High-Risk Percutaneous Intervention in the Drug-Eluting Stent Era

Risicovolle percutane interventies in het drug-eluting stent tijdperk

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Thesis

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Erasmus University Rotterdam
by command of the
Rector Magnificus

Prof.dr. S.W.J. Lamberts

and according to the decision of the Doctorate Board
The public defence shall be held on

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by

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Born at Forlì, Italy

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Alla mitica *Malaguttona*
e a tutto ciò che di grandioso possiamo fare assieme

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chapter 1 Introduction and overview of the Thesis

Introduction and overview of the Thesis

High-risk Intervention in the Drug-eluting stent era

The introduction and fast uptake of drug-eluting stents in the world market has been a major breakthrough in the field of interventional cardiology. While in-stent restenosis has long been considered the main limitation hampering long-term efficacy of coronary stenting, the development of stents able to temporarily elute drugs to the injured arterial wall has been shown to be an effective and overall safe approach to suppress intimal hyperplasia. The sirolimus eluting stents have virtually abolished restenosis in the First-In-Man (FIM)[1] and in the RAndomized study with sirolimus-eluting Bx Velocity balloon-expandable stent in the treatment of patients with de novo native coronary artery lesions (RAVEL)[2] studies. This led to the approval of this device in Europe in 2002. The results of the randomized, double-blind Sirolimus Eluting Stent in de Novo Coronary Lesions (SIRIUS) trial, involving 1055 patients[3], were subsequently used to gain approval of the device by the Food and Drug Administration (FDA) in the United States in 2003.

The randomized, double blind TAXUS-IV, involving 1314 patients[4], assessed the safety and efficacy of the slow-release paclitaxel-eluting stent in single, previously untreated lesions and led to FDA approval of this active stent in 2004.

Other drugs, including zotarolimus, everolimus, tacrolimus, biolimus A9, and new delivery systems are currently being tested in conjunction with new or traditional metallic stents in randomized controlled trials[5-8]. The great majority of these new active stents however remains in the investigational phase at present and even if approval for clinical use has already been obtained for some of them in Europe, concerns regarding their safety/efficacy profile and/or limited data availability are currently limiting their use worldwide. This thesis will entirely focus on the first two drug eluting stents introduced in the market, the Cypher sirolimus-eluting stent (Cordis, Johnson & Johnson) and the Taxus slow-release paclitaxel-eluting stent (Boston Scientific), attempting to unravel some of the remaining issues regarding their use in patients undergoing high-risk coronary interventions.

The concept of "high-risk intervention" is sometimes elusive and potentially misleading since this term has been applied to a great variety of different conditions in the medical literature[9-12]. Throughout this thesis, interventions at coronary arteries are considered to be at high risk based on specific anatomical location or extension of the treated disease (Parts 1, 4 and partially 5); due to the clinical context in which intervention is performed (Part 3) or if undertaken in patients with reduced left ventricular systolic function (Part 5).

The interventions which are performed under these circumstances are at high-risk based on the concept that the rate of major adverse events is known to be relatively higher in such settings. At the some time, the presence of these conditions makes intervention at coronary arteries a treatment with well-established prognostic implications. Thus, particular attention to improve the therapeutic and safety profile of catheter-based intervention in these patient/lesion subsets is warranted.

Prognostic implications of coronary revascularisation in the setting of stable coronary artery disease

In patients with one or two coronary artery disease without involvement of left main coronary artery and good left ventricular function, percutaneous coronary intervention does not confer any clear benefit in terms of long-term hard clinical outcomes compared with conservative medical treatment, especially in cases where the proximal left anterior descending artery is not involved[13]. Indeed, a trend for increased risk of myocardial infarction in patients undergoing percutaneous coronary intervention compared to conservative management has been observed[13]. This evidence is in agreement with historical data comparing surgical revascularisation versus medical treatment. Yusuf et al. performed a systematic overview using individual patient data from the seven randomised trials comparing a strategy of initial coronary artery bypass graft surgery (CABG) with one of initial medical therapy to assess the effects on mortality in patients with stable coronary heart disease[14].

The CABG group had significantly lower mortality than the medical treatment group at 5 years (10.2 vs. 15.8%; odds ratio 0.61 [95% CI 0.48-0.77], p = 0.0001), 7 years (15.8 vs. 21.7%; 0.68 [0.56-0.83], p < 0.001), and 10 years (26.4 vs. 30.5%; 0.83 [0.70-0.98]; p = 0.03). The risk reduction was greater in patients with left main artery disease than in those with disease in three vessels or one or two vessels (odds ratios at 5 years 0.32, 0.58, and 0.77, respectively). The absolute benefits of surgery were most pronounced in patients in the highest risk categories. This effect was most evident when several prognostically important clinical (reduced left ventricular ejection fraction) and angiographic (left main disease, three vessel disease, especially with proximal left anterior descending artery) risk factors were integrated. In low-risk patients, the data showed again a non-significant trend towards greater mortality with surgical revascularisation.

Thus, taking together the results generated by comparing surgical or percutaneous revascularisation versus medical management, current evidence suggests that coronary revascularisation in patients with stable coronary artery disease reduces hard clinical end-point only when specific high-risk features are present, including anatomic/angiographic variables (left main coronary artery disease, three vessel disease, involvement of proximal anterior descending artery) and clinical characteristics (reduced left ventricular ejection fraction).

Prognostic implications of percutaneous revascularisation in the setting of ST-segment elevation myocardial infarction

Patients presenting with ongoing ST-segment elevation myocardial infarction are well known to derive greater benefit from primary percutaneous intervention with improved safety compared to the pharmacological approach.

Primary percutaneous intervention is associated with a 37% relative reduction in the odds of 30-day mortality when compared with in-hospital fibrinolytic therapy, which is only slightly attenuated to 28% when accelerated t-PA trials are separately considered[15].

Similarly, the incidence of re-infarction is reduced from 7% to 3% and stroke from 2% to 1% with the use of systematic mechanical compared to standard pharmacological reperfusion[16]. Thus, despite the benefit of pre-hospital thrombolysis in patients presenting with short duration of symptoms (less than 2 or 3 hours) is actively debated, especially in cases where transportation time may exceeds 60 minutes, percutaneous coronary intervention in patients with on-going ST-segment elevation myocardial infarction has clear prognostic implications in term of both mortality and morbidity[17].

Outline of the Thesis

Thesis-Part 1

The first part of the thesis examines the safety and efficacy of drug eluting stent implantation in patients with left main coronary artery disease. In chapter 2, observational proof from the prospective Rapamycin Eluting- and Taxus-Stent Evaluated At Rotterdam Cardiology Hospital Registries (RESEARCH and T-SEARCH) that the use of DES in this subset of patients lead to an improved outcome without safety concerns is provided. Chapter 3 focuses on comparative angiographic and clinical efficacy of sirolimus eluting versus paclitaxel-eluting stents, while chapter 4 and 5 evaluate the role of intravascular ultrasound guidance and single versus bifurcation stenting in the treatment of elective unprotected left main coronary artery and in all-comers distal left main disease, respectively. Chapter 6 reports findings on a limited and retrospectively selected group of patients who underwent serial angiographic follow-up at 6 and 12 months after drug-eluting stent implantation for the treatment of left main coronary artery disease. By a pooled analysis of 340 patients treated for elective unprotected left main coronary artery disease at three European referral centers, the temporal distribution of major adverse events has been analyzed in chapter 7.

Finally, the prognostic implications of distal location of the disease within the trunk of the left main stem and its interaction with surgical risk status have been analyzed in chapter 8, both with and without the presence of surgical high risk conditions.

Thesis-Part 2

This section of the thesis examines plaque composition in relation to coronary ostia. In chapter 9, the reference segment is the 10 mm segment located at the ostium of the three major coronary arteries, i.e. left anterior descending, circumflex and right coronary arteries in relation to those segments which are more distally located along the vessel, while in chapter 10 the focus is on left main coronary artery with respect to the ostial segments of left anterior descending or circumflex arteries. By contrasting plaque composition in those coronary segments known to be at high- (proximal segments of the main three coronary arteries) with those at low- (left main coronary artery and distal tract of coronary vessels) risk for developing acute coronary occlusions or prone to rupture lesions, we primarily intended to analyze whether lipid rich plaque regions co-localize where culprit lesions are known to be more frequently located. This may carry implications for locally applied preventive treatment of plaque rupture in the future.

Thesis-Part 3

This section focuses on the treatment of patients with ST-segment elevation myocardial infarction in the drug-eluting stent era. Chapter 11 describes the study design while chapter 12 reports the principal findings of the randomized comparison of tirofiban infusion followed by sirolimus eluting stent implantation versus the use of abciximab and with bare metal stenting in this subset of patients. Chapter 12 reports on a sub-analysis evaluating the value of platelet reactivity in predicting response to treatment and 1-year outcome in a subset of the enrolled patients.

Thesis-Part 4

The safety and efficacy of sirolimus eluting stent in patients with multivessel disease has been evaluated in this thesis section based on sub-analyses of the Revascularization Therapies Study (ARTS) II. In Chapters 14, 15, 17, the effect of clinical presentation (stable versus unstable coronary artery disease), the use and impact on outcomes of glycoprotein 2b/3a inhibitors and the impact of disease location in proximal left anterior descending artery have been evaluated, respectively. Finally, in chapter 17, the role of a recently described angiographic scoring system, the so called Syntax score, has been tested on those patients presenting with three vessel disease in the context of ARTS II study.

Thesis-Part 5

This last section of the thesis describes the use and the effect on haemodynamic variables of a new percutaneous left ventricular assist device, the Impella RECOVER LP 2.5 in patients with depressed left ventricular ejection fraction or extensive coronary artery disease undergoing left ventricular pressure-volume loops analysis.

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Part. 1. Intervention for the left main coronary artery stenosis

Chapter 2 Short- and Long-term Clinical Outcome after Drug-Eluting Stent Implantation for the Percutaneous Treatment of Left Main Coronary Artery Disease. Insights from the Rapamycin Eluting- and Taxus-Stent Evaluated At Rotterdam Cardiology Hospital Registries (RESEARCH and T-SEARCH).

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Interventional Cardiology

Short- and Long-Term Clinical Outcome After Drug-Eluting Stent Implantation for the Percutaneous Treatment of Left Main Coronary Artery Disease

Insights From the Rapamycin-Eluting and Taxus Stent Evaluated At Rotterdam Cardiology Hospital Registries (RESEARCH and T-SEARCH)

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Background—The impact of drug-eluting stent (DES) implantation on the incidence of major adverse cardiovascular events in patients undergoing percutaneous intervention for left main (LM) coronary disease is largely unknown.

Methods and Results—From April 2001 to December 2003, 181 patients underwent percutaneous coronary intervention for LM stenosis at our institution. The first cohort consisted of 86 patients (19 protected LM) treated with bare metal stents (pre-DES group); the second cohort comprised 95 patients (15 protected LM) treated exclusively with DES. The 2 cohorts were well balanced for all baseline characteristics. At a median follow-up of 503 days (range, 331 to 873 days), the cumulative incidence of major adverse cardiovascular events was lower in the DES cohort than in patients in the pre-DES group (24% versus 45%, respectively; hazard ratio [HR], 0.52 [95% CI, 0.31 to 0.88]; $P=0.01$). Total mortality did not differ between cohorts; however, there were significantly lower rates of both myocardial infarction (4% versus 12%, respectively; HR, 0.22 [95% CI, 0.07 to 0.65]; $P=0.006$) and target vessel revascularization (6% versus 23%, respectively; HR, 0.26 [95% CI, 0.10 to 0.65]; $P=0.004$) in the DES group. On multivariate analysis, use of DES, Parsonnet classification, troponin elevation at entry, distal LM location, and reference vessel diameter were independent predictors of major adverse cardiovascular events.

Conclusions—When percutaneous coronary intervention is undertaken at LM lesions, routine DES implantation, which reduces the cumulative incidence of myocardial infarction and the need for target vessel revascularization compared with bare metal stents, should currently be the preferred strategy. **(*Circulation*. 2005;111:1383-1389.)**

Key Words: stents ■ angioplasty ■ arteries

Despite the recognition that coronary revascularization, in selected patients with multivessel disease, can presently be accomplished by either a surgical or a percutaneous approach with no significant difference in long-term mortality,[1,2] coronary artery bypass grafting (CABG) is still considered the treatment of choice in patients with left main (LM) disease.[3] Several trials have reported on the safety and feasibility of stent implantation to treat LM stenosis.[4,5] However, particularly in this subset of patients, restenosis remains a major, and potentially fatal, complication, precluding more widespread use of percutaneous coronary intervention (PCI).[4,6] In the first observational report of patients treated with a sirolimus-eluting stent (SES) for LM disease, a low rate of binary restenosis and a favorable clinical outcome were reported.[7] However, the benefit of drug-eluting stents (DES) on the short- and long-term incidence of major adverse cardiovascular events in this setting, compared with bare metal stents (BMS), remains largely unknown.

The purpose of the present study was to investigate, in this subset of patients undergoing revascularization in a tertiary referral center, the differential impact of DES as opposed to conventional BMS on the occurrence of short- and long-term major cardiovascular events.

Methods

Study Design and Patient Population

Since April 16, 2002, SES (Cypher, Johnson & Johnson, Cordis unit) have been used as a default strategy for every PCI at our institution as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. From the first quarter of 2003, paclitaxel-eluting stents (PES) (Taxus, Boston Scientific Corporation) became commercially available, replacing SES as the strategy of choice in every PCI because of cost-effectiveness considerations, as part of the Taxus Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registry. As a policy, all elective patients presenting with significant (>50% by visual estimation) LM disease, referred to our institution for coronary revascularization, are evaluated by both interventional cardiologists and cardiac surgeons, and the decision to opt for PCI or surgery is reached by consensus on the basis of a comprehensive evaluation of the following items: suitable anatomy and lesion characteristics for stenting and size and quality of vessels distal to the disease and of arterial and/or venous conduits for grafting. Finally, patient and/or referring physician preferences for a percutaneous approach, with both aware of the procedural risks and contraindications to surgery on the basis of the presence of comorbidity as evaluated by a cardiac surgeon, are also considered.

From April 16, 2002, to December 31, 2003, a total of 95 consecutive patients were treated exclusively with ≥1 DES in the LM as part of an elective or nonelective revascularization procedure and constitute the DES group of the present report. Fifty-two patients in the first cohort (of whom procedural details and medium-term follow-up were previously reported for 31[7]), received SES exclusively (available, at that time, in diameters from 2.25 to 3.00 mm), whereas in the following group of 43 patients, PES (available in diameters from 2.25 to 3.5 mm) were implanted. A control group for comparison was composed of 86 consecutive patients who received conventional BMS (available in diameters from 2.5 to 5.00 mm) for LM treatment in the period immediately before the introduction of SES. The following BMS were used: BX Sonic or BX Velocity in 35% (Cordis, Johnson & Johnson Company), R-Stent in 29% (Orbus Medical Technologies), Multi-Link Penta in 28% (Guidant Corp), Multi-Link Tetra in 8% (Guidant Corp), and other stents in 4%. Therefore, the total study population comprised all 181 consecutive patients who underwent percutaneous LM treatment from April 2001 to December 2003 with either BMS or DES in the 2 study phases, respectively. To stratify the study population into high– and low–surgical risk groups, the Parsonnet surgical risk score was calculated for each patient.[8] A score >15 was used to identify patients at high risk, as previously suggested.[6,9] Protected LM segment was defined as the presence of at least 1 patent arterial or venous conduit to at least 1 left coronary segment. Nonelective treatment was defined as a procedure performed on referral before the beginning of the next working day.[10]

This protocol was approved by the hospital ethics committee and is in accordance with the Declaration of Helsinki. Written informed consent was obtained from every patient.

Procedures and Postintervention Medications

All interventions were performed according to current standard guidelines, and the final interventional strategy, including the use of glycoprotein IIb/IIIa inhibitors, 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 Thrombolysis in Myocardial Infarction (TIMI) 3 flow grade. All patients were advised to maintain the use of aspirin lifelong. One-month clopidogrel treatment (75 mg/d) was recommended for patients treated in the pre-DES phase. For patients treated with either SES or PES, clopidogrel was prescribed for 6 months.

End Point Definitions and Clinical Follow-Up

The primary outcome was the occurrence of major adverse cardiac events, defined as (1) death, (2) nonfatal myocardial infarction (MI), or (3) target vessel revascularization. Patients with >1 event have been assigned the highest ranked 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. MI was diagnosed by a rise in the creatine kinase level to more than twice the upper normal limit with an increased creatine kinase-MB fraction. Target vessel revascularization was defined as a repeated 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, including the ostium of the left anterior descending artery (LAD) and/or circumflex artery. Information about in-hospital outcomes was obtained from an electronic clinical database for patients maintained at our institution and by review of hospital records for those discharged to referring hospitals (patients were referred from a total of 14 local hospitals). Postdischarge survival status was obtained from the Municipal Civil Registries. Information on occurrence of MI or repeated interventions at follow-up was collected by consulting our institutional electronic database and by contacting referring physicians and institutions and all living patients.

Statistical Analysis

Continuous variables are shown as mean±SD and were compared by Student unpaired *t* test. Categorical variables are presented as counts and percentages and were compared with the Fisher exact test. Survival curves were generated by the Kaplan-Meier method, and survival among groups was compared with the log-rank test. Cox proportional hazards models were used to assess risk reduction of adverse events. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Univariate analysis was performed with the consideration of all variables reported in Tables 1 and 2. Multivariate analyses, with consideration of all variables with a value of $P<0.10$, were performed to identify independent predictors of adverse events. Probability was significant at a level of <0.05. All statistical tests were 2-tailed. Statistical analysis was performed with the use of Statistica 6.1 (Statsoft Inc).

