichaam bij patiënten met boezem fibrillatie dan warfarine. In de D-fine studie evenwel, bleek een korte behandeling aan dezelfde dosis, bovenop de standaard bloedplaatjesremming met clopidogrel en aspirine, evenwel minder effectief in het onderdrukken van de stollingsactivatie tijdens en onmiddellijk na PCI dan heparine . (Hoofdstuk 2.4) De eventuele noodzaak tot (aanvullend) antistolling tijdens PCI bij patiënten chronisch behandeld met één van de nieuwe orale anticoagulantia zal per medicijn dienen te worden bepaald in de nabije toekomst. De D-fine studieconcept biedt de geschikte structuur voor het testen van nieuwe anticoagulantia in de nabije toekomst.

De meerwaarde van een antitrombotische behandeling na plaatsen van een coronaire stent hangt in belangrijke mate af van de balans tussen preventie van ischemische eindpunten en het ontstaan van gedocumenteerde bloedingen. Toch zijn niet alle bloedingen na PCI vergelijkbaar naar hun ontstaan en hun belang. Bloedingen ter hoogte van een vasculaire prikplaats zijn talrijk doch dragen aanzienlijk minder bij tot latere sterfte en/of het ontstaan van spontane myocard infarcten op 12 maanden, dan bloedingen op andere locaties. (Hoofdstuk 2.3) Er bestaan meerdere criteria en definities om bloedingen te beoordelen welke dan ook afwisselend gebruikt worden in klinische studies. Elk van deze definities heeft zijn specifieke beperkingen. Allen nemen ze de transfusie van rode bloedcellen in overweging bij het wegen van de ernst van de bloeding. Transfusie van rode bloedcellen vertaalt zich dan ook consequent, en dit onafhankelijk van andere factoren, in latere sterfte. De binding van NO aan vrij hemoglobine kan hierbij een oorzakelijke rol spelen. (Deel 3) De prognostische impact van bloeding varieert ook naar gelang de gebruikte definitie(s). Ook voor bloeding werd de vergelijking tussen verschillende studies gedurende lange tijd gehinderd door het ontbreken van een consensus definitie. Deze consensus kwam er uiteindelijk in 2010 (de BARC-consensus definitie voor bloeding)(Bijlage 2.1)

Bloedplaatjes spelen een centrale rol in de normale hemostase en bij coronaire athero-thrombose. De optimale duur van dubbele plaatjesremming na het plaatsen van een stent in de kransslagaders en de kosten(risico)/baten van een langdurige dubbele plaatjesremming blijft een punt van discussie. De Prodigy studie (hoofdstuk 2.2) plaatste

de huidige behandelrichtlijn waarbij een 2-ledige bloedplaatjesremmening op basis van aspirine en clopidogrel wordt opgelegd voor een periode van 12-maanden na plaatsen van een actieve stent, op losse schroeven. The PRODIGY studie toonde een duidelijke toename in (BARC-)bloedingen (Bijlage 2.1) en transfusies bij het aanhouden van een tweeledige bloedplaatjesremming voor een periode van langer dan 6 maanden. Een significante meerwaarde naar het voorkomen van majeure ischemische verwikkelingen kon echter niet worden aangetoond.

Ook met betrekking tot clopidogrel rees onzekerheid. De farmaco-kinetische en farmacodynamische effecten van clopidogrel blijken zeer variabel en ze kunnen worden beïnvloed door een genetische polymorfisme. Dit uit zich in een gewijzigd farmacodynamisch en therapeutische effect (clopidogrel "non-responders"). De bloedplaatjesremming kan evenwel individueel worden bijgestuurd, toegespitst op de residuele individuele bloedplaatjes reactiviteit (VerifyNow at the point-of-care test voor Aspirine en P2Y12). Deze bloedplaatjesremming op maat, waarbij zo nodig een glycoproteine IIb/IIIa receptor blocker aan de behandeling werd toegevoegd, resulteerde in een vermindering van het totaal aantal ischemische verwikkelingen binnen een periode van 30 dagen. (Hoofdstuk 2.6)