Results

Baseline and Procedural Characteristics

Baseline and procedural characteristics are shown in Table 1 and Table 2. The 2 groups were well matched for all baseline characteristics, including comorbidities. Overall, the average left ventricular ejection fraction was slightly >40%, and approximately half of the patients in both groups were admitted with acute coronary syndromes. Acute MI was the indication to the procedure in 19%; 10% of the patients presented with severe hemodynamic compromise at entry. The distal LM was involved in two thirds of cases in both groups, whereas patients treated with DES had significantly more 3-vessel disease, more bifurcation stenting, a higher number of stents, and greater total stent length per patients. The nominal stent diameter, as a result of limited size availability, was on average smaller in the DES group, which explains the more common practice of postdilatation in this group of patients. Procedural success was 99% in patients receiving DES: in 1 patient who presented with acute MI and shock, a final TIMI 1 flow grade was obtained, and the patient died 3 hours after the procedure. The procedural success was 98% in patients treated in the pre-DES phase: in 2 patients with acute MI and TIMI 0 flow grade in the left coronary artery, the LM and proximal LAD were stented, and subsequently CABG was performed because of residual critical stenosis in the left circumflex artery.

TABLE 1. Baseline Characteristics of the Study Population

Variables	Pre-DES Group (n=86)	DES Group (n=95)	*P*
Age, y *	66±10	64±12	0.18
Men, %*	62	66	0.53
Body mass index, kg/m^2*	26±4	27±4	0.31
Diabetes, %*	22	30	0.23
Non–insulin-dependent, %	17	20	0.71
Insulin-dependent, %	5	10	0.17
Hypertension, %*	57	53	0.65
Hypercholesterolemia, %	55	56	0.88
Current smoking, %	19	18	0.8
Creatinine, μmol/L*	102±80	95±31	0.36
LVEF, %*	42±13	41±14	0.85
Medical history, %			
Protected LM	22	16	0.17
PCI	35	28	0.42
MI	41	38	0.58
Transient ischemic attack/stroke	8	11	0.81
Heart failure*	16	20	0.36
Severe COPD*†	5	8	0.38
Peripheral arterial disease*	24	22	0.86
Carotid artery disease*	6	6	0.98
Clinical presentation, %			
Stable angina	50	48	0.8
Unstable angina	33	33	1
Acute MI*	17	20	0.70
Cardiogenic shock at entry*	9	12	0.66
Parsonnet score	16±11	19±12	0.17

LVEF indicates left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease.

*Parameters included in the Parsonnet classification.

†Resulting in functional disability or hospitalization, requiring chronic bronchodilator therapy, or forced expiratory volume in 1 second <75% of predicted.[8]

Thirty-Day Outcomes

There were no significant differences between the DES and the pre-DES groups in the incidence of major adverse cardiovascular events during the first 30 days (Table 3). In the DES group, all deaths except 3 occurred in patients presenting with ST-segment elevation acute MI and cardiogenic shock at entry. In all these patients except 4 with severe peripheral artery disease, an intra-aortic balloon was placed during PCI. In the elective population, a total of 2 deaths occurred; both patients presented with unstable angina with mild troponin elevation and were refused by surgeons because of old age (84 years), low left ventricular ejection fraction (≤30%), and diabetic chronic renal insufficiency in 1 patient and diffuse 3-vessel disease associated with small-caliber vessels in the second. In this second patient the right coronary artery was occluded. The reason for death was pulmonary infection, which developed 19 days after the procedure in the first patient, and cardiogenic shock, which developed during the intervention, resistant to hemodynamic support (left ventricular assist device) in the other patient. In the pre-DES group, all 6 deaths occurred in patients with ST-segment elevation acute MI, of whom 4 were in cardiogenic shock at entry. No documented thrombotic stent occlusion occurred in the first 30 days or thereafter.

TABLE 2. Angiographic and Procedural Characteristics of the Study Population

Variables	Pre-DES Group (n=86)	DES Group (n=95)	*P*
Lesion location, %			
Ostium	18	27	0.20
Body	40	37	0.31
Distal	66	65	0.9
Pure LM disease, %	2	3	1
LM plus 1-vessel disease, %	29	17	0.4
LM plus 2-vessel disease, %	42	21	<0.001
LM plus 3-vessel disease, %	27	59	0.003
Right coronary artery >70% stenosis, %	27	53	0.02
Right coronary artery occlusion, %	13	19	0.43
No. of implanted stents	1.2±0.5	1.4±0.6	0.01
Nominal stent diameter, mm	3.6±0.5	3.1±0.32	<0.001
Total stent length per patient, mm	20±9	24±13	0.02
Predilatation, %	67	71	0.62
Cutting balloon, %	5	6	0.94
Rotational atherectomy, %	1	3	0.8
Directional atherectomy, %	6	0	0.007
Postdilatation, %	58	80	0.01
Larger balloon inflated, mm	4±0.6	3.9±0.4	0.07
Maximal pressure, atm	17±2	17±3	0.85
Bifurcation stenting, %	10	26	0.02
Culotte*	11	36	0.4
T technique*	88	44	0.35
Crush*	0	12	0.56
Kissing technique*	0	8	0.91
Intravascular ultrasonography, %	23	27	0.36
Glycoprotein IIb/IIIa inhibitors, %	26	28	0.83
Intra-aortic balloon pump, %	16	15	0.88
Left ventricular assist device, %	0	2	0.52
Minimal lumen diameter, mm, preintervention	1.05±0.59	1.09±0.44	0.58
Minimal lumen diameter, mm, postintervention	2.97±0.6	2.83±0.49	0.09
Reference vessel diameter, mm, postintervention	3.37±0.6	3.25±0.5	0.2

*Relative to patients with bifurcation stenting.

Long-Term Outcome

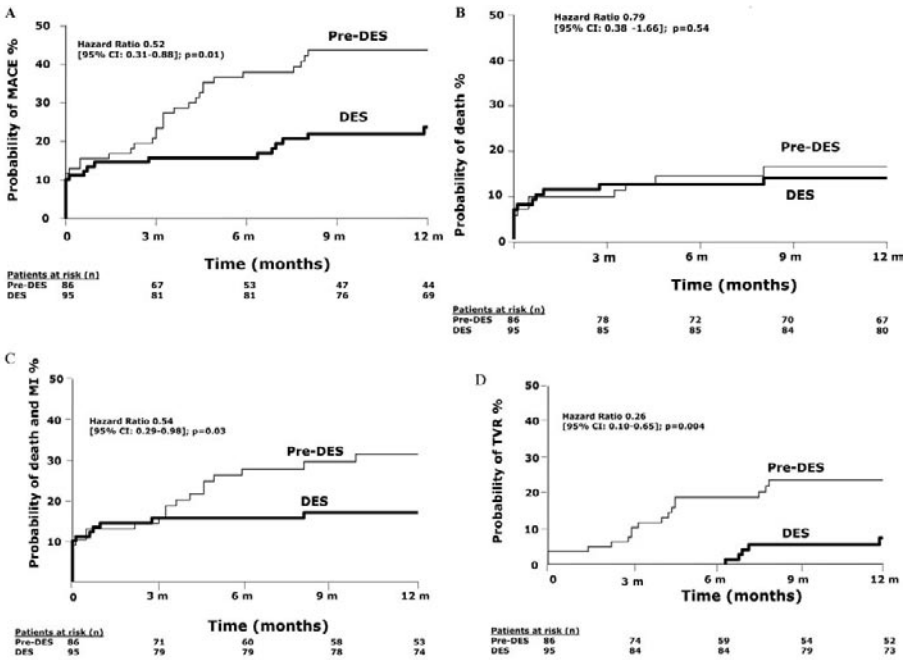
After a median follow-up of 503 days (range, 331 to 873 days), the cumulative incidence of major adverse cardiovascular events (death, MI, or target vessel revascularization) was significantly lower in the DES patients than in the pre-DES patients (24% versus 45%, respectively; hazard ratio

TABLE 3. Thirty-Day Outcomes

Variables	Pre-DES Group (n=86)	DES Group (n=95)	P*
Death, n (%)	6 (7)	10 (11)	0.60
Nonfatal MI, n (%)	8 (9)	4 (4)	0.24
Death or nonfatal MI, n (%)	14 (16)	14 (15)	0.84
Target vessel revascularization, n (%)	2 (2)	0 (0)	0.22
Repeated PCI	1 (1)	0 (0)	
CABG	1 (1)	0 (0)	
Any event, n (%)	16 (19)	14 (15)	0.56
Stent thrombosis, n (%)†	0 (0)	0 (0)	1

*By Fisher exact test.
†Angiographically documented.

[HR], 0.52 [95% CI, 0.31 to 0.88]; $P=0.01$) (Figure, A). Mortality was similar in the DES (14%) and pre-DES cohort (16%; HR, 0.79 [95% CI, 0.38 to 1.66]; $P=0.54$) (Figure, B), whereas there was a significant reduction in both the rate of MI (4% versus 12%, respectively; HR, 0.22 [95% CI, 0.07 to 0.65]; $P=0.006$) and composite death/MI (Figure, C) as well as in the need for target vessel revascularization (6% versus 23%, respectively; HR, 0.26 [95% CI, 0.10 to 0.65]; $P=0.004$) (Figure, D) in the DES group. Seventy-four percent of the deaths were cardiac, whereas 3 of 13 in the DES group and 4 of 14 in the pre-DES phase were attributed to extracardiac reasons. In Table 4, the baseline and procedural characteristics of those patients in the DES group who underwent target vessel revascularization during follow-up are reported. In all cases, the lesion was located in the distal LM, in 50% of cases diabetes was present, and all except 1 were women. In 3 cases, in-stent restenosis occurred; in 2 patients intimal hyperplasia developed at the distal edge of the stent, whereas in 1 patient severe ostial side branch restenosis (circumflex artery) necessitated reintervention. In all cases, restenosis was focal (<10 mm in length) and was successfully treated with repeated PCI. In the pre-DES group, 13 cases of pure in-stent restenosis, of which 3 were focal, were treated with PCI (9 patients) or CABG (4 patients). In 2 patients, diffuse intimal hyperplasia associated with progression of atherosclerotic disease in other vessels was treated with CABG, and in 5 patients (3 with ST-segment elevation acute MI as the indication for LM intervention), staged reintervention with CABG (in 4 patients) and PCI (in 1 patient) was performed because revascularization remained incomplete at the time of the index procedure.



One-year adverse events in patients treated with BMS before the introduction of DES (pre-DES group) and in patients treated exclusively with DES implantation (DES group). Cumulative risk of major adverse cardiovascular events (MACE) (A), death (B), death or MI (C), and target vessel revascularization (TVR) (D) is shown.

TABLE 4. Characteristics of Patients in the DES Group Who Underwent Target Vessel Revascularization During Follow-Up

	Patient No.					
	1	2	3	4	5	6
Age, y	66	77	36	70	52	56
Gender	F	F	F	M	F	F
Diabetes	Yes	No	No	Yes	No	Yes
Lesion location	Distal	Distal	Distal	Distal	Distal	Distal
Severe calcification	Yes	No	No	No	No	No
Stent type	SES	SES	PES	PES	PES	PES
Stent No.	2	2	1	2	1	2
Total stent length, mm	16	36	20	48	16	36
Bifurcation stenting	No	Yes	No	Yes	No	Yes
Technique	...	Crush	...	Culotte	...	Culotte
Postdilatation	Yes	Yes	Yes	Yes	Yes	Yes
Final kissing	No	No	No	Yes	No	No
Gap between stents	No	No	No	No	No	No
Stent underexpansion	Yes	No	No	No	No	No
Restenosis location	In-stent	In-stent*	RS	In-stent	DER	DER*
Revascularization type	PCI	PCI	PCI	PCI	PCI	PCI
QCA after PCI						
Reference vessel diameter, mm	3.74	3.27	3.53	2.65	2.44	2.76
Minimal lumen diameter, mm	2.12	1.06	3.34	2.49	1.94	2.32
Lesion length, mm	13.4	19.7	13.5	21.3	8.9	18.9
QCA at follow-up						
Reference vessel diameter, mm	3.87	3.43	3.21	2.32	1.82	2.36
Minimal lumen diameter, mm	1.23	0.57	0.98	0.99	0.6	0.71
Restenosis length, mm	5.8	9.06	3.6	5.48	7.72	9.5

QCA indicates quantitative coronary angiography; In-stent, restenosis located within the stent margins; RS, restenosis located in the side branch (the ostium of the circumflex artery); and DER, distal edge restenosis located within the 5-mm segment distal to the stent.

*More than 1 focal site.

Predictors of Adverse Events

The Parsonnet score, ranging from 2.5 to 55.5 (mean value, 18±2; interquartile range, 16.5) was 16±11 and 19±12 in the pre-DES and DES groups, respectively (P=0.17) (Table 1), with a trend toward a higher rate of patients considered at high surgical risk (58% versus 46%, respectively; P=0.13) in the DES compared with the pre-DES cohort.

On univariate analysis, Parsonnet classification, use of intra-aortic balloon pump, presence of shock at entry, lesion located in the distal LM, nonelective PCI, troponin elevation at entry, TIMI flow grade before and after PCI, reference vessel diameter, left ventricular ejection fraction, and the use of DES were identified as significant predictors of adverse events. On multivariate analysis, Parsonnet classification, troponin elevation at entry, lesions located at distal site, reference vessel diameter, and the use of DES were independent predictors of major adverse cardiovascular events (Table 5).

Discussion

Despite the feasibility and the high procedural success rate of percutaneous LM intervention, the long-term incidence of adverse events in the pre-DES "era" was often reported to be unacceptably high in this subset of patients.[4,6] This reflected the inclusion of high-risk patients, such as those not considered "good surgical candidates," as well as the dramatic impact of treated vessel failure in this specific anatomic context. In consecutive patients receiving elective BMS for unprotected LM treatment, the 3-year cumulative incidence of death was recently reported to be ≈16%.[6] In that series, 28% of the population was at high surgical risk. More than 50% of our study population was at high surgical risk according to the Parsonnet classification, thus explaining the relatively high rate of adverse events we observed. In this setting, when patients treated with DES were compared with those treated with BMS, a marked benefit with respect to the rate of major adverse cardiac events, as evidenced by a 47% relative risk reduction, emerged in the former. This was mainly due to the difference in the incidence of MI (67% relative risk reduction) and target vessel revascularization (65% relative risk reduction), with no effect on mortality. The higher prevalence of 3-vessel disease and bifurcation stenting in the DES group makes the observed benefit even more convincing. The difference in the incidence of events between

TABLE 5. Univariate and Multivariate Cox Proportional Hazards Analysis

Variables	*P*	Hazard Ratio (95% CI)	χ^2
Univariate analysis			
Distal LM disease	0.003	2.7 (4.8–1.53)	13.3
DES use	0.019	0.54 (0.9–0.32)	5.48
Nonelective PCI	0.0047	2.1 (3.5–1.3)	8
Intra-aortic balloon pump use	0.0002	2.9 (4.9–1.7)	14
LVEF, %	0.00001	0.95 (0.97–0.93)	20
Parsonnet score	>0.00001	1.07 (1.09–1.05)	44
Reference vessel diameter	0.00001	0.36 (0.58–0.32)	19
Shock at entry	>0.00001	4.48 (7.9–2.5)	21
TIMI flow before PCI	0.03	0.75 (0.96–0.58)	4.3
TIMI flow after PCI	0.03	0.58 (0.85–0.39)	4.7
Troponin T >0.02 μg/L at entry	0.0002	3.15 (5.26–1.9)	18
Multivariate analysis 1			
Distal LM disease	0.0007	2.94 (5.5–1.57)	76
DES use	0.00009	0.33 (0.57–0.19)	
LVEF, %	0.09	0.98 (1.001–0.95)	
Parsonnet score	0.0009	1.04 (1.07–1.01)	
Reference vessel diameter	0.005	0.51 (0.79–0.33)	
Troponin T >0.02 μg/L at entry	0.02	2.3 (4.4–1.2)	
Multivariate analysis 2			
Distal LM disease	0.00017	3.3 (6.1–1.7)	68
DES use	0.00018	0.35 (0.6–0.20)	
LVEF, %	0.00013	0.95 (0.98–0.94)	
Reference vessel diameter	0.0011	0.48 (0.74–0.30)	
Shock at entry	0.006	3.49 (8.6–1.4)	
Troponin T >0.02 μg/L at entry	0.016	2.27 (4.2–1.17)	

Multivariate analysis model 1 was performed with all major adverse cardiovascular event predictors on univariate analysis; in multivariate analysis model 2, the Parsonnet score was removed because of colinearity between the variables included in the model and those used in the calculation of the score, such as left ventricular ejection fraction (LVEF), use of intra-aortic balloon pump, and presence of shock.

the 2 groups emerged slowly after the procedure, with no clear advantage at 30 days, possibly reflecting the specific mechanism of action of DES on intimal hyperplasia.

The overall advantage of DES remained significant after adjustment for the Parsonnet score, the anatomic site of obstruction, and troponin status at entry. Therefore, our data suggest that when percutaneous treatment of LM coronary artery disease is undertaken, DES should be used as the default strategy.

The LM bifurcation was frequently involved (>60%) in our series, and even when the obstruction was more proximally located and did not directly involve the LAD or left circumflex artery ostia, its treatment often required the management of LM bifurcation. To date, the results of SES implantation to treat bifurcated lesions have been relatively disappointing, with high rates of restenosis in the side branch.[11] Our present findings are in keeping with these previous observations, confirming that in the DES era distal LM location is an independent predictor of adverse events at follow-up. Furthermore, because the strategy and technical aspects of bifurcation management were left entirely to the preference of treating physicians, no clear conclusions can be drawn in this regard.

Inconsistent findings have been reported thus far with regard to the effect of DES on long-term cumulative incidence of MI. In the first randomized clinical trials comparing SES or PES with BMS, no difference in the incidence of MI was observed.[12,13] Second-generation randomized trials assessing the benefit of DES in patients selected to be at intermediate risk for in-stent restenosis or all-inclusive registries reported trends toward MI reduction in the DES group, but none of them reached statistical significance.[14,15] Recently, a clear reduction in the cumulative incidence of MI in the DES group was reported in the SES-SMART trial, in which a selected group of high-risk patients has been evaluated.[16] Similarly, in our patient population, a reduced incidence of MI was observed in the DES group. Of note, 2 and 1 cases of MI in the pre-DES phase were related to target vessel revascularization and not related to target vessel revascularization, respectively. Whether this difference between studies is the reflection of a type II error in studies enrolling patients at low or intermediate risk remains unclear, but when the retrospective nature of our investigation is considered, data from prospective studies are needed to confirm our findings.

Limitations of the Study

The present study is a single-center experience from a tertiary referral center and lacks the clear advantages of a multicenter randomized study. In keeping with the aim of our investigation, an "all-comers" population has been enrolled, clearly resulting in a heterogeneous group of patients. Further studies, with larger sample sizes, are required to investigate the differential impact of DES versus BMS in prespecified subgroups, stratified according to clinical presentation (stable versus unstable) or protected versus unprotected type of treatment.

Despite the fact that the study was conducted over a relatively short period, we cannot exclude the possibility that improvements in technique or differences in drug prescription could have partially accounted for the difference observed in terms of major adverse cardiovascular events between groups. However, conducting randomized trials that seek to assess the efficacy of DES versus BMS in this specific subset of patients seems unlikely, and our understanding of the benefit of drug-coated stents to treat this group of patients will probably also rely in the near future on well-conducted registries that are able to record and monitor our daily clinical practice.

Conclusions

The use of DES as a default strategy to treat LM disease was associated with a significant reduction in adverse events. The effectiveness of DES persisted even after adjustment for clinical and procedural variables, including the Parsonnet

surgical risk score. Our findings apply to a selected group of patients referred for percutaneous LM treatment and suggest that in this setting routine DES implantation, by reducing the cumulative incidence of major adverse cardiovascular events, should be currently regarded as the strategy of choice. Until new evidence is provided by randomized clinical trials directly comparing the surgical and percutaneous approaches, CABG should remain the preferred revascularization treatment in good surgical candidates presenting with LM coronary artery disease.

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Chapter 3 Sirolimus- versus Paclitaxel-Eluting Stent Implantation for the Percutaneous Treatment of Left Main Coronary Artery Disease. A Combined RESEARCH and T-SEARCH Long-term Analysis

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Sirolimus-Eluting Versus Paclitaxel-Eluting Stent Implantation for the Percutaneous Treatment of Left Main Coronary Artery Disease

A Combined RESEARCH and T-SEARCH Long-Term Analysis

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OBJECTIVES The purpose of this study was to investigate the long-term clinical and angiographic profile of sirolimus-eluting stent (SES) versus paclitaxel-eluting stent (PES) in patients undergoing percutaneous intervention for left main (LM) coronary disease.

BACKGROUND The long-term clinical and angiographic impact of SES as opposed to PES implantation in this subset of patients is unknown.

METHODS From April 2002 to March 2004, 110 patients underwent percutaneous intervention for LM stenosis at our institution; 55 patients were treated with SES and 55 with PES. The two groups were well balanced for all baseline characteristics.

RESULTS At a median follow-up of 660 days (range 428 to 885), the cumulative incidence of major adverse cardiovascular events was similar (25% in the SES group vs. 29%, in the PES group; hazard ratio 0.88 [95% confidence interval 0.43 to 1.82]; $p = 0.74$), reflecting similarities in both the composite death/myocardial infarction (16% in the SES group and 18% in the PES group) and target vessel revascularization (9% in the SES group and 11% in the PES group). Angiographic in-stent late loss (mm), evaluated in 73% of the SES group and in 77% of the PES group, was 0.32 ± 74 in the main and 0.36 ± 0.59 in the side branch in the SES group vs. 0.46 ± 0.57 ($p = 0.36$) and 0.52 ± 0.42 ($p = 0.41$) in the PES group, respectively.

CONCLUSIONS In consecutive patients undergoing percutaneous LM intervention, PES may perform closely to SES both in terms of angiographic and long-term clinical outcome. (J Am Coll Cardiol 2006;47:507–14) © 2006 by the American College of Cardiology Foundation

Routine drug-eluting stent (DES) implantation, by reducing the need for target vessel revascularization (TVR) and angiographic restenosis, has been recently proposed as the preferred strategy in poor surgical candidates undergoing percutaneous left main coronary artery (LM) intervention (1–3).

The longest average follow-up available for this treatment is currently one year, and whether sirolimus-eluting stent (SES) or paclitaxel-eluting stent (PES) is performing better in these patients is unknown (1–3).

Similarly, even for more conventional lesions, the differential safety and efficacy profile of these two DES options is largely debated (4–8). When taken together, current evidence possibly suggests that in more complex lesion/patient subsets, SES performs better and more safely than PES (4–7,9).

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The percutaneous management of LM lesions is a challenging intervention, where bifurcated vessels, extensive wall calcification, and poor hemodynamic tolerance often coexist during treatment.

The purpose of the present study was to investigate, in a high-risk subset of patients undergoing revascularization in a tertiary referral center, the differential long-term impact of SES compared with PES in terms of clinical and angiographic outcome. Intravascular ultrasound analysis has also been carried out at follow-up to quantity neointimal hyperplasia volume.

METHODS

Study design and patient population. Since April 16, 2002, SES (Cypher; Johnson & Johnson-Cordis, Warren, New Jersey) has been used as a default strategy for every PCI at our institution as part of the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. From the first quarter of 2003, PES (Taxus; Boston Scientific Corp., Natick, Massachusetts) became commercially available, replacing SES as the strategy of choice in every PCI,

Abbreviations and Acronyms

BMS = bare-metal stent
BR = binary restenosis
CX = left circumflex coronary artery
DES = drug-eluting stent
IVUS = intravascular ultrasound
LAD = left anterior descending coronary artery
LL = late loss
LM = left main coronary artery
MACE = major adverse cardiac events
MI = myocardial infarction
MLD = minimal luminal diameter
PES = paclitaxel-eluting stent
RCA = right coronary artery
SES = sirolimus-eluting stent
TVR = target vessel revascularization

as part of the Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry. As a policy, all elective patients presenting with significant (>50% by visual estimation) LM disease, referred to our institution for coronary revascularization, are evaluated both by interventional cardiologists and by cardiac surgeons, and the decision to opt for PCI or surgery is reached by consensus as previously described (1).

From April 16, 2002, to March 6, 2004, a total of 110 consecutive patients were treated exclusively with one or more DES in the LM as part of an elective or nonelective revascularization procedure and constitute the patient population of the present report. Fifty-five patients first received exclusively SES, available at that time in diameters from 2.25 to 3.00 mm, and then 55 patients received PES, available in diameters from 2.25 to 3.5 mm. To ensure comparability between the two study groups, the Parsonnet surgical risk score, based on both clinical presentation profile and comorbidities, and the William Beaumont Hospital simplified scoring system were calculated for each patient (10,11). Nonelective treatment was defined as a procedure carried out on referral before the beginning of the next working day (12).

The protocol was approved by the hospital ethics committee and is in accordance with the Declaration of Helsinki. Written informed consent was obtained from every patient.

Procedures and postintervention medications. All interventions were performed according to current standard guidelines, and, except for the stent utilization, the final interventional strategy was left entirely to the discretion of the operator. Angiographic success was defined as residual stenosis <30% by visual analysis in the presence of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3. All patients were advised to maintain aspirin lifelong, and clopidogrel was prescribed for 6 months in both groups.

End point definitions and clinical follow-up. The occurrence of major adverse cardiac events, defined as death, nonfatal myocardial infarction, or target vessel revascularization, was recorded. Patients with more than one event were assigned the highest ranked event, according to the previous list. End point definitions were previously reported (1). In order to make the clinical follow-up of the two sequential cohorts of patients comparable, clinical outcome of the SES cohort was censored at two years.

Quantitative angiographic and intravenous ultrasound analysis. Quantitative analyses of all angiographic data were performed with the use of edge-detection techniques (CAAS II; Pie Medical, Maastricht, the Netherlands). A value of 0 mm was assigned for the minimal luminal diameter (MLD) in cases of total occlusion at baseline or follow-up. Binary restenosis (BR) was defined as stenosis of >50% of the luminal diameter in the target lesion. Acute gain was defined as the MLD after the index procedure minus the MLD at baseline angiography. Late loss (LL) was defined as the MLD immediately after the index procedure minus the MLD at angiographic follow-up. Quantitative angiographic measurements of the target lesion were obtained in the in-lesion zone (including the stented segment as well as the margins 5 mm proximal and distal to the stent). Intravascular ultrasound (IVUS) analysis was performed after administration of 200 μg of intracoronary nitroglycerin, with an automated pullback at 0.5 mm/s. All IVUS procedures were recorded on VHS videotape, and

Table 1. Baseline Characteristics of the Study Population

Variables	SES Group (n = 55)	PES Group (n = 55)	p Value
Age (yrs)*	64 ± 12	63 ± 12	0.54
Males (%)*	64	58	0.84
Body mass index (kg/m^2)*	23 ± 4	25 ± 5	0.31
Diabetes (%)*	34	24	0.29
Hypertension (%)*	54	53	>0.99
Hypercholesterolemia (%)	58	56	>0.99
Current smokers (%)	16	20	0.8
Creatinine (μmol/l)*	96 ± 32	100 ± 80	0.68
LV ejection fraction (%)*	44 ± 16	44 ± 12	0.95
Medical history (%)			
Protected left main	18	15	0.80
PCI	31	33	>0.99
Myocardial infarction	38	47	0.44
TIA/stroke	9	11	0.74
Heart failure*	16	16	>0.99
COPD severe*†	4	5	>0.99
Peripheral arterial disease*	22	16	0.63
Carotid artery disease*	9	5	0.71
Clinical presentation (%)			
Stable angina	49	45	0.86
Silent ischemia	0	4	0.12
Unstable angina	33	33	>0.99
Acute myocardial infarction*	15	18	0.72
Cardiogenic shock at entry*	9	9	>0.99
Parsonnet score	20 ± 13	17 ± 11	0.27
William Beaumont Hospital score‡	7.7 ± 4.28	7.36 ± 4.7	0.73

*Parameter included in the Parsonnet classification. †Resulting in functional disability, hospitalization, requiring chronic bronchodilatator therapy, or FEV1 <75% of predicted. ‡Based on age >65 years, creatinine elevation, multivessel disease, and occurrence of myocardial infarction within the previous 14 days.

COPD = chronic obstructive pulmonary disease; LV = left ventricular; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent; TIA = transient ischemic attack.

images were digitized for analysis. A computer-based contour detection was performed with Qurad QCU analysis software (Curad, Wijk Bij Duurstede, the Netherlands) as previously described (13). Intimal hyperplasia volume was calculated as stent volume minus luminal volume. Percentage intimal hyperplasia was defined as intimal hyperplasia volume divided by stent volume.

Statistical analysis. The sample size was calculated on the assumption that average late loss in the SES and PES group would be around 0.15 mm and 0.35 mm, respectively, based on previous findings. To detect this effect size with a sigma value of 0.3, 85% power, and a type I error (alpha) of 0.05, 32 patients per group were required. Continuous variables are shown as mean ± standard deviation (SD) and were compared using Student unpaired *t* test. Categorical variables are presented as counts and percentages and compared with the Fisher exact test. Survival curves were generated by the Kaplan-Meier method, and survival among groups was compared using the log rank test. Cox proportional hazards models were used to assess risk reduction of adverse events. Multivariable analysis, considering all variables reported in Tables 1 and 2 with a p value of less than 0.10, was performed to adjust for possible confounders and identify whether the stent received was an independent predictor of adverse events. Probability was significant at a level of <0.05. All statistical tests were two-tailed. Statistical analysis was performed with Statistica 6.1 software (Statsoft, Tulsa, Oklahoma).

RESULTS

Baseline and procedural characteristics. Baseline and procedural characteristics are shown in Tables 1 and 2. The two groups were well matched for all baseline characteristics. In both cohorts, half of the patients presented with a left ventricular ejection fraction of 45% or less or with acute coronary syndrome as indication to treatment, and 9% of the patients presented with severe hemodynamic compromise at entry. The distal LM was overall involved in two-thirds of cases. In the SES group, nominal stent diameter was smaller—reflecting the unavailability of stent bigger than 3.0 mm during the study period—and cumulative stent length tended to be shorter than in the PES group. Bifurcation stenting was equally employed in both groups with a clear preference for T-stenting and for culotte technique in the SES and PES groups, respectively.

Thirty-one patients (56%) in the SES and 25 (45%) in the PES group received intervention in one or more non-LM lesion(s) during index procedure (p = 0.18). Complete

Table 2. Angiographic and Procedural Characteristics of the Study Population

Variables	SES Group (n = 55)	PES Group (n = 55)	p Value
Lesion location (%)*			
Ostium	27	22	0.51
Body	29	24	0.54
Distal	64	76	0.28
Pure left main disease (%)	5	5	>0.99
LM plus 1-vessel disease (%)	18	18	>0.99
LM plus 2-vessel disease (%)	20	24	0.82
LM plus 3-vessel disease (%)	57	53	0.87
Right coronary artery >70% stenosis (%)	69	64	0.88
Right coronary artery occlusion (%)	24	20	0.82
Number of implanted stents	1.43 ± 0.53	1.50 ± 0.6	0.49
Nominal stent diameter (mm)	3.00 ± 0.25	3.29 ± 0.28	<0.001
Total stent length per patient (mm)	23 ± 11	27 ± 13	0.07
Predilation (%)	71	60	0.15
Cutting balloon (%)	7	7	>0.99
Rotational atherectomy (%)	2	4	>0.99
Directional atherectomy (%)	0	0	>0.99
Postdilatation (%)	82	72	0.15
Bigger balloon inflated (mm)	3.75 ± 0.48	3.70 ± 0.5	0.48
Maximal pressure (atm)	18 ± 5	19 ± 3	0.55
Bifurcation stenting (%)	29	33	0.84
Culotte	0	20	0.009
T-technique	20	5	0.05
Crush	7	4	0.67
Kissing technique	2	4	>0.99
Intravascular ultrasonography (%)	33	27	0.53
IIb/IIIa inhibitors (%)	33	27	0.68
Intra-aortic balloon pump (%)	20	18	>0.99
Left ventricle assist device (%)	5	0	0.24
Temporary pacing during procedure (%)	7	9	>0.99

*Location of disease was not mutually exclusive among LM segments.
LM = left main coronary artery; other abbreviations as in Table 1.

Table 3. 30-Day and Long-Term Outcomes

Variables	SES Group	PES Group	p Value*
30-day outcome			
Whole population	(n = 55)	(n = 55)	
Death, n (%)	7 (13)	3 (5)	0.32
Nonfatal MI, n (%)	2 (4)	2 (4)	>0.99
Death or nonfatal MI, n (%)	9 (16)	5 (9)	0.40
TVR, n (%)	1 (2)	0 (0)	>0.99
Any event, n (%)	10 (18)	5 (9)	0.27
Stent thrombosis, n (%)†	0 (0)	0 (0)	
Elective population	(n = 43)	(n = 43)	
Death, n (%)	2 (5)	0 (0)	0.49
Nonfatal MI, n (%)	2 (5)	2 (5)	>0.99
Death or nonfatal MI, n (%)	4 (9)	2 (5)	0.68
TVR, n (%)	1 (2)	0 (0)	>0.99
Any event, n (%)	5 (12)	2 (5)	0.44
Stent thrombosis, n (%)†	0 (0)	0 (0)	>0.99
Long-term outcome			
Whole population	(n = 55)	(n = 55)	
Death, n (%)	6 (11)	7 (13)	0.70
Nonfatal MI, n (%)	2 (4)	4 (7)	0.25
Death or nonfatal MI, n (%)	9 (16)	10 (18)	0.90
TVR, n (%)	5 (9)	6 (11)	0.67
Any event, n (%)	14 (25)	16 (29)	0.74
Stent thrombosis, n (%)†	0 (0)	0 (0)	>0.99
Elective population	(n = 43)	(n = 43)	
Death, n (%)	2 (5)	2 (5)	0.98
Nonfatal MI, n (%)	2 (5)	4 (9)	0.22
Death or nonfatal MI, n (%)	4 (9)	6 (14)	0.51
TVR, n (%)	5 (12)	5 (12)	0.82
Any event, n (%)	9 (21)	11 (25)	0.55
Stent thrombosis, n (%)†	0 (0)	0 (0)	>0.99

*By Fischer exact test for 30-day outcome and by log rank test for long-term outcome.
†Angiographically documented.
MI = myocardial infarction; TVR = target vessel revascularization; other abbreviations as in Table 1.

revascularization was achieved in 27 (49%) patients in the SES and 36 (65%) in the PES group (p = 0.17).

Overall procedural success was 98%. In one patient receiving SES, presenting with acute MI and shock, a final TIMI flow grade 1 was obtained. An abrupt irreversible occlusion of the circumflex occurred in one PES patient after deployment of a stent in the left main and proximal left anterior descending coronary artery (LAD).

Thirty-day outcomes. There were no significant differences between the SES and PES groups in the incidence of major adverse cardiac events (MACE) (death, target vessel revascularization, or myocardial infarction [MI]) during the first 30 days (Table 3). Eight deaths occurred in 10 patients presenting with ST-segment elevation acute myocardial infarction and cardiogenic shock at entry. One elective patient, undergoing LM treatment under left ventricular assist device due to end-stage heart disease, died 2 days after for cardiogenic shock, while the second elective patients died for non-cardiovascular reasons after 19 days. No documented thrombotic stent occlusion occurred in the first 30 days or thereafter.