**PCI opent de deur naar secundaire cardiovasculaire preventie.**

Er is een behoefte aan betere primaire en secundaire cardiovasculaire preventie in Europa. (HOOFDSTUK 5.1) Uiteindelijk, is het arts-patiënt contact rond het tijdstip van de PCI een uitgelezen moment voor het optimaliseren van de secundaire cardiovasculaire preventie. De SYNTAX (SX-) risico score, gebaseerd op eenvoudige (baseline) angiografische criteria, is voorspellend voor het verder risico op ischemische verwikkelingen na plaatsen van een actieve stent en vervolgens ook cumulatief per jaar voor de belangrijke ischemische cardiovasculaire eindpunten. (HOOFDSTUK 5.2-3) De SX-score voorspelt, onafhankelijk van de klinische presentatie van de patiënt op het ogenblik van de studie procedure, de prognose na een bepaalde therapeutische interventie. Tot twee-derden van de patiënten in de routine klinische praktijk welke een PCI ondergaan voor de behandeling van een stabiel, atherosclerotisch letsel (SX-score > 8) hebben een hogere kans op een ischemische verwikkeling over een periode tot 2 jaar dan patiënten welke een PCI ondergingen voor een acuut syndroom. Verder onderzoek moet uitmaken of en in welke mate zij eventueel baat zouden kunnen hebben bij een meer intensieve bloedplaatjesremming, zoals ook de patiënten met een acuut coronair syndroom. (HOOFDSTUK 5.5)

**Indien er ook maar iets fout gaat, herstel het!**

De invasieve behandeling van complexe patiënten en/of letsels, met een aanzienlijk risico op hemodynamische collaps tijdens of na de procedure, is een bijzondere aspect geworden van gespecialiseerde Interventiecentra. Gespecialiseerde hartcentra garanderen een 24uur op 7 dagen toegang tot gespecialiseerde zorg met inbegrip van ervaren interventie cardiologen/intensivisten en een directe toegang tot hartchirurgie en mechanische hemodynamische ondersteuning. Voor geselecteerde hoog risico patiënten, kan de hemodynamische ondersteuning met een Tandemheart® bijdragen tot een een verbeterde overleving. (HOOFDSTUK 4.2-4.3) Het plaatsen van een Tandemheart® kan bij de meeste patiënten niet operatief gebeuren. (HOOFDSTUK 4.4) De cardiovasculaire verwikkelingen verbonden met het gebruik van de Tandemheart® zijn aanvaardbaar. (HOOFDSTUK 4.2-4.4) De klinische ervaring met deze en gelijkaardige systemen neemt toe. Vooraanstaande centra en onderzoekers dragen zinvolle informatie bij tot de verdere ontwikkeling van deze technologie. Het ogenblik is nu gekomen om de stap te zetten naar een volwaardig, patiënten gebonden onderzoek met betekenisvolle eindpunten zoals overleving en vasculaire morbiditeit. Procedure gebonden eindpunten zijn hierbij in ruime mate vergelijkbaar met deze voorgesteld voor de percutane aortaklep implantaties. (BIJLAGE.6.2)

**besluit:**

Dit proefschrift heeft verschillende belangrijke conclusies. De grote uitdaging bij het opzetten van grote, wereldwijde klinische studies met een lange-termijn verloop heeft betrekking tot de definitie, het verzamelen en de eenduidige beoordeling van de klinische eindpunten. Het geringe aantal eindpunten eigen aan het gebruik van de huidige actieve stents, impliceert de inclusie van grote patiënten aantallen en verlegt het accent van superioriteit naar non-inferioriteit studies. Zulke studies onderstrepen meteen het belang van optimaliseren van secundaire preventie en de algemene medische behandeling van de patiënten na stenting. Dit geldt zeker niet alleen voor patiënten behandeld in de context van een acuut coronair syndroom. De overgrote meerderheid van patiënten welke een PCI ondergaan voor een stabiel, atherosclerotisch letsel, hebben een hogere kans op een ischemische verwikkeling binnen een periode van 1-en 2 jaar vergeleken met patiënten welke een percutane behandeling ondergaan voor een acuut syndroom. Verder onderzoek zal moeten uitmaken of en in welke mate zij eventueel baat zouden kunnen hebben bij een meer intensieve bloedplaatjesremming. Het voorkomen van bloedingen is hierbij een belangrijke overweging.

## ACKNOWLEDGEMENTS

***"Where you end up strongly depends upon where you started!"***

I must corroborate words of some of my illustrious predecessors, trying to put pen to paper this part is probably is one of the most challenging aspects of this thesis. It relates to my confrontation with this fascinating institute they call "THE THORAXCENTRE". It is all about attitude, some politics, but mostly and above all the camaraderie, respect and fascination.