Long-term clinical outcome. After a median follow-up of 660 days (range 428 to 885 days), the cumulative incidence

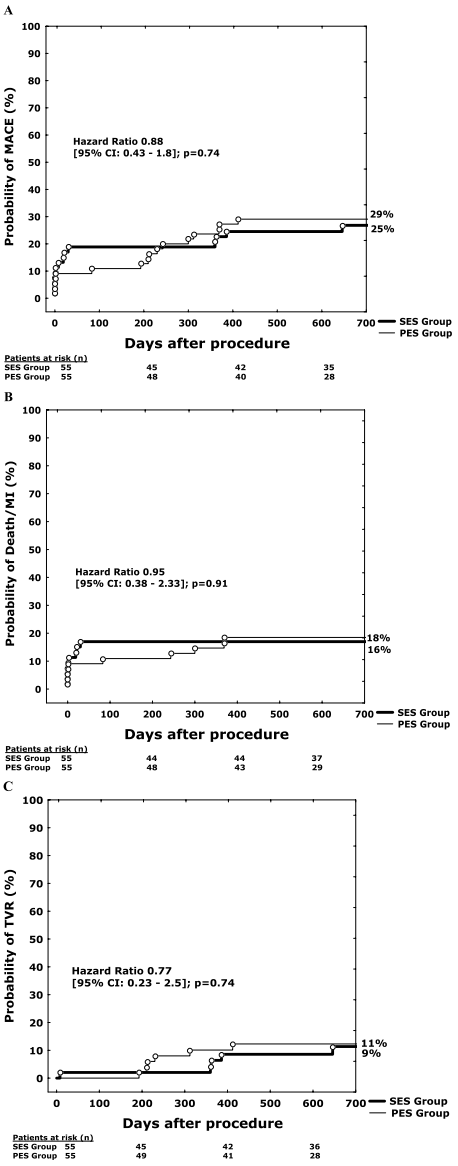

Figure 1. Adverse events in patients treated with sirolimus-eluting stent (SES group) and in patients treated exclusively with paclitaxel-eluting stent implantation (PES group). **(A)** Cumulative risk of major adverse events (MACE); **(B)** death or myocardial infarction (MI); and **(C)** target vessel revascularization (TVR). CI = confidence interval.

of MACE did not significantly differ in the SES compared to the PES patients (25% vs. 29%, respectively; hazard ratio [HR] 0.88 [95% confidence interval (CI): 0.43 to 1.82]; p = 0.74) (Fig. 1A). The composite death/MI was 16% in the SES and 18% in the PES group (HR 0.95 [95% CI: 0.38 to 2.33]; p = 0.90) (Fig. 1B), and cumulative incidence of TVR was 9% in the SES and 11% in the PES group (HR 0.77 [95% CI: 0.23 to 2.56]; p = 0.66) (Fig. 1C).

In the elective patient population (43 patients in each group), the cumulative incidence of MACE was similar in the SES (21%) and PES groups (25%; HR 0.77 [95% CI 0.32 to 1.8]; p = 0.55). The composite of death/MI was 9% in the SES and 14% in the PES group (HR 0.66 [95% CI 0.19 to 2.3]; p = 0.52), and the need for TVR was 12% in both groups (HR 0.87 [95% CI 0.24 to 3]; p = 0.8).

The cumulative incidence of MACE was similar in patients receiving single-vessel stenting (24% in the SES and 27% in the PES group) and those treated with bifurcation stenting (31%, HR 1.38 [95% CI 0.47 to 4]; p = 0.55; and 33%, HR 1.22 [95% CI 0.45 to 3.3]; p = 0.69; respectively.

After adjustment for nominal stent diameter and total stent length at multivariable Cox regression analysis, SES implantation as opposed to PES failed to emerge as an independent predictor of MACE (HR 0.79 [95% CI 0.5 to 1.5]; p = 0.66). The same remained true after forcing the Parsonnet score into the model.

Angiographic outcome. Thirty-five patients in the SES (73% of eligible patients) and 38 patients in the PES group (77% of those eligible) underwent angiographic follow-up. Data regarding the quantitative coronary angiography for main and side branches are presented in Tables 4 and 5, respectively.

MAIN BRANCH. In the SES and PES groups, the main treated branch circumflex was LM-LAD in 22 (63%) and 21 (55%) patients, respectively followed by LM-circumflex in 6 (17%) and 8 (21%), LM alone in 5 (14%) and 6 (16%), and LM-intermediate branch in 2 (6%) and 3 (8%), respectively. In unprotected patients in the SES and PES groups, LM-LAD was the main treated branch in 77% and in 63%, respectively, followed by LM alone in 15% and 17%, LM-circumflex in 8% and 14%, and LM-intermediate branch in 0% and 6%, respectively.

Baseline and follow-up angiographic variables did not differ in the two study groups. No difference was noted in terms of BR in the two groups as the result of a similar in-stent and in-lesion LL (Table 4).

SIDE BRANCH. All baseline angiographic variables were well matched between SES and PES groups in the side branches receiving stent. At follow-up, both LL and BR were similar in the two study groups. For those side branches that did not undergo stenting as part of LM treatment, despite a bigger reference vessel diameter in the SES than in the PES group, the pattern of LL was around zero in both groups (Table 5).

Table 4. Quantitative Coronary Angiography Analysis of the Main Branch

Variables	SES Group (n = 35)	PES Group (n = 38)	p Value
Before procedure			
RVD (mm)	3.20 ± 0.57	3.2 ± 0.73	0.82
MLD (mm)	1.26 ± 0.74	1.38 ± 0.49	0.62
Diameter stenosis (%)	60 ± 24	59 ± 16	0.85
Lesion length (mm)	9.5 ± 3.34	10 ± 4.44	0.56
After procedure			
In-stent			
RVD (mm)	3.10 ± 0.5	3.2 ± 0.6	0.43
MLD (mm)	2.76 ± 0.5	2.81 ± 0.5	0.32
Acute luminal gain (mm)*	1.50 ± 0.78	1.43 ± 0.75	0.66
Diameter stenosis (%)	10.7 ± 10	10.8 ± 9	0.97
In-lesion			
RVD (mm)	2.86 ± 0.6	2.77 ± 0.66	0.54
MLD (mm)	2.47 ± 0.54	2.46 ± 0.58	0.61
Acute luminal gain (mm)*	1.21 ± 0.84	1.10 ± 0.83	0.54
Diameter stenosis (%)	13 ± 10	11 ± 9	0.45
Follow-up			
In-stent			
RVD (mm)	3.19 ± 0.6	3.01 ± 0.6	0.31
MLD (mm)	2.44 ± 0.85	2.35 ± 0.6	0.60
Diameter stenosis (%)	21.3 ± 25	22.8 ± 19	0.76
Late loss (mm)†	0.32 ± 74	0.46 ± 0.57	0.36
Binary restenosis, n (%)‡	3 (9)	5 (13)	0.71
Reocclusion, n (%)§	2 (6)	0 (0)	0.24
In-lesion			
RVD (mm)	3.00 ± 0.66	2.89 ± 0.66	0.41
MLD (mm)	2.24 ± 0.83	2.2 ± 0.63	0.77
Diameter stenosis (%)	22 ± 24	22 ± 19	0.97
Late loss (mm)†	0.22 ± 0.73	0.25 ± 0.46	0.86
Binary restenosis, n (%)‡	3 (9)	4 (11)	>0.99
Reocclusion, n (%)	2 (6)	0 (0)	1

*Difference between MLD after procedure and MLD before procedure. †Difference between MLD at follow-up and MLD after procedure. ‡All non-occlusive restenosis were focal (length <10mm). §All two restenotic reocclusions occurred in protected LM lesions.

MLD = minimal lumen diameter; PES = paclitaxel-eluting stent; RVD = reference vessel diameter; SES = sirolimus-eluting stent.

COMBINED ANALYSIS. When both main and side branches were evaluated on a patient basis, in-lesion BR occurred in 7 (20%) and 12 (32%) patients in the SES and PES groups, respectively (p = 0.44). All cases of nonocclusive restenosis were focal (length <10 mm).

IVUS analysis. Overall, 46 patients (18 in the SES and 28 in the PES group) underwent IVUS investigation at follow-up. Their baseline and procedural characteristics did not differ from those receiving angiographic examination without IVUS (data not shown). In 11 patients in the SES and 16 in the PES group, LM-LAD was evaluated; the study vessel was LM-CX in 4 SES and 7 PES and LM alone in 3 SES and 5 PES patients. In two patients per group, stent malapposition was noted. As shown in Table 6 the degree of neointimal hyperplasia did not differ between the two study groups.

DISCUSSION

Since their introduction to the market, DES use has steadily increased. Depending on the health care system, they are

Table 5. Quantitative Coronary Angiography Analysis in the Side Branches

Variables	Stented Branches			Nonstented Branches		
	SES Group	PES Group	p Value	SES Group	PES Group	p Value
Before procedure	n = 12	n = 15		n = 21	n = 23	
RVD (mm)	2.63 ± 0.67	2.70 ± 0.61	0.69	2.44 ± 0.72	2.00 ± 0.55	0.02
MLD (mm)	1.16 ± 0.52	1.27 ± 0.77	0.69	1.68 ± 72	1.47 ± 0.67	0.31
Diameter stenosis (%)	56 ± 21	54 ± 24	0.61	27 ± 28	26 ± 25	0.96
Lesion length (mm)	10 ± 4	11 ± 8	0.76	5.7 ± 3	4.9 ± 2.1	0.30
After procedure						
RVD (mm)	2.73 ± 0.79	2.85.0 ± 0.57	0.65	2.26 ± 0.7	2.00 ± 0.6	0.12
MLD in-stent (mm)	1.95 ± 0.43	2.32 ± 0.45	0.041	—	—	
MLD in-lesion (mm)	1.9 ± 0.38	2 ± 0.55	0.46	1.7 ± 0.58	1.48 ± 0.69	0.27
ALG in-stent (mm)	0.79 ± 0.57	1 ± 0.6	0.62	—	—	
ALG in-lesion (mm)	0.72 ± 0.55	0.75 ± 0.76	0.89	0.01 ± 0.66	0.009 ± 0.5	0.97
Diameter stenosis (%)	25 ± 18	18 ± 11	0.17	23 ± 25	20 ± 23	0.66
Follow-up						
RVD (mm)	2.70 ± 0.54	2.56 ± 0.60	0.40	2.30 ± 0.69	2.00 ± 0.55	0.20
MLD in-stent (mm)	1.6 ± 0.45	1.8 ± 0.49	0.35	—	—	
MLD in-lesion (mm)	1.54 ± 0.58	1.62 ± 0.65	0.73	1.83 ± 0.63	1.40 ± 0.77	0.059
Diameter stenosis (%)	39 ± 23	29 ± 25	0.24	21 ± 14	33 ± 32	0.13
LL in-stent (mm)	0.36 ± 0.59	0.52 ± 0.42	0.41	—	—	
LL in-lesion (mm)	0.33 ± 0.42	0.39 ± 0.62	0.78	0.13 ± 0.44	0.07 ± 0.62	0.23
BR in-stent, n (%)*	3 (25)	3 (20)	>0.99	—	—	
BR in-lesion, n (%)*	3 (25)	2 (13)	0.63	1 (5)	6 (26)	0.10
Reocclusion, n (%)	2 (6)	0 (0)	0.24	0 (0)	2 (9)	0.49

*All non-occlusive restenosis were focal (length <10 mm).
ALG = acute luminal gain; BR = binary restenosis; LL = late loss; other abbreviations as in Table 4.

now partially or almost completely replacing bare-metal stents (BMS) during coronary intervention.

Recently, some concerns for the consequences of using these devices liberally have been raised, which emphasizes the need to scrutinize those patient/lesion subsets that were excluded from landmark randomized trials, particularly beyond conventional eight to nine months' follow-up (14–17). Yet in both controlled and observational studies, a potential differential efficacy and safety profile between SES and PES has been observed, especially in patient populations considered to be at higher risk for adverse events. Thus, current available evidence reinforces the idea that it would be improper to attribute a class effect to DES and that a high-risk patient population should be better evaluated to further compare the safety/efficacy profile of these two stents.

The percutaneous management of LM lesions is a challenging intervention, where bifurcated vessels, extensive wall calcification, and poor hemodynamic tolerance often coexist during treatment as natural extensions of the anatomic characteristics of the lesions (18,19). Moreover, percutaneous LM intervention, being usually reserved to poor surgical candidates, is often undertaken in patients with low ejection fraction or renal dysfunction, which are known predictors of adverse events even in patients receiving DES (16).

Table 6. Quantitative Intravascular Ultrasound (IVUS) Results

IVUS Variables	SES Group n = 18	PES Group n = 28	p Value
IVUS volumes (mm^3)			
Luminal	237 ± 183	250 ± 167	0.80
Vessel	473 ± 371	528 ± 351	0.63
Stent	256 ± 194	267 ± 174	0.81
Intimal hyperplasia	19.3 ± 26	28 ± 60	0.44
Intimal hyperplasia/10 mm*	6.3 ± 9	9.6 ± 13	0.74
Percentage intimal hyperplasia (%)	7.5 ± 8	10 ± 14	0.68

*Calculated as intimal hyperplasia volume divided by the length of the region of interest expressed in mm (24 ± 19 in the SES and 29 ± 19 in the PES group; p = 0.49), multiplied by 10.
PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent.

The main results of our analysis show that, as predicted by the risk status of the patients, the overall event rate was higher than that previously reported for non-LM lesions. However, the safety/efficacy profile of the two DES evaluated was apparently maintained at long-term follow-up, with PES performing closely to SES in terms of both clinical and angiographic outcome.

This statement is based on the following findings:

1. The great majority of events occurred in both groups within one year, considering either the whole (86% in the SES and 81% in the PES) or the elective population (78% in the SES and 73% in the PES group). No early or late angiographically confirmed stent thrombosis has been observed, with only one sudden death occurring in an 86-year-old woman affected by a hematological malignancy seven months after the index procedure.
2. The short- and long-term clinical event rate in the two study groups was not different, and at multivariable analysis the stent implanted failed to emerge as an independent predictor of adverse events.
3. Angiographic and IVUS investigation demonstrated that late loss and neointimal hyperplasia volume were similar in the two groups of patients. The angiographic

outcome of the nonstented side branches was also remarkably similar between the two groups.

Among these observations, the last one was unexpected and deserves special attention.

In all major randomized controlled trials evaluating the benefit of SES versus BMS, the average in-stent LL for SES was reported to be constantly equal to or below 0.20, whereas the same figure for PES, based on PES versus BMS studies, was around two times higher. The Prospective, Randomized, Multi-Center, Comparison of the Cypher Sirolimus-Eluting and the Taxus Paclitaxel-Eluting Stent Systems (REALITY) study showed a difference between these two DES in terms of angiographic end points that was even bigger, with a mean in-stent LL of 0.9 in SES and 0.31 in the PES group (5). Conversely, in the current investigation we failed to show any difference between the two stents in terms of in-stent or in-segment LL or BR, either in the main branch or in the stented side branches. Interestingly, this was confirmed by the IVUS analysis. Although the difference was more striking for SES, the LL in both groups were actually much higher than the figures expected. The explanation for this discrepancy can only be speculative for the moment and it may suggest that angiographic response to DES is lesion/patient-specific. Data so far available in the literature are inconclusive in this regard. Park et al. (2) recently reported an average late loss of 0.05 mm in 102 patients receiving SES for the treatment of unprotected left main disease, whereas the same figure in 85 LM patients at higher risk status, treated with either PES or SES, was cumulatively reported to be 0.58 mm (3). Unfortunately, in that study no distinction between SES and PES was made (3).

The lack of availability of SES sizes bigger than 3.0 mm during the study period, which imposed an aggressive overdilation strategy to match LM reference diameter, might have theoretically played a role. However, this technical issue was at least partially encountered in the series reported by Park et al. (2) as well.

Alternatively, this difference between studies could possibly reflect a selection bias, with patients at higher clinical risk based on previous cardiovascular history and comorbidities being more prone to develop a more aggressive intimal proliferation after DES. To investigate this possibility in an exploratory fashion (this analysis was not prespecified for the current study), we pooled the LL for both main branch and all stented side branches as the outcome variable in a linear regression model. At univariate analysis including all variables reported in Tables 1 and 2 we found protected status to be the strongest predictor for high LL ($\beta = 0.47$ [95% CI 0.24 to 0.7]; $p = 0.001$; adjusted $R^2 = 0.39$). Accordingly, we observed that in patients receiving unprotected LM intervention (n = 59) LL was cumulatively lower (0.31 ± 0.41 vs. 0.63 ± 72; $p = 0.037$) than in patients receiving protected treatment (n = 14), and, of note, all occlusive binary restenosis occurred in the protected group of patients.

Interestingly, none of the variables reported in Tables 1 and 2 differed significantly between patients receiving protected versus unprotected LM intervention, with the overall Parsonnet score being 16 ± 7.5 in protected versus 18 ± 10 in unprotected patients ($p = 0.4$).

The observed difference in LL between protected versus unprotected LM intervention might possibly outline a role for shear stress as potential modulator of vessel response to DES, as recently suggested by our group (20). This analysis was exploratory in nature and clearly beyond the scope of the current investigation. However, it underscores the need to consider DES performance in the context of the patient population in which the device was actually tested.

Taken together, our observations suggest that DES may perform more effectively in good than in poor surgical candidates, which reinforces the interest in assessing the value of this treatment as compared with conventional surgical approach in a properly designed randomized trial.

Study limitations. The present study is a single-center experience from a tertiary referral center and lacks the clear advantages of a multicenter randomized study. In particular, despite the fact that the study was conducted over a relatively short period, we cannot exclude the possibility that improvements in technique or differences in drug prescription could have partially confounded our main results.

Accordingly, the results of our study are encouraging, but they cannot be conclusive. Studies with bigger sample sizes and more prolonged clinical follow-ups are clearly required to rule out the occurrence of less common device-related side effects.

Clinical implications of the combined RESEARCH and T-SEARCH analysis. In the overall results of the unselected RESEARCH versus T-SEARCH comparison, a shift toward more complex lesions has been noted from SES to PES cohort (8). This difference was not confirmed in our current analysis, which focused on LM lesions cumulatively treated over a longer period of time: more patients in the SES group received concomitant intervention in non-LM lesions and fewer reached complete revascularization than in the PES cohort. However, the stent length was greater in the PES group. When this finding is combined with the observed shift from T-stenting in the SES period to culotte in the PES period as bifurcation technique, it may suggest that operators have become progressively more familiar with DES over time and that full lesion coverage with DES had been more frequently performed in the PES than in the SES group. The impact of these confounders on our final result remains incompletely understood.

When taken together, the combined RESEARCH and T-SEARCH analysis may reinforce the concept that in an uncontrolled setting such as our clinical practice, the coronary device in itself should probably be regarded among the principal but clearly not as the only component of the long-term procedural success in the DES era. Rather, the two

drug-eluting stents available on the market should always be put in the context of the characteristics of the treated patients and the operator's experience to better forecast their effect on short- and long-term outcome.

Conclusions. After a median follow-up of two years, no late serious adverse events, possibly suggesting a time-dependent change in the therapeutic profile of the investigated devices, were observed.

In a consecutive group of patients undergoing percutaneous LM intervention, PES may perform closely to SES in terms of both clinical and angiographic outcome.

A multinational multicenter randomized study is currently ongoing to estimate the clinical value of PES-supported LM intervention with respect to conventional surgical treatment.

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Chapter 4 Comparison of Early Outcome of Percutaneous Coronary Intervention for Unprotected Left Main Coronary Artery Disease in the Drug-Eluting Stent Era With versus Without Intravascular Ultrasonic Guidance.

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Comparison of Early Outcome of Percutaneous Coronary Intervention for Unprotected Left Main Coronary Artery Disease in the Drug-Eluting Stent Era With Versus Without Intravascular Ultrasonic Guidance

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The aim of this study was to assess the short- and mid-term clinical impact of intravascular ultrasound guidance in 58 patients referred for elective percutaneous treatment of unprotected left main coronary artery disease with drug-eluting stents. The use of intravascular ultrasound, used in 41% of the procedures, was not associated with additional clinical benefit with respect to angiographic-assisted stent deployment.

(Am J Cardiol 2005;95:644–647)

Intravascular ultrasound (IVUS) guidance is considered mandatory by some groups for percutaneous treatment of left main (LM) coronary artery disease,[1] in particular, when drug-eluting stents (DESs) are used.[2,3] No definitive evidence for such a practice in LM treatment exists. Previous studies, assessing the value of bare metal stenting, failed to show any additional benefit of IVUS guidance in LM percutaneous treatment.[4] We investigated the differential impact of IVUS guidance on the short- and mid-term clinical events in patients referred for LM percutaneous revascularization with DESs.

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In our institution, all elective patients presenting with symptomatic coronary artery disease and significant (>50% by visual estimation) LM disease are routinely treated with coronary artery bypass graft surgery. However, the decision to perform percutaneous coronary intervention (PCI) may be considered based on a comprehensive evaluation of several variables, including contraindications to surgery due to the presence of co-morbidity, patient preference for a percutaneous approach, and LM anatomy suitable for stenting.

For percutaneous procedures, both sirolimus-eluting stents (Cypher, Johnson & Johnson-Cordis unit, Cordis Europa, NV, Roden, The Netherlands) and paclitaxel-eluting stents (Taxus, Boston Scientific Corp., Natick, Massachusetts) have been used as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital and the Taxus-Stent Evaluated At Rotterdam Cardiology Hospital registries, respectively. These protocols were approved by the hospital ethics committee and are in accordance with the Declaration of Helsinki. Written informed consent was obtained from every patient.

Angiographic success was defined as residual stenosis <30% by visual estimate in the presence of Thrombolysis In Myocardial Infarction grade flow 3. All patients were advised to continue aspirin therapy lifelong. Clopidogrel (300 mg loading dose before the procedure and 75 mg/day) was prescribed for 6 months.

Using a validated on-line quantitative coronary angiographic system (CAAS II, Pie Medical, The Netherlands), reference vessel diameter, minimal luminal diameter, and percent diameter stenosis were measured at baseline and after the procedure in single-matched views showing the smallest lumen diameter.

IVUS use was left to the operator's discretion. Images were obtained after intracoronary injection of nitrates using commercially available IVUS (30-MHz Ultracross or 40-MHz Atlantis, both from Boston Scientific Corp., or 20-MHz Eagle Eye from Volcano Inc., Rancho Cordova, California) and motorized pullback (0.5 or 1 mm/s). All analyses were performed on-line by experienced operators. The external elastic membrane area and lumen cross-sectional area were measured using computerized planimetry according to validated protocols.[5] IVUS criteria for stent optimization were complete stent-to-vessel wall apposition, adequate stent expansion (defined as stent cross-sectional area >80% of the average reference cross-sectional area by visual estimation), and full lesion coverage.[5] The number of procedures with IVUS guidance performed by each operator was also evaluated.

The primary outcome was the occurrence of major adverse events, defined as death (either cardiac or

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TABLE 1 Baseline Characteristics of Study Group

Variable	IVUS Imaging: Yes (n = 24)	IVUS Imaging: No (n = 34)	p Value
Age (yrs)	62 ± 12	64 ± 13	0.47
Men	15 (62%)	25 (73%)	0.37
Cardiac risk factors			
Diabetes	9 (37%)	10 (29%)	0.52
Hypertension	14 (58%)	20 (59%)	0.97
Hypercholesterolemia*	15 (62%)	23 (68%)	0.68
Current smoker	4 (17%)	7 (21%)	0.75
Previous PCI	12 (50%)	7 (21%)	0.02
Previous myocardial infarction	9 (37%)	17 (50%)	0.35
Unstable angina pectoris†	8 (33%)	11 (32%)	0.82
Ejection fraction (%)	52 ± 10	44 ± 14	0.02
Serum creatinine (μmol/L)	89 ± 19	90 ± 28	0.85

*Defined as total cholesterol >220 mg/dl or known statin therapy.
†Defined as cardiac chest pain at rest, without an increase in creatine kinase levels or new electrocardiographic Q waves.
Data are presented as mean ± SD or number (percent).

TABLE 2 Angiographic and Procedural Characteristics of Study Group

Variable	IVUS Imaging: Yes (n = 24)	IVUS Imaging: No (n = 34)	p Value
Lesion location			
Ostial	7 (29%)	3 (9%)	0.08
Midshaft	7 (29%)	9 (26%)	0.9
Distal	10 (42%)	22 (65%)	0.08
3-vessel coronary disease	11 (46%)	25 (73%)	0.03
Right coronary occluded	3 (12%)	9 (26%)	–
No. of implanted stents	1.5 ± 0.5	1.4 ± 0.5	0.27
Total stent length (mm)	27 ± 14	23 ± 12	0.23
Nominal stent diameter (mm)	3.2 ± 0.4	3.2 ± 0.3	0.52
Predilatation	12 (50%)	21 (62%)	0.37
Postdilatation	22 (92%)	26 (76%)	0.17
Bigger balloon inflated (mm)	4 ± 0.5	3.7 ± 0.4	0.01
Maximal pressure (atm)	17.8 ± 3.6	17.8 ± 2.1	0.86
Intra-aortic balloon pump or left ventricular assist device	1 (4%)	5 (15%)	0.38
Glycoprotein IIb/IIIa inhibitors	11 (46%)	8 (23%)	0.08
Bifurcation stenting*	7/10 (70%)	11/22 (50%)	0.45
T-technique	3	6	–
Culotte-technique	2	3	–
Crush-technique	2	1	–
V-technique	0	1	–
Final kissing balloon*	4/10 (40%)	10/22 (45%)	1.00
Interventions in other vessels	13 (54%)	20 (59%)	0.72

*Considered only patients with distal LM disease.
Data are presented as mean ± SD or number (percent).

noncardiac), nonfatal myocardial infarction, or target vessel revascularization. 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 with an increased creatine kinase-MB fraction. Target vessel revascularization was defined as a repeat intervention (either surgical or percutaneous) to treat a lesion within the stent or within 5 mm distal or proximal to the stent, including the ostium of the left anterior descending artery or circumflex artery, or both.

Continuous variables are expressed as mean ± SD and were compared using Student's unpaired *t* test. Categorical variables are presented as counts and percentages and compared with the chi-square or Fisher's exact tests. Survival curves were generated by the Kaplan-Meier method and survival between groups was compared using the log-rank test. Cox proportional- hazards models were used to assess risk reduction of adverse events. Univariate and stepwise multivariate analysis (considering variables with a p value <0.1 at univariate analysis) were performed with the variables reported in Tables 1 and 2, and the quantitative angiographic and IVUS results in Table 3 to identify independent predictors of adverse events. A p value <0.05 was considered statistically significant. All statistical tests were 2-tailed.

From April 16, 2002, to December 31, 2003, a total of 95 patients were treated with ≥1 DES for LM disease. We excluded 21 patients with acute myocardial infarction or cardiogenic shock undergoing emergency PCI (performed on referral before the beginning of the next working day[6]) and 16 patients with protected LM (with ≥1 patent bypass graft on the left coronary artery). Thus, our group consisted of 58 patients electively treated for unprotected LM disease. IVUS was performed in 24 patients (41%). In particular, it was performed before and after the procedure in 14 cases, only before the procedure in 4, and only after the procedure in 6. Clinical and procedural characteristics are listed in Tables 1 and 2, whereas quantitative coronary angiographic results and IVUS analysis are presented in Table 3. IVUS guidance permitted optimization of stent deployment in 29% of cases. In particular, 4 cases (17%) of incomplete stent apposition and 1 case (4%) of stent underexpansion on IVUS prompted additional postdilatation, and in 2 cases (8%), incomplete lesion coverage required a second stent deployment. Six operators performed all the procedures (range of procedures per operator 5 to 13) and 3 performed IVUS extensively (67% to 80%), whereas the other operators performed IVUS in 11% to 27% of cases (p for trend <0.01). Procedural success was achieved in all procedures.

The overall rate of major events was 15% at a median follow-up of 433 days (range 178 to 780). At 30 days, the rates of mortality and major adverse events were 3% and 7%, respectively. There were 2 periprocedural non–Q-wave myocardial infarctions, with a creatine kinase-MB peak of 61 and 69 U/L, respectively; both patients underwent multivessel coronary stenting. One death occurred the day after the

TABLE 3 Quantitative Coronary Angiography and Quantitative Coronary Ultrasound Results of Study Group

Variable	IVUS Imaging: Yes (n = 24)	IVUS Imaging: No (n = 34)	p Value
Quantitative coronary angiography			
Reference vessel diameter (mm)	3.37 ± 0.40	3.21 ± 0.56	0.24
Lesion length (mm)	7.47 ± 3.05	7.33 ± 3.11	0.89
Before intervention			
Minimal luminal diameter (mm)	1.19 ± 0.40	1.13 ± 0.39	0.53
Diameter stenosis (%)	62.0 ± 11.3	62.4 ± 13.8	0.91
After intervention			
Minimal luminal diameter (mm)	2.93 ± 0.45	2.83 ± 0.50	0.45
Diameter stenosis (%)	14.5 ± 10.1	12.1 ± 11.1	0.24
Quantitative coronary ultrasound before intervention			
Lumen cross-sectional area (mm^2)	4.4 ± 0.77	–	–
External elastic membrane area (mm^2)*	20.2 ± 2.56	–	–
Minimal luminal diameter (mm)	2.03 ± 0.20	–	–
After intervention			
Lumen cross-sectional area (mm^2)	12.0 ± 1.86	–	–
Minimal luminal diameter (mm)	3.68 ± 0.28	–	–

*External elastic membrane area could not be analyzed in 3 patients (12% of patients in the IVUS group) because of extensive calcification.
Data are presented as mean ± SD.

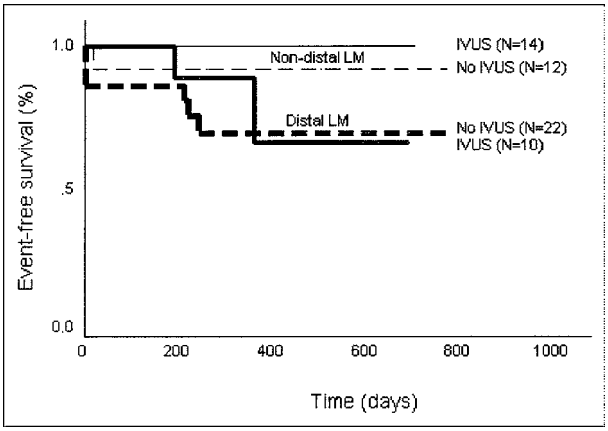

FIGURE 1. Kaplan-Meier major adverse events: free survival curves of IVUS versus non–IVUS-guided procedures, stratified according to the anatomic location of atherosclerotic disease in the LM artery.

procedure in a patient with severe left ventricular dysfunction due to a previous myocardial infarction and diffuse 3-vessel disease who developed cardiogenic shock during the intervention; the patient's condition initially stabilized with a left ventricular assist device, but the patient finally succumbed. Another death occurred 19 days after the procedure in an elderly patient with a low ejection fraction and diabetic chronic renal insufficiency. The cause of death was severe sepsis due to a pulmonary infection. A third death occurred 9 months after the index procedure due to a low-cardiac output syndrome after coronary artery bypass surgery performed because of progression of atherosclerotic disease in other vessels. Finally, there were 4 target vessel revascularizations: 2 patients underwent repeat PCI, whereas the others underwent surgical revascularization. Overall, the mortality rate was 5%, the myocardial infarction rate was 3%, and the target vessel revascularization rate was 7%.

The incidence of major adverse events was 2 of 24 (8%) in the IVUS group and 7 of 34 (20%) in the non-IVUS group ($p = 0.18$). At univariate analysis, the only significant predictors of events were distal LM involvement and reference vessel diameter. At multivariate analysis, distal LM disease remained a significant predictor of adverse events, with a hazard ratio of 7.7 (95% confidence interval 1 to 62.6, $p = 0.05$). To test the effect of IVUS guidance in different anatomic LM subsets, we stratified patients into 2 groups: nondistal versus distal LM involvement. In the former, IVUS was performed in 14 of 26 patients (54%) and the rate of events was low: only 1 noncardiac death (4%) occurred after a non–IVUS-guided procedure. In the latter, IVUS was performed less often ($p = 0.08$) (i.e., in 10 of 32 patients [31%]), but the rate of events was not significantly different between IVUS and non-IVUS procedures ($p = 0.69$), with 2 events in 10 patients (20%) versus 6 in 22 patients (27%), respectively (Figure 1).

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Although IVUS guidance has been strongly recommended in percutaneous LM treatment, our results do not support the hypothesis that routine use of IVUS is mandatory to optimize clinical outcome. The rate of events did not differ significantly between IVUS and angiographic-guided procedures, where the use of IVUS was left to the discretion of the operator. Furthermore, the anatomic location of the atherosclerotic disease in the LM artery was the only independent predictor of events at follow-up, further strengthening this observation. When ostial or mid-LM disease is treated with DESs, the rate of cardiac events is particularly low. Thus, routine IVUS does not confer any benefit in this subpopulation with an excellent outcome. In patients with distal LM involvement, the rate of events was significantly higher, but also in this instance, no significant clinical benefit occurred in the IVUS sub-

group. However, because IVUS was used in a smaller number of patients with respect to the group with nondistal LM involvement, it is possible that routine IVUS guidance is useful when the distal LM artery is diseased, and such a strategy warrants further evaluation.

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Chapter 5. Single-vessel versus Bifurcation Stenting for the Treatment of Distal Left Main Coronary Artery Disease in the Drug Eluting Stenting Era. Clinical and Angiographic Insights into the RESEARCH and T-SEARCH Registries

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Single-vessel versus Bifurcation Stenting for the Treatment of Distal Left Main Coronary Artery Disease in the Drug Eluting Stenting Era

Clinical and Angiographic Insights into the RESEARCH and T-SEARCH Registries

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Background: Routine drug eluting stent (DES) implantation has recently improved outcome in patients undergoing percutaneous treatment of left main (LM) coronary artery. However, even in the DES era, distal LM treatment remains an independent predictor of poor outcome. Whether single-vessel (SVS) or bifurcation stenting (BS) should be performed to optimize treatment of such a lesion is unclear.
Methods: From April 2002 to June 2004, 94 patients affected by distal LM disease (DLMD) underwent percutaneous intervention at our institution either with SVS (n=48) or BS (n=46). The two groups were well balanced for all baseline characteristics but extension of disease in the LM carina.
Results: After a median follow-up of 587 days (range: 328-1179), the cumulative incidence of MACE was similar between the two groups (31% in the BS vs. 28% in SVS group; HR 0.96 [95% CI: 0.46-1.49]; p=0.92), with no difference for the composite death/myocardial infarction or target vessel revascularization (TVR). After adjustment for confounders, technique of stenting was not a predictor of either MACE or TVR. Angiographic analysis –performed in 81% of eligible patients in SVS and 87% in the BS group– confirmed the equivalency between single-vessel versus bifurcation stenting.
Conclusions: In consecutive patients undergoing catheter-based distal LM intervention, single-vessel or bifurcation stenting may perform equally under both clinical and angiographic perspective in current DES era.

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INTRODUCTION

Routine drug eluting stent (DES) implantation, by reducing the need for target vessel revascularization (TVR) and angiographic restenosis, has been recently shown to favourably affect outcome with respect to bare metal stents (BMS) in patients undergoing percutaneous left main (LM) intervention(1-3). However, the rate of major cardiovascular events in the DES era remains high in the first series of patients reported(1, 3).
This appears to be especially true for patients undergoing treatment of distal LM disease.
Some early observational studies in the BMS era identified distal location of the disease with respect to LM anatomy as a major determinant of restenosis in patients receiving percutaneous treatment of the LM(4). Similarly, others and we have reported that even in the DES era the great majority of lesions, which undergo TVR at follow-up, are located in the distal tract of the LM(1, 3). Taken together, current evidence may suggest that special attention must be paid to optimize treatment of distal LM disease.
Two recent randomized trials, in which mainly non-LM bifurcated lesions were treated with the use of DES, reported no advantage of scaffolding the whole bifurcation carina compared to the simpler single-vessel stenting approach(5, 6).
Whether this holds true also for the treatment of distal LM, where bigger reference size of the vessels involved in the bifurcation might theoretically better accommodate the stent-related intima hyperplasia, remains largely unknown.
Thus, the purpose of the present study was to investigate the clinical and angiographic outcome of single-vessel versus bifurcation stenting to treat distal LM lesions in patients undergoing DES-supported revascularisation in a tertiary referral center.