For me , it started already in 1999 when I entered THE "THORAXCENTRE" to take a role as cardiologist and critical care physician responsible for the Cardiac Intensive Care department. My period as *'a senior'* in the THORAXCENTRE was one of steep descends and exciting heights, of profound love and some disappointment. It proved out to be a turning point in both my personal life and in my professional career.

Dear friends, get me right, the "THORAXCENTRE" de facto can never be perceived an inmoveable, staid institute, since it is always on the move, ready to explore and conquer new horizons. And for sure, the "THORAXCENTRE' is much more than just a hospital, more than a research institute, it is an attitude in life … every role counts. (*personal communication of P.W. Serruys*) Indeed, from my first introduction I understood, the "THORAXCENTRE" to be an impressive structure dedicated to top patient care and ground breaking clinical research. The 23th floor with the department of experimental cardiology and biomedical engineering, the clinical epidemiology group, the audiovisual department...and most importantly 'the fellows'. These amazing young researchers, next door, fighting their way to the forefront of clinical research. You can reach out to them, approach them, but most of all you can be touched by them! Pedro, Stephane, Benno, Jeroen, Peter, Patrick, Manel, Marco, Koen, Robert Jan, Ken, Marco, Joost, Emanuele, Johanna, Nicolo, Scot, Vasim, and, and many, many others… thank you all !!!

During this period of active clinical duty in the hospital, I had the pleasure to work with some wonderful people and took important lessons in life. From Agie (Dr. Agie Balk), who 'directed' the clinical department and was my direct commander in chief. She is a hard worker and possesses a good political radar. She cared, corrected, even confronted ( when necessary). Agie, I know I haven't always made your life easy, but please know, I do respect you. From Marcel (Marcel van den Brand), the king of kindness, and of course from Professor Pim (Pim de Feyter), a gentleman, a great physician, a human thought in the world of technology. [Please God, if I could only reach the level of his ankles...!] Pim thank you a lot for your wisdom, your remarkable capacity to get straight to the crux of the problem, your on-going support and 'de lekkere pannenkoeken' in the cafeteria. I am very honoured that you accepted accept to take part in my thesis committee! I certainly want to involve and thank the remarkable team of nurses, technicians and secretaries

at the " Thoraxcentre" CCU and Cath Lab (Marjo, Atie, Matie, Titia, Jurgen, Emile, Gio… and again the many, many others). I still feel part of this team even though our paths separated some years ago.

In 2001, I accepted an exciting job offer from the Hartcentrum Hasselt. The call of the family to return home, closer to them, overwhelmed my ambition to build a clinical and academic career in Rotterdam. However, already at that time I realised: "I left, to stay…". I moved my clinical duties back to Belgium yet immediately negotiated a one day release from patient care to invest into clinical research… 'back to the future' in Rotterdam. I definitely owe my friends and colleagues of the Hartcentrum Hasselt for this.

So there I was, back in Rotterdam, but this time 'at the other side of the street', at Cardialysis. a heaven on earth for every clinical researcher working in the field of cardiology. 'An art gallery where artists design and expose their projects, professionals run the business'. I'm deeply indebted to every-one, but I keep a special place in my heart for Yvonne (Van Lint) for the on-going help and emotional support, to Marie-Angèl (Morel, alias mam's, 'mormel') for her kindness, natural enthusiasm and knowledge (my personal advice to others: "never ever underestimate this lady!"), Peter-Paul (Kint) who always keeps an overview, Janette (Simons) my right and left hand in trial management for her optimism and wonderful laugh (easy to find in the corridors, just follow the sound!), Hector Garcia and Eugene Mc Fadden (no words!) and of course Gerrit-Anne van Es. Gerrit-Anne, my brother in arms, working with you is real fun and I hope we can continue for many years from now. You introduced me into this challenging field of trial design and execution. You took me by the hand during the big conventions. We shared our love for the numbers, you brought me the basics of statistics. I could not think about a better person next to me at this exciting moment.

Some extra words, for some special personalities:

Marco (Valgimigli)…, now a lifelong friend. I think we don't need words either. Yet, here I cannot resist. The first time we met was indeed during a research meeting at Cardialysis. I still remember! I didn't know much about the new Italian 'fellow' in front of me, he was never introduced to me before. However, I quickly understood that my best contribution during that meeting was to keep silent, listen and enjoy… You were at that time what you are still now: 'instant brilliant'. Your proper PhD was 'handmade', 'a masterpiece', 'impressive'; every project you got your hands on turned out into a success. You certainly should have been awarded a 'Magna Cum Laude'. From there on you inspired, motivated and helped other young (and some 'a little bit' less young) people to achieve their goals in research. You continued to initiate new projects and explored new horizons in cardiovascular medicine: This merits the title 'professor'. I'm happy that you accepted to stand next to me on this important moment.