METHODS

Study Design and Patient Population

Since April 16 2002, SES (Cypher™, Johnson & Johnson-Cordis unit) have been used as a default strategy for every PCI at our institution as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. From the first quarter of 2003, PES (Taxus™, Boston Scientific Corporation) became commercially available, replacing SES as the stent of choice in every PCI, as part of the Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registry. As a policy, all elective patients presenting with significant (>50% by visual estimation) LM disease, referred to our institution for coronary revascularisation, are evaluated both by interventional cardiologists and cardiac surgeons and the decision to opt for PCI or surgery is reached by consensus, as previously described(1).
From 16th April 2002 to June 28 2004, a total of 130 consecutive patients were treated exclusively with one or more DES in the LM as part of an elective or non-elective revascularisation procedure. Ninety-four patients, presenting with distal LM disease, defined as significant lumen obstruction (>50%) at visual estimation occupying the third distal of the LM shaft with the entire lesion or part of it either directly involving the ostium of the left anterior descending and/or circumflex artery—including the intermediate branch if presenting with a reference diameter ≥2.5 mm— or in close contact with at least one of the ostia, constitute the patients population of the present report. Thirty-seven patients in the first cohort received exclusively SES –available, at that time, in diameters from 2.25 to 3.00 mm- while, in the following group of 63 patients, PES –available in diameters from 2.25 to 3.5 mm- were implanted.

The Parsonnet surgical risk score, based on both clinical presentation profile and comorbidities, was calculated for each patient as previously described(7). Similarly, in order to assess clinical outcome in the two study groups based on a previously validated PCI risk-score, the William Beaument Hospital simplified scoring system was also calculated for each patient(8).
Protected LM segment was defined by the presence of at least one patent arterial or venous conduit to at least one left coronary segment. Non-elective treatment was defined as a procedure carried out on referral before the beginning of the next working day(9).
This protocol was approved by the hospital ethics committee and is in accordance with the declaration of Helsinki. Written informed consent was obtained from every patient.

Procedures and Post-Intervention Medications
All interventions were performed according to current standard guidelines and the final interventional strategy, including single- versus bifurcation stenting and the use of glycoprotein IIb/IIIa inhibitors, was entirely left 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 3 grade flow. All patients were advised to maintain aspirin lifelong, while clopidogrel was prescribed for 6 months in both groups.

Endpoint Definitions and Clinical Follow-up
The occurrence of major adverse cardiac events, defined as 1) death, 2) non-fatal myocardial infarction, or 3) target vessel revascularization was recorded. Patients with more than one event have been assigned the highest ranked event, according to the previous list. All deaths were considered to be of cardiac origin unless a non-cardiac origin was established clinically or at autopsy. Myocardial infarction was diagnosed by a rise in the creatine kinase level to more than twice the upper normal limit with an increased creatine kinase-MB fraction. Target vessel revascularization 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, including the ostium of the left anterior descending artery (LAD) and/or circumflex artery (LCx). Information about in-hospital outcomes was obtained from an electronic clinical database for patients maintained at our institution and by review of hospital records for those discharged to referring hospitals (patients were referred from a total of 14 local hospitals). Post-discharge survival status was obtained from the Municipal Civil Registries. Occurrence of MI or repeat interventions at follow-up were collected by consultation of our institutional electronic database, by contacting referring physicians and institutions and all living patients.

Statistical Analysis
Continuous variables are shown as mean±SD or median and interquartile range (IQR) and were compared using Student's unpaired *t*-test. Categorical variables are presented as counts and percentages and compared with the Fisher's exact test. Survival curves were generated by the Kaplan-Meier method and survival among groups was compared using the log-rank test. Cox proportional hazards models were used to assess risk reduction of adverse events. Multivariable analysis, considering all variables reported in table 1 with a p value of less than 0.10, was performed to adjust for confounders and identify whether the treatment strategy was an independent predictor of adverse events. Probability was significant at a level of <0.05. All statistical tests were 2-tailed. Statistical analysis was performed on Statistica 6.1 (Statsoft Inc. Tulsa, Oklahoma).

Table 1. Baseline Characteristics of the Study Population

Variables	Single-Vessel Stenting (N=48)	Bifurcation Stenting (N=46)	P value
Age (ys)*	64±12	63±11	0.95
Males (%)*	67	60	0.74
Body Mass Index (kg/m^2) *	24±4	24±4	0.98
Diabetes (%)*	25	28	0.82
Hypertension (%)*	58	69	0.62
Hypercholesterolemia (%)	61	70	0.80
Current Smokers (%)	17	22	0.64
Creatinine (μmol/L)*	102±52	100±45	0.82
LV Ejection Fraction (%)*	44±12	45±14	0.51
Medical History			
Protected LM (%)	19	15	0.79
PCI (%)	37	24	0.37
Myocardial Infarction (%)	40	39	>0.99
Clinical Presentation			
Stable Angina (%)	48	54	0.86
Unstable Angina (%)	27	28	>0.99
AMI* (%)	23	15	0.45
Cardiogenic Shock at Entry* (%)	10	9	>0.99
Parsonnet Score (%)	18±14	18±11	0.77
Parsonnet score > 15 (%)	24 (50)	23 (50)	>0.99
Bifurcation lesion classification			
Isolate distal LM Stenosis (%)	22	2	0.02
Distal LM plus ostial LAD or LCx (%)	35	28	0.67
Distal LM plus both LAD/ LCx ostia (%)	31	61	0.06
Isolate LAD or LCx ostium stenosis (%)	12	9	0.72
LM plus 1-vessel Disease (%)	17	15	0.79
LM plus 2-vessel Disease (%)	21	33	0.37
LM plus 3-vessel Disease (%)	60	48	0.60
Number of implanted stents	1.2±0.46	2.2±0.48	<0.0001
Nominal stent diameter (mm)	3.17±0.27	3.21±0.30	0.56
Total stent length per patient (mm)	20±7	38±11	<0.0001
Gp IIb/IIIa inhibitors (%)	33%	35%	>0.99
SES/PES (%)	40/60	35/65	0.67
Final kissing ballon (%)	23	61	0.02

LV: left ventricular; AMI: acute myocardial infarction; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent; LAD: left anterior descending artery; LM: left main; LCx: circumflex artery; *: parameters included in the Parsonnet score.

RESULTS

Baseline and Procedural CharacteristicsAmong the 94 patients with *de novo* left main lesions included in this analysis, 48 (51%) received single-vessel stenting (LM plus LAD or LM plus LCx) while 46 (49%) received bifurcation stenting: the culotte technique was performed in 17 (37%), T-stenting in 15 (33%), crush-stenting in 8 (17%) and V-stenting in 6 (13%). Baseline and procedural characteristics of the patient population, stratified into the treatment-received, are shown in **TABLE 1**. The two groups were well matched for all clinical characteristics, including the Parsonnet surgical risk score.

The anatomical location and extension of the LM disease was the main driver of the choice to use a single- or double-vessel stenting, with single-vessel stenting (SVS) performed as the strategy of choice in case of isolate distal LM stenosis, while bifurcation stenting (BS) was the most frequent approach in cases of distal LM disease involving both LAD and LCx ostia.

Clinical Outcome

Short- and long-term outcome is reported in **Table 2**.

Table 2. 30-Day and long-term Outcomes

VARIABLES	SINGLE-VESSEL STENTING	BIFURCATION STENTING	P VALUE*
	(N=48)	(N=46)	
30-day Outcome			
Death, no (%)	4 (8)	3 (7)	>0.99
Non-fatal MI, no (%)	3 (6) ‡	1 (2)	0.62
Death or non fatal MI, no (%)	7 (15)	4 (9)	0.53
TVR, no (%)	0 (0)	0 (0)	>0.99
Any Event, no (%)	7 (15)	4 (9)	0.53
Stent thrombosis, no (%)†	0 (0)	0 (0)	>0.99
Long-term outcome			
Death, no (%)	5 (10)	5 (11)	0.98
Non-fatal MI, no (%)	5 (4)	2 (7)	0.44
Death or non fatal MI, no (%)	10 (21)	7 (15)	0.39
TVR, no (%)	5 (10)	6 (13)	0.38
Any Event, no (%)	15 (31)	13 (28)	0.92
Stent thrombosis, no (%)†	0 (0)	0 (0)	>0.99

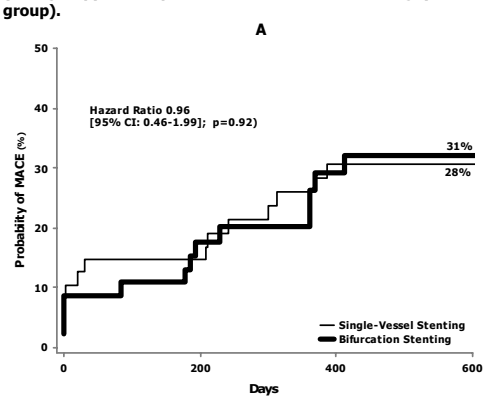
*: By Fischer's exact test for 30-days outcome and by log-Rank Test for long-term outcome
†: Angiographically documented
‡: in 2 cases CK-MB increased more than 2 but less than 3 times the upper limit of normal; setting the threshold for the definition of periprocedural myocardial infarction at 3 times the upper limit of normal, in accordance with current ACC/AHA guidelines, would result in one event per group at 30 days.

After a median follow-up of 587 days (range: 328-1179), the cumulative incidence of MACE was very similar in both groups (31% in the SB vs. 28% in SVS group; HR 0.96 [95% CI: 0.46-1.49]; p=0.92) (**FIGURE 1A**): the composite death/MI was 21% in the SVS and 15% in the BS group (HR 0.64 [95% CI: 0.23-1.78]; p=0.39), while cumulative incidence of TVR was 10% and 13% in patients receiving SVS and BS, respectively (HR 1.03 [95% CI: 0.3-3.2]; p=0.38) (**FIGURE 1B**). Stratifying the patient population into surgical risk-status according to Parsonnet score, the treatment received failed to be a predictor of MACE both in the low- (HR 1.3 [95% CI: 0.38-4.59]; p=0.66), or in the high-risk (HR 0.86 [95% CI: 1.34-2.17]; p=0.74) group. The median (IQR) value of the William Beaument Hospital simplified scoring system was 7(4-11); the rate of MACE was 17% vs. 13% (p>0.99) in patients with a total score below 7 and 46% vs. 43% (p>0.99) in patients scoring above the median value, in the SVS and BS group, respectively.

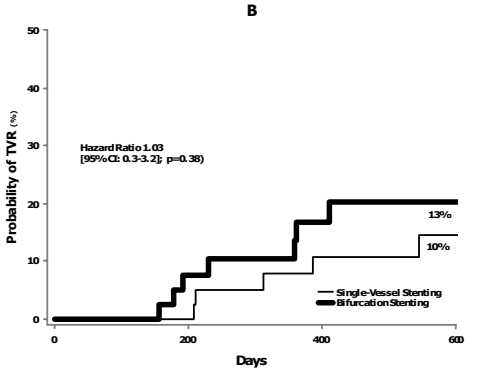
Similarly, the MACE rate did not differ in the single-vessel versus bifurcation stenting group when the cohorts of patients receiving SES (31% in both groups, p=0.93) or PES (31% and 27% in the SVS and BS, respectively; p=0.89) were separately analyzed.

The stenting technique employed in the treatment of the left main coronary artery failed to impact on outcome

Fig. 1 Adverse events in patients affected by distal left main disease, treated either with single-vessel stenting (SVS group) technique or with bifurcation stenting (BS group).



Cumulative risk of major adverse events



Target vessel revascularization

even in the subgroup of patients undergoing elective intervention (HR 1.01 [95% CI: 0.40-2.5]; p=0.78) with an observed MACE rate at long-term follow-up of 33% and 31% in the SVS and BS group, respectively.
After adjustment for total stent length, bifurcation lesion classification, use of IVUS and performance of final kissing, BS failed to emerge as an independent predictor of MACE or TVR.
The same held true when bifurcation lesion classification, as factor potentially able to bias the comparison, was removed from multivariable analysis.

Quantitative Coronary Analysis
Thirty-five patients (81% of eligible patients) in the SVS and 36 (87% of eligible patients) in the BS group underwent coronary angiography at follow-up.
Main branch vessel size, minimal lumen diameter, lesion length and degree of stenosis were similar at baseline in the SVS and BS groups (**TABLE 3**). At both in-stent and in-lesion analyses, ALG was similar between the two groups immediately after the procedure as was the case for LL at follow-up. Thus, no difference in the net luminal gain was observed in the main branch between patients receiving or not receiving a stent in the SB.
In the side branch analysis, RVD tended to be bigger, with longer lesion length and greater degree of stenosis in BS group with respect to patients undergoing SVS (**TABLE 3**). ALG in the side braches receiving stenting was bigger than in those not receiving stent, thus offsetting the higher LL observed in the stent group, with an overall NLG of 0.04±0.75 in the BS and 0.47± 0.68 in the SVS group (p=0.023).
When patients undergoing balloon angioplasty in the side branch were compared to those receiving stent (BS group) (**TABLE 4** and **FIGURE 2**), in-lesion analysis showed that the two groups were well matched for all baseline quantitative measures. Immediately after the procedure, ALG tended to be bigger while DS smaller in patients receiving stent. However, at follow-up LL was significantly higher in the SB group, which completely compensated the bigger gain obtained immediately after the procedure compared to the balloon group, with a final net luminal gain almost identical between patients treated with stent or balloon angioplasty.Finally, on a patient-basis, the cumulative in-lesion BR for both main and side branches occurred in 26% and 25% of the cases in the single vessel and bifurcation stenting group, respectively (p>0.99).

DISCUSSION
The treatment of stenosis at a bifurcation remains one of the most challenging lesion subsets in coronary angioplasty. Bifurcation lesions carry a risk of SB occlusion due to plaque redistribution, the so-called "plaque shift" across the carina of the bifurcation. Yet, with the advent of metallic stent, the acute risk of side branch closure has remarkably decreased. However, the long-term outcome of side branches may be often disappointing when both branches have to be stented(10, 11). Thus, provisional stenting of the side branch has been regarded as the strategy of choice in the BMS era to handle bifurcation lesions(12).
These two-treatment strategies, manly main branch stenting plus provisional stenting of the side branch versus default double-vessel stenting, were recently compared in two randomized trials accomplished with unrestricted use of SES(5, 6). They both showed no advantage of bifurcation stenting over the more simple one-vessel stenting technique, with some safety concerns related to the unexpectedly high rate for stent thrombosis in the group allocated to double-vessel stenting in one of the two investigations(6). Colombo et al. excluded patients with LM lesions while only three patients with distal LM were enrolled in the second study. Thus, whether single-vessel or bifurcation stenting should be the strategy of choice in patients presenting with distal LM stenosis remains currently unclear. The bigger reference size of the vessels involved in the bifurcation might better accommodate the stent-related intima hyperplasia, thus giving a theoretical advantage to the full stent-coverage of the LM carina with respect to balloon-based treatment of the side branch.
The main finding of our investigation is that the short- and long-term outcome of patients undergoing distal LM intervention was similar with respect to MACE rate for patients receiving single-vessel or bifurcation stenting. This remained true in both low and high surgical risk cohorts of patients and was not affected by the stent type employed. Patients receiving bifurcation stenting, despite being well matched for all clinical characteristics with respect to patients treated with single-vessel stenting, were more frequently affected by a true bifurcation lesion with a greater disease extension in the ostia of main left coronary arteries. After adjusting for this important confounder at multivariable analysis, the treatment technique failed to be predictive of outcome. This clinical observation was supported further by our angiographic findings.
The angiographic outcome of the MB did not differ in the SVS compared to BS group. It has been recently proposed in benchtop models of arterial bifurcations that maximizing the total cross sectional area of both branches through aggressive stent-based scaffolding could have an adverse effect on MB flow pattern and in so doing impair long-term MB patency(13). Our data do not support this hypothesis. Acute luminal gain in the SB was almost double in the stented compared to the non-stented cohorts of patients, while LL and NLG in MB resulted to be very similar at follow-up between the two groups. Excluding the cases where, thanks to favorable anatomy, the no touch policy in the SB was carried out, angiographic quantitative data in the SB undergoing stenting were well matched at baseline compared to those treated with balloon angioplasty. This stratification process allowed us to perform a univariate direct comparison between these two groups: stenting a SB led to a greater ALG with respect to the balloon angioplasty after the procedure. However, even if probably reduced compared to historical reports with BMS(10, 11), the price of stenting remains in the DES era a moderate positive LL, while there was a mild additional gain (which means a negative LL) in the SB undergoing balloon-based treatment. Thus, NLG in SB treated with either technique was nearly identical at follow-up despite clear differences in the process that led to this final result.