Yoshi (Onuma). Japanese, extremely hard working, clever…master of D-bases and power point. I very much look forward to working with you in the near future.

Arie-Pieter Kappetein. Although we didn't get a chance to work together, yet (!), our friendship was instant and I feel very privileged for this. I appreciated our breakfast meetings in San Francisco and timeless discussions.

Paul Cummins- Mr. EuroIntervention, Mr. You Tube... You are 'instrumental' in many ways. I would also like this opportunity to acknowledge the entire Europa organisation and the EuroPCR team: JeanMarco, William Wijns, Jean Fajadet, Frederic and Marc Doncieux, Sylvie, Sally.

Stephan Windecker, Peter Jüni and Bindu Kalesan. Our collaboration only took off recently, however with lighting pace! Working with you is a joy. I respect your judgement and admire your good clinical sense. I look forwards to future collaborations…there are many years ahead of us.

Professor Felix Zijlstra, also promoter to this thesis. We only met recently. You welcomed me as a research affiliate to the Thoraxcentre and provided full support to this thesis and future research. Thanks a million! Of course I would like to thank all members of this thesis committee, and professor Paul Dendale, professor Stefan Janssens, professor Frank Leebeek, professor Freek Verheugt, each and every-one of you are special and mean a lot to me.

Now, it is time to attribute some words to the one and only Professor Patrick Washington Serruys, a once in a lifetime experience. Dear Professor, dear Patrick, Sir (!). You opened my eyes, so I could see. You taught me to listen, so I could hear. You touched me so I could feel. You supported me, so I could walk. You even opened the doors, so I could pass through. You always made me feel a true member of "The Thoraxcentre", even at a time I was no longer a staff cardiologist. Please accept my gratitude, my lifelong friendship and my deepest respect.

And finally to my family. Voor mijn oogappels, Nathan en Ignace, kerels! Ik heb geen ogenblik spijt van mijn stap terug dichter bij jullie. Jullie zien openbloeien was, en vooral ook is, een unieke beleving. De momenten samen zijn zeer erg welkom en geven me de kracht om door te gaan. Barbara dank je voor dit fantastische geschenk! Aan mijn moeder en vader, dank voor de kans en de vrijheid om mijn eigen weg te zoeken …

## CURRICULUM VITAE

Pascal Vranckx was born on September 11th, 1967 in Leuven, Belgium. He obtained his doctor's degree in medical science magna cum laude in 1989 at the University of Leuven where he also gained postdoctoral degrees in intensive care medicine and hospital management and public health. He performed his training in internal medicine, cardiology and intensive care medicine at the same university. Previously, he was clinical director of the Cardiac Intensive Care Unit at the Thoraxcentre, Erasmus Medical Center, Rotterdam (1999–2001).

Pascal Vranckx is now a Clinical Consultant in interventional cardiology and Medical Director of the Cardiac Intensive Care and Interventional Cardiology at Hartcentrum in Hasselt, Belgium. He is a research affiliate to the department of cardiology (Thoraxcentre), Erasmus Medical Center in Rotterdam, The Netherlands. He is also clinical consultant and chair of the Clinical Events Committee Core Laboratories at Cardialysis in Rotterdam, The Netherlands.

Pascal Vranckx has authored over 50 publications and over 10 chapters in textbooks and is an associate editor of the *ESC Textbook of Acute Cardiology and Intensive Care Medicine 2010* and is deputy editor of *EuroIntervention* and editor of the European Heart Journal: acute cardiac care.

### Awards:

Educational Grant Young Cardiologists Club, Belgian Society of Cardiology 1997

Best poster award, abstracts spring meeting Belgian Society of Intensive Care Medicine and Emergency Medicine 1997

Membership:

Pascal Vranckx is a member of the European Society of Cardiology, the Belgian Working Group on Acute Cardiology and the Working Group on Acute Cardiac Care, the Belgian Society of Intensive Care Medicine and Emergency Medicine, the European Society of Intensive Care Medicine, and is also a member of the medical committee of the Belgian Red Cross Flanders.

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