Table 3 Quantitative Coronary Analyses

Variables	SVS group Stented Vessel	BS group Stented Vessel	P-value	SVS Group non stented vessel	BS Group Stented Vessel	P-value
	Main Branch			Side Branches		
Before PCI	(N=35)	(N=36)		(N=35)	(N=36)	
RVD (mm)	3.05±0.59	2.98±0.59	0.65	2.3±0.7	2.6±0.7	0.08
MLD (mm)	1.13±0.66	1.22±0.59	0.55	1.5±0.7	1.2±0.6	0.10
Diameter stenosis (%)	63±20	58±21	0.35	32±28	54±20	0.0008
Lesion length (mm)	9.98±3.75	9.69±.3.83	0.76	5.75±	9.5±5.5	0.0038
After PCI In-Stent						...
RVD (mm)	3.10±0.66	2.93±0.0.48	0.24	...	2.67±0.68	...
MLD (mm)	2.69±0.51	2.58±0.40	0.33	...	2.22±0.42	...
Acute Luminal Gain (mm)*	1.57±0.72	1.36±0.69	0.22	...	0.96±0.54	...
Diameter stenosis (%)	12±10	11±9	0.75	...	18±11	...
After PCI In-Lesion						
RVD (mm)	3.10±0.66	3.00±0.48	0. 53	2.27±0.7	2.56±0.65	0.1
MLD (mm)	2.69±0.51	2.58±0.40	0.33	1.58±0.7	2.0±0.44	0.0055
Acute Luminal Gain (mm)*	1.57±0.72	1.36±0.72	0.22	0.09±0.7	0.8±0.6	<0.0001
Diameter stenosis (%)	12±10	11±9	0.75	24±26	20±14	0.07
Follow-up In-Stent						
RVD (mm)	3.10±0.80	2.9±0.47	0.25	...	2.73±0.59	...
MLD (mm)	2.24±0.83	2.17±0.59	0.70	...	1.8±0.61	...
Diameter stenosis (%)	25±25	24±20	0.87	...	33±21	...
Late Loss (mm) *	0.45±71	0.42±0.67	0.79	...	0.41±0.54	...
Net lumen gain (mm)	1.10±0.79	0.95±0.77	0.41	...	0.54±0.69	...
Binary Restenosis, no. (%)*	4 (11)	5 (13)	>0.99	...	5 (14)	...
Follow-up In-Lesion						
RVD (mm)	2.73±0.79	2.72±0.56	0.97	2.32±0.66	2.52±0.65	0.24
MLD (mm)	2.01±0.78	2.01±0.57	0.97	1.53±0.69	1.68±0.65	0.41
Diameter stenosis (%)	24±25	25±20	0.86	33±25	33±22	0.48
Late Loss (mm) *	0.26±0.72	0.25±0.50	0.95	0.04±0.42	0.32±0.55	0.023
Net lumen gain (mm) *	0.89±0.83	0.82±0.90	0.72	0.04±0.75	0.47±0.68	0.024
Binary Restenosis, no. (%)†	4(11)	4(11)	>0.99	7 (20)	5 (14)	0.76

SVS: single-vessel stenting; BS: bifurcation stenting; ALG: acute luminal gain, BR: binary restenosis In-Les.: in-lesion, LL; late loss, MLD: Minimal lumen diameter; RVD: Reference vessel diameter *: See text for definitions. †: All restenosis were focal (length <10 mm)

Limitations of the Study

The present study is a single-center experience from a tertiary referral center and lacks the clear advantages of a multicenter randomized trial. Due to the retrospective nature of our investigation, we cannot provide intention-to-treat data. Operators were left free to employ single vessel or bifurcation stenting technique according to their practice/preference. Accordingly, our analysis may be subject to considerable risk of being biased, with patients showing greater plaque burden at the level of the bifurcation or presenting with complications or unsatisfactory results during the procedure being at much higher probability to receive bifurcation over single vessel stenting. A prospective randomized comparison based on intention to treat data would be ideally required to validate our findings. In consideration of our limited sample size, the chance our results are affected by a type II error is not negligible. Assuming a background event rate as presently observed in the BS group, our sample size would allow us to reach 80% of statistical power only hypothesising a relative risk reduction or a relative risk increase of 70% or more than 90%, respectively. Thus studies with bigger sample size should aim to investigate whether a small difference in long-term clinical outcome may exist between SVS versus BS. It may be argued that 4 different techniques were employed in patients receiving bifurcation stenting and that the overall results of the study in the bifurcation stenting group may have been confounded by the different performance of each different employed technique. The MACE rate in the bifurcation stenting group proved to be consistent, however, among the four bifurcation techniques employed in the present study (data not shown). This possibly reinforces the concept that, in the DES era, the outcome after treatment of stenosis at a bifurcation may not be strictly related to the employed bifurcation technique as it was known to be in the BMS era(10, 11)

Conclusions

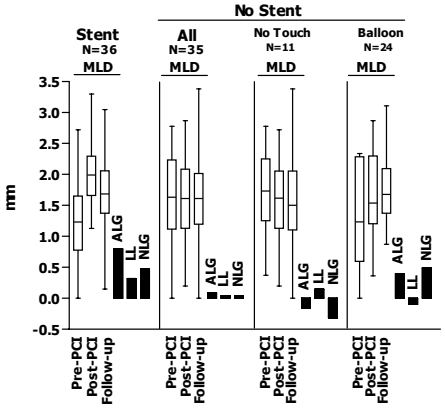
In consecutive patients undergoing percutaneous treatment for distal LM disease, short- and long-term clinical outcome and quantitative angiographic results did not differ in relation to the treatment accomplished: single-vessel versus bifurcation stenting. When our data are put into perspective with available evidence, the choice to adopt a single-vessel or a bifurcation stenting in the treatment of a LM bifurcation lesion in the DES era should be probably tailored to the individual patient, based on the complex interplay between coronary anatomy, operator's preference and foreseeable risk of thrombotic complication(6, 14).

Table 4. QCA in Side Branches

VARIABLES	STENTED SIDE BRANCH* (N=36)	BALLOONED SIDE BRANCH (N=24)	P VALUE
BEFORE PROCEDURE			
RVD (mm)	2.63±0.67	2.65±0.81	0.94
MLD (mm)	1.21±0.59	1.39±0.72	0.38
Diameter stenosis (%)	54±20	43±29	0.16
Lesion length (mm)	9.8±3.8	8.5±5.3	0.18
AFTER PROCEDURE			
RVD (mm)	2.56±0.64	2.58±0.78	0.91
MLD (mm)	2.00±0.44	1.80±0.75	0.27
Acute Luminal Gain (mm) †	0.79±0.60	0.40±0.86	0.09
Diameter stenosis (%)	20±14	30±24	0.07
FOLLOW-UP			
RVD (mm)	2.68±0.66	2.71±0.68	0.69
MLD (mm)	1.68±0.55	1.89±0.61	0.31
Diameter stenosis (%)	33±22	29±17	0.56
Late Loss (mm)†	0.32±0.55	-0.10±0.60	0.03
Net luminal gain (mm) †	0.47±0.68	0.49±0.76	0.92
Binary Restenosis, no. (%)	5 (14)	3 (13)	>0.99

* In-lesion analyses were used for this comparison. †: See text for definitions MLD: minimal lumen diameter; RVD: reference vessel diameter.

Fig. 2



Minimal lumen diameter (MLD), Acute luminal gain (ALG), late loss (LL) and net luminal gain (NLG) in side branches left untreated (no touch group) or treated either with stent implantation (Stent group) or with balloon angioplasty (Balloon group).

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Chapter 6. Persistence of neointimal growth 12 months after intervention and occurrence of delayed restenosis in patients with left main coronary artery disease treated with drug eluting stents

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Persistence of Neointimal Growth 12 Months After Intervention and Occurrence of Delayed Restenosis in Patients With Left Main Coronary Artery Disease Treated With Drug-Eluting Stents

To the Editor: Although long-term follow-up after drug-eluting stent (DES) implantation shows a sustained clinical benefit in several registries and randomized trials (1), little is known about the pattern of neointimal growth beyond the first six to nine months. In particular, when exactly neointima growth after DES implantation begins to subside remains largely unknown.

The mechanism of action of DES on neointimal proliferation seems to be partially explained by a delay in vascular response, which has supported the concern that late restenosis (i.e., occurring beyond six months) might occur in humans (2).

This would be of clinical relevance especially for patients receiving DES implantation for the treatment of left main coronary artery (LMCA) disease, in whom restenosis is considered a major, and potentially fatal, complication after percutaneous intervention.

Up to March 6, 2004, a total of 110 consecutive patients were treated exclusively with one or more DES in the LMCA as part of an elective or non-elective revascularization procedure at our institution. Seventy-three patients received 6-month angiographic follow-up, of whom 15 underwent paired angiographic measures at 12 months, which was not preceded by target vessel reintervention, and constitute the patient population of the present report.

Quantitative angiographic analyses were performed with the use of edge-detection techniques (CAAS II, Pie Medical, Maastricht, the Netherlands). Binary restenosis was defined as stenosis of more than 50% of the luminal diameter in the target lesion. Late loss was defined as the minimal lumen diameter (MLD) immediately after the index procedure minus the MLD at angiographic follow-up.

Continuous variables are shown as median and interquartile range and were compared using Wilcoxon test or a general liner mixed model followed by post-hoc analysis after log transformation for normalization. Probability was significant at a level of <0.05.

The characteristics of the study population (Table 1) did not differ with respect to the patients receiving no or six-month angiographic follow-up only.

The reason for repeating a second coronary angiogram included risk-stratification before non-cardiac major surgery in three (Patients #1, #6, and #14), evidence of inducible ischemia at noninvasive stress test in two (Patients #4 and #15), a staged procedure for the treatment of the right coronary artery in one (Patient #13), and the willingness to repeat a second coronary angiogram in the remaining nine after counselling about the potential consequence of in-stent restenosis at the time of the index procedure. No major adverse cardiovascular event previously occurred in this cohort of patients, and all except one were asymptomatic at the time of repeated catheterization.

Quantitative coronary analysis on paired measurements in the main treated branch (i.e., LMCA or LMCA and the proximal tract of the left anterior descending artery) is shown in Table 1. When all intervened coronary segments were cumulatively considered ($n = 20$), including the stented proximal tract of the circumflex artery in five patients receiving bifurcation stenting, the MLD decreased from 2.78 (2.49 to 2.95) after the procedure to 2.44 mm (2.07 to 3.09) ($p = 0.37$) and 2.25 (1.85 to 2.70) ($p = 0.005$ vs. post-procedure and $p = 0.054$ vs. 6-month) at 6 and 12 months, respectively. The late loss (mm) increased from 0.29 (0.07 to 0.4) at 6 months to 0.63 (0.37 to 0.76) after 12 months ($p < 0.001$) (Fig. 1). Cumulatively, Patient #13, presenting with mild intimal hyperplasia at 6 months, received a target vessel revascularization at 12 months due to severe focal in-stent restenosis in the mid-shaft of the LMCA (Fig. 1C), while a focal restenosis in the ostium of the circumflex artery detected at 12-month follow-up in Patient #2 was left untreated due to normal coronary reserve at non-invasive nuclear stress imaging.

Previous serial angiographic analyses showed that intimal hyperplasia peaks after 12 to 16 weeks after intervention and that restenosis rarely occurs beyond 3 months after bare metal stent implantation (3). These observations justify current practice to perform angiographic follow-up six to eight months after percutaneous coronary revascularization, when the intimal growth has ceased and the net lumen gain is likely to be maintained over time. Indeed, a partial regression of the in-stent intimal hyperplasia at longer-term follow-up in patients receiving bare metal stents has been reported (3).

When exactly neointima growth after DES implantation begins to subside remains largely unknown, but based on experimental findings, a late *catch up* phenomenon has been hypothesized (2). Of some concern is the fact that similar argumentations have been previously raised after intravascular brachytherapy, based on findings on animals, which were subsequently confirmed in humans (4). In the longest available angiographic follow-up after DES implantation, neointimal growth has been shown to mildly nonsignificantly progress beyond one year (1). Whether this would result in delayed restenosis remained unclear.

In our small series of patients undergoing serial angiographic monitoring, a significant increase of late loss between 6 and 12 months was noted, and, more importantly, one patient developed late in-stent restenosis of the LMCA, which necessitated reintervention.

Our preliminary findings raise several unanswered questions. This study was not pre-specified, as it was urged by the one-year

Table 1. Baseline and Procedural Characteristics and Serial Quantitative Coronary Analysis of the Main Treated Branch

	Patient No.														
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Age, yrs	68	69	64	63	48	46	70	30	50	72	70	72	78	56	64
Gender	M	M	M	M	M	M	F	M	F	M	F	M	M	M	F
Diabetes	No	Yes	No	No	No	No	No	No	No	No	Yes	No	Yes	No	No
Creatinine (μmol/l)	79	69	85	90	94	98	53	68	68	73	61	70	92	187	254
Protected LMCA	No	No	No	No	Yes	No	No	No	No	No	Yes	No	No	No	No
Clinical presentation	STEMI	SA	SA	SA	SA	SA	STEMI	SA	UA III B	UA II B	SA	UA III A	SA	UA III B	UA II B
Parsonnet score	19.5	12	6.5	3.5	9	6.5	19.5	25.5	19	2.5	19	2.5	14	18	21
Lesion location	Mid	Distal	Distal	Ostial	Ostial	Mid	Distal	Distal	Mid	Mid	Distal	Mid	Distal	Ostial	Distal
Severe calcification	No	No	No	No	Yes	No	No	No	No	No	No	Yes	No	No	Yes
Stent type	SES	SES	SES	SES	SES	SES	SES	SES	SES	SES	PES	PES	PES	PES	PES
Stent no.	1	2	1	1	1	1	1	2	1	2	2	2	2	1	2
Total stent length, mm	18	51	18	8	18	33	18	26	33	16	36	16	40	32	28
Bifurcation stenting	No	Yes	No	No	No	No	No	Yes	No	No	Yes	No	Yes	No	Yes
Technique	—	T-stent	—	—	—	—	—	Crush	—	—	Culotte	—	Culotte	—	V-stent
Post-dilation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes
Final kissing	No	No	No	Yes	No	No	No	No	No	No	No	No	Yes	No	Yes
QCA post-PCI															
RVD (mm)	3.95	3.05	3.40	2.61	3.42	3.58	3.68	2.89	3.16	3.43	2.42	3.40	2.70	3.53	2.89
MLD (mm)	3.57	3.04	2.77	2.56	3.41	2.91	3.60	2.89	2.49	3.11	2.43	2.95	2.26	3.51	2.71
Vessel stenosis (%)	10	0	18	2	0	19	2	0	21	9	0	13	16	6	6
QCA at 6-month follow-up															
RVD (mm)	3.89	3.12	3.9	2.67	3.52	3.38	3.53	3.04	2.67	3.59	2.45	3.93	2.24	3.59	2.61
MLD (mm)	3.51	3.04	3.09	2.49	3.21	3.28	2.99	1.96	2.07	3.33	2.01	3.64	1.86	3.11	2.27
Vessel stenosis (%)	10	3	21	7	9	3	15	35	22	7	18	7	17	13	13
QCA at 12-month follow-up															
RVD (mm)	3.79	2.74	3.45	2.50	3.20	3.44	3.12	3.12	2.66	3.26	2.55	3.37	3.17	3.78	2.58
MLD (mm)	2.84	2.70	2.40	2.37	2.18	3.12	2.87	1.92	1.95	2.99	1.62	2.81	1.03	3.01	2.27
Vessel stenosis (%)	25	1	29	5	31	9	8	38	27	8	36	17	81	20	12

LMCA = left main coronary artery; MLD = minimal lumen diameter; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent; QCA = quantitative coronary analysis; RVD = reference vessel diameter; SA = stable angina; SES = sirolimus-eluting stent; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina followed by Braunwald classification.

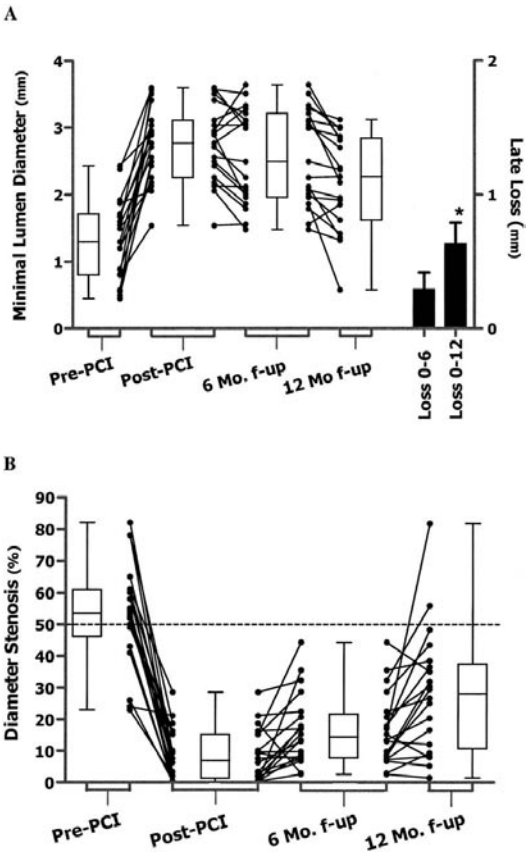

Figure 1. Change of minimal lumen diameter (MLD) **(A)** and lumen diameter stenosis **(B)** as a consequence of treatment in 20 intervened coronary segments, including the LMCA (and the proximal tract of the left anterior descending artery if stented) in 15 patients and the proximal segment of the circumflex artery in 5 patients who received bifurcation stenting. **(A)** At 12 months, the MLD (mm) reduced significantly compared to post-intervention ($p < 0.001$) and tended to be smaller than that noted at 6 months ($p = 0.054$). The late loss passed from 0.29 (0.07 to 0.4) at 6 months to 0.63 (0.37 to 0.76) after 12 months ($p < 0.001$). *$p < 0.001$ vs. late loss recorded at six months. **(B)** The vessel diameter stenosis (%) passed from 54 (50 to 60) before to 7 (2 to 10) after the procedure ($p < 0.001$), to 14 (9 to 18) at 6 months ($p = 0.3$ vs. post-procedure) and to 28 (17 to 35) at 12 months ($p = 0.066$ vs. 6 months). PCI = percutaneous coronary intervention.
Continued on next page.

findings on Patient #13. Importantly, the increase in late loss from 6 to 12 months turned out to be a consistent observation also in other LMCA-intervened patients, triggering the present report. It remains unclear based on our data whether intima hyperplasia peaks at 12 months or even later after DES LMCA stenting. Whether our results are applicable also to non-left main lesions is currently unknown.

Recently, Wessely et al. (5) reported on two patients treated with sirolimus-eluting stent in the left anterior descending artery and right coronary artery who presented at 13 and 19 months, respectively, with recurrence of symptoms and angiographically confirmed in-stent restenosis. Of note, both patients had undergone previous coronary angiogram at seven months, which showed no evidence of intima growth at that stage.

The finding that intima growth may persist well beyond the conventional six to eight months after intervention may cast a shadow of doubt on current attempts to employ power transformation of late loss at six to eight months to predict long-term stent performance.

The clinical implications of the delayed occurrence of in-stent restenosis after DES in patients undergoing intervention for LMCA disease remain unclear.

A prolonged clinical and angiographic surveillance in this subset of patients seems to be warranted.

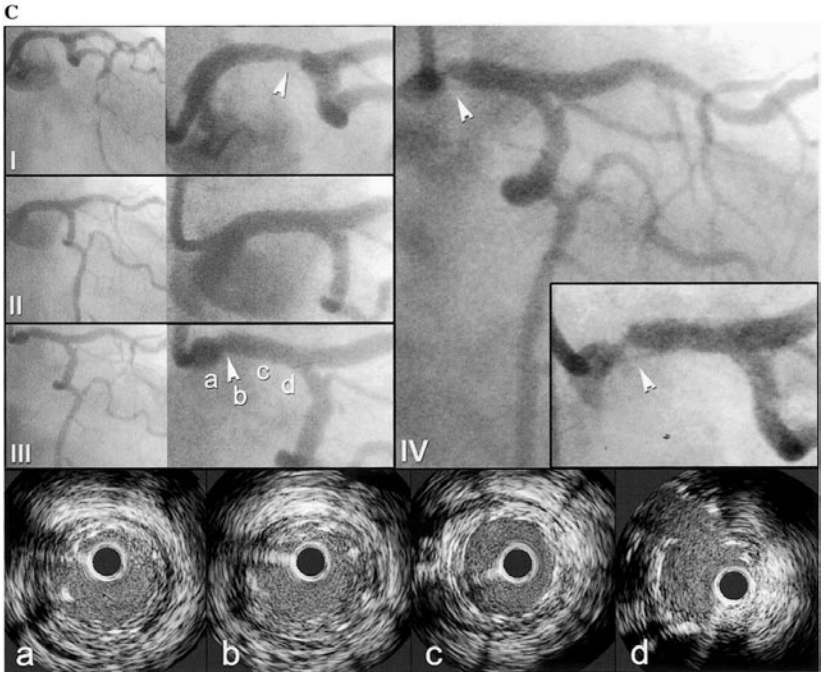

Figure 1 Continued. **(C)** Sequential coronary angiographies showing the left main coronary artery (magnified at the right) and the proximal and mid-tract of circumflex and anterior descending arteries of Patient #13. **Panel I:** A stenosed distal left main coronary artery with its magnification in the right quadrant and a subocclusion circumflex artery are visible before treatment. **Panel II:** Angiographic result immediately after treatment. At six months **(panel III)**, a moderate focal restenosis in the proximal tract of the left main coronary artery was present **(arrowhead)** that did not cause significant obstruction of the lumen at intravascular ultrasound (IVUS) investigation **(lower panel)** and did not result to be flow-limiting, with a fractional flow reserve of 0.85. At 12 months **(panel IV)**, control angiogram revealed a tight in-stent restenosis **(arrowhead)**, magnified in the insert, through which the IVUS probe could not be negotiated and required reintervention. **Lower panel** is showing four IVUS cross-sections (Atlantis 40 Mhz, Boston Scientific, Natick, Massachusetts) from the left main coronary artery at six months: **(a)** proximal edge of the stent in the left main coronary artery, with a malapposed strut visible at 7 o'clock; **(b)** in-stent concentric growth of intimal hyperplasia at the minimal lumen area; **(c)** minor degree of in-stent eccentric hyperplasia located in the mid-tract of the left main coronary artery at 9 o'clock; **(d)** left main coronary artery carina, showing no sign of intimal hyperplasia, with the stented circumflex artery originating at 11 o'clock.

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Chapter 7. Revisiting the Incidence and Temporal Distribution of Cardiac and Sudden Death in Patients Undergoing Elective Intervention for Unprotected Left Main Coronary Artery Stenosis in the Drug Eluting Stent Era. A pooled analysis on 340 patients treated at three European referral centers

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Submitted for publication

Revisiting the Incidence and Temporal Distribution of Cardiac and Sudden Death in Patients Undergoing Elective Intervention for Unprotected Left Main Coronary Artery Stenosis in the Drug Eluting Stent Era.

A pooled analysis on 340 patients treated at three European referral centers

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Background: Whether restenosis remains a major, and potentially fatal, complication after percutaneous intervention for left main coronary artery (LMCA) stenosis and whether routine surveillance angiography should be a necessary part of the follow-up of these patients in current drug eluting stent (DES) era is largely debatable.
Methods and Results: Patients who underwent *elective* treatment of *unprotected* LMCA with DES in three referral centres in Europe were pooled as follows: i) 147 patients treated in Massy, between 12 August 02 and 31 December 04; ii) 107 patients, treated in Milan, San Raffaele hospital and Columbus clinic, between 16th April 02 and 31st July 04 iii) 86 patients treated at the Thoraxcenter, Rotterdam, between 16th April 2002 and 28th June 04 leading to a total 340 elective consecutive patients. The rate of in-hospital mortality was 0.6% (2/340). The out of hospital event rate in terms of cardiac death or myocardial infarction was 1.2% between discharge and 3 month, 0.6% between three and 6 months and 0.6% between 6 months and 1 year. Two (0.6%) sudden and unexpected deaths were cumulatively observed, at 8 days and 2 months after intervention, respectively. The rate of confirmed or possible stent thrombosis was 0.9%. At 1 year, the out of hospital cumulative incidence of cardiac death or MI was 2.4%. In the cohort of patients who refused to undergo angiographic surveillance, no death and no MI occurred.
Conclusions: Cardiac and sudden death and the incidence of stent thrombosis after LMCA intervention with DES were reasonably low and compared favourably with what reported in non-LMCA lesions. At the time intimal hyperplasia is expected to peak (i.e. beyond 6 months), no increase of adverse events, in terms of death or myocardial infarction was observed.

Submitted

INTRODUCTION

Following the widespread adoption of drug eluting stents in current practice and their growing use in off-label indications, there is clear need to re-evaluate some of the dogmas on the treatment of the left main coronary artery (LMCA) stenosis, when undertaken percutaneously. In particular, whether restenosis remains a major, and potentially fatal, complication after LMCA treatment and whether routine surveillance angiography is needed to decrease the risk of cardiac and sudden death related to intimal hyperplasia is largely debatable and controversial.
In the ULTIMA registry, two hundred seventy-nine consecutive patients who had elective or emergent LMCA treatment with PCI at 1 of 25 sites between 1993 and 1998 were studied[1, 2]. Forty-six percent of these patients were deemed inoperable or at high surgical risk. Thirty-eight patients (13.7%) died in hospital. The 1-year incidence was 24.2% for all-cause mortality and 20.2% for cardiac mortality. An excess of deaths was observed predominantly in patients initially deemed inoperable. However, 2% per month death rate among hospital survivors was noted over the first 6 months. Of concern, most of the myocardial infarction (MI) cumulatively observed at one year, occurred in the first three months after treatment. Based on these findings, the interpretation that restenosis may lead to major fatal or non fatal complications in this cohort of patients was put forward and the need to perform routine surveillance angiography at 2 and 4 months after treatment was subsequently formulated. This recommendation was in agreement with previous studies showing that intimal hyperplasia after bare metal stenting peaks 12-16 weeks after intervention.
However, the uptake of this recommendation varied considerably between centres and, even when this recommendation has been followed, a single angiographic follow-up at 6 months, not two at 2 *and* 4 months, has been mainly carried out[3-6].
The discrepancy between what has been recommended and clinical practice has several potential explanations.
Firstly, the evidence on which the need to perform routine angiographic surveillance relies is rather weak. Whether the clustering of events in the few months after LMCA treatment is directly related to the development of restenosis remains speculative since no protocol-mandated angiographic follow-up was prespecified in the ULTIMA registry. Moreover, almost 50% of the included population was deemed to be inoperable or at high-surgical risk, which may in itself explain the high incidence of adverse events observed in the study population (mortality rate at 1 year was 79%, 24% and 3% in high, intermediate and low risk patients, respectively). No demonstration that the performance of routine early angiographic follow-up translates into a

clinical benefit in this patient population exists. Finally, there is concern for the iatrogenic hazard related to multiple angiographic follow-ups in this cohort of patients. Drug eluting stent (DES) implantation, by reducing the need for target vessel revascularization (TVR) and angiographic restenosis, has been recently shown to favourably affect outcome compared to bare metal stents (BMS) in patients undergoing percutaneous left main (LM) intervention. Current evidence suggests that both the magnitude and the peak of intimal growth may markedly differ in patients treated with DES as compared to BMS, which may offer the unique opportunity to re-evaluate the temporal incidence of major adverse events in this cohort of DES-treated patients.
Against this background, the principal aim of the present survey was to accrue data regarding the rate and temporal distribution of cardiac and sudden death or out of hospital MI in patients undergoing unprotected and elective LMCA intervention in the DES era. These observations might help re-examining the notion that in-stent restenosis may lead to fatalities or myocardial necrosis in patients undergoing percutaneous LMCA intervention. The second exploratory objective was to collect information in terms of clinical outcome on patients who refuse to undergo angiographic follow-up after LMCA treatment. This information may be critical in assessing the need for routine angiographic surveillance in this cohort of patients.

Patients' selection
Patients who underwent *elective* treatment of *unprotected* LMCA with DES in three referral centres in Europe were pooled as follows:

- One hundred forty seven patients, treated in Massy (France), between 12 August 02 and 31 December 04, [12 (8%) treated with sirolimus-eluting stent (SES) and 135 (92%) receiving paclitaxel-eluting stent (PES)]. This cohort of patients had a mean (SD) clinical follow-up of 6.8 ± 2.12 months. All patients were initially scheduled to undergo 6-month angiographic surveillance, which was actually performed in 65% of eligible patients. No data regarding this cohort of patients has been previously reported.
- One hundred seven patients, treated in Milan (Italy), San Raffaele hospital and Columbus clinic, between 16th April 02 and 31st July 04 [55 (51%) treated with sirolimus-eluting stent (SES) and 52 (49%) receiving paclitaxel-eluting stent (PES)]. All eligible patients underwent 1-year clinical follow-up. All patients were scheduled to undergo angiographic surveillance at 6 months, which was performed in 85% of those eligible. Six month outcome of the first 85 patients here included has been previously reported[5].
- Eighty-six patients treated at the Thoraxcenter, Rotterdam (the Netherlands) between 16th April 2002 and 28th June 04 [36 (41%) treated with sirolimus-eluting stent (SES) and 50 (59%) receiving paclitaxel-eluting stent (PES)]. All eligible patients underwent 1-year clinical follow-up. For research purpose, all patients were initially scheduled to undergo angiographic follow-up, which was finally carried out in 76% of those eligible. A subset of this cohort of patients has also previously reported[3].

Thus, from 16th April 2002 to December 31 2004, a total of 340 consecutive patients were treated, in three referral European centres, exclusively with one or more DES in the LMCA as part of an elective revascularisation procedure and constitute the patients population of the present report.

Procedures and post-intervention medications
All interventions were performed according to current standard guidelines and the final interventional strategy, including the use of glycoprotein IIb/IIIa inhibitors and stenting techniques, was entirely left to the discretion of the operator, except for the stent utilization. All patients were advised to maintain aspirin lifelong, while clopidogrel was prescribed for at least 6 months in patients treated in Rotterdam or Milan or 2 months only for those undergoing treatment in Massy.

Endpoint definitions
The primary outcome of interest was the occurrence of total and cardiac mortality.
All deaths were considered to be of cardiac origin unless a non-cardiac origin was established clinically or at autopsy. Myocardial infarction (MI) was diagnosed by a rise in the creatine kinase level to more than twice the upper normal limit with an increased creatine kinase-MB fraction. The cumulative rate of post-discharge MI will be presented for all included patients, while occurrence of in-hospital myocardial infarction is available for only those patients enrolled at the Thoraxcenter.

RESULTS
Mortality rate
In-hospital
The rate of in-hospital mortality was 0.6% (2/340). Overall, two fatal episodes occurred. Patient #1, affected by unstable angina following a recent MI (Braunwald class III C) presented with distal LMCA stenosis. The proximal and mid LAD and circumflex arteries were also diffusely diseased. This patient was refused by surgeons due to severe left ventricular dysfunction (left ventricular ejection fraction=25%) and underwent an elective intervention under left ventricular assist device (Tandem Heart). The procedure was successful but during the positioning of the last stent in the circumflex artery a dissection of ascending aorta occurred. The patient died immediately after surgery: The Patient #2 was a 90 years old female admitted for unstable angina. Coronary angiogram revealed severe triple vessel disease. The patient was considered too old for surgery. She had an uncomplicated and successful intervention but died 2 days after the procedure for hemorrhagic shock due to a severe groin haematoma, despite blood transfusion.

Sudden death
Cumulatively, two sudden and unexpected deaths occurred (0.6%): i) patient #3 died suddenly 8 days after the procedure; ii) Patient #4 died 2 months after intervention after anti-platelet therapy discontinuation because of concomitant acute pancreatitis.

Cumulatively total and cardiac mortality
There were a total of 13 fatal events (13/340, 3.8%), of which 8 (2.3%) were considered to be of cardiac origin as detailed in table 1. However, since patient #2 died as

Table 1 Baseline and procedural characteristics of patients who died for cardiac or procedure-related reasons

Patient No.	1	2	3	4	5	6	7	8	9
Age, ys	54	90	77	82	71	53	54	80	75
Gender	M	F	M	M	M	F	M	M	M
Enrolling Site	Rot.	Mas.	Mas.	Mil.	Mas.	Mil.	Mil.	Rot.	Mas.
Diabetes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes
Renal insufficiency	No	No	No	No	Yes	No	No	NO	No
Clinical Presentation	UA IIIC	UA IIIB	SA	UA	SA	UA	UA	UA IIIC	UA
Euroscore	12	8	4	13	6	3	9	8	13
Comorbidities	COPD	No	No	COPD, PVD, CVA	Dialysis	Hypothyroidi	PVD, Obesity	PVD, Obesity	COPD
Refused for Surgery	Yes	Yes	No	Yes	No	No	No	Yes	No
Lesion location	Distal	Distal	Distal	Distal	Ostial	Distal	Distal	Distal	Distal
Severe calcification	Yes	Yes	No	No	Yes	No	No	Yes	No
Stent type	SES	PES	PES	SES	PES	PES	SES	PES	PES
Stent No.	2	1	2	2	1	2	3	1	1
Total Stent Length, mm	25	76	71	41	55	44	84	24	43
Bifurcation Stenting	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Technique	T-stent	Provisional T 1 stent	T-stent	Crush	NA	Culotte	Crush	...	Provisional T 1 stent
Post-dilatation	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Final Kissing	No	Yes	Yes	Yes	NA	Yes	Yes	No	Yes
Cardiac Death				Yes		Yes	yes		
Reasons	AAD	GH	SD1	SD2	PO1	CABG1	PO2	CABG2	PCI
Days after PCI	0	2	8	56	60	136	164	243	312

UA: Unstable Angina; SA: stable angina; PCI; percutaneous coronary intervention; SES; sirolimus eluting stent; PES; paclitaxel eluting stent; Mas.; Massy; Mil. Milan; Rot.;Rotterdam; COPD: chronic obstructive pulmonary; PVD: peripheral vascular disease; CVA; previous cerebrovascular accident. Reasons for death: AAD; dissection of the ascending aorta during index procedure, the patient died immediately after surgery; GH; groin haematoma with subsequent haemorrhagic shock despite blood transfusion; SD1: sudden death; SD2: sudden death following antiplatelet therapy discontinuation due to acute pancreatitis; PO1; Pulmonary oedema during dialysis; CABG1: due to recurrent angina, the patient was admitted in a peripheral hospital and submitted to CABG (angiogram not available), the patient died in the intensive care unit immediately after surgery, PO2: pulmonary oedema in patient known to have severe mitral and aortic regurgitation while he was in the waiting list for surgery. CABG2: the patient underwent intervention for the right coronary artery resulted in acute pericardial effusion due to vessel perforation (Figure X). The patient died 2 days after surgery; PCI: the patient presented with restenosis in the ostium of the LAD, during reintervention a thrombotic embolus occurred in the left main, the procedure ended successfully but the patient died 2 days later for cardiogenic shock

consequences of the index intervention (hemorrhagic shock due to groin hameatoma), there were 9 (2.6%) cardiac or index procedure- related deaths. In the remaining 4 patients, death occurred due to pulmonary infection (n=1), massive bleeding during dialysis (n=2) and ischemic stroke (n=1).

Rate of stent thrombosis

One single episode of angiographically confirmed stent thrombosis (ACT) occurred (0.3%) 3 months after intervention in a patient who was still under double anti-platelet treatment. Hypothesizing that the two observed episodes of sudden deaths were attributable to ACT, the rate of confirmed or possible stent thrombosis was 0.9%.

Rate of myocardial infarction

In-Hospital (n=84): There was no episode of Q-wave MI, while 4 (4/86; 4.6%) episodes of CK-MB elevation above twice upper limit of normal (ULN) occurred. By elevating the threshold of CKMB rise to 3 times ULN, as currently recommended by ACC/AHA guidelines, the rate of MI was 1.1% (1/86). No episode of CK-MB elevation above 5 times ULN occurred.

Follow-up (n=340): There was one single episode of myocardial infarction which occurred at 3 month due to ACT, as previously described. Thus, the cumulatively rate of out of hospital MI at 1 year was 0.3%.

Cardiac death or myocardial infarction

The out of hospital event rate in terms of cardiac death or myocardial infarction was 1.2% between discharge and 3 month, 0.6% between three and 6 months and 0.6% between 6 months and 1 year. At 1 year, the out of hospital cumulative incidence of cardiac death or MI was 2.4%.

To explore the safety of avoiding systematic angiographic follow-up in this cohort, patients treated in Massy and Rotterdam were pooled, with a final population of 233 patients. Patients treated in Milan were not considered for this analysis due to the high rate of angiographic follow-up carried out in this cohort. Between discharge and 6 months, the rate of death was 3.4%, with no MI occurring after discharge. After 6 months, 160 (69%) patients underwent angiographic control. In this group, the rate of death from 6 to 12 months was 1.3%, with two cardiac deaths, both occurring due to complications during target vessel revascularization (in one case during PCI, in the second case the patient died one day post-CABG). In the cohort of patients who refused to undergo angiographic surveillance, no death and no MI occurred.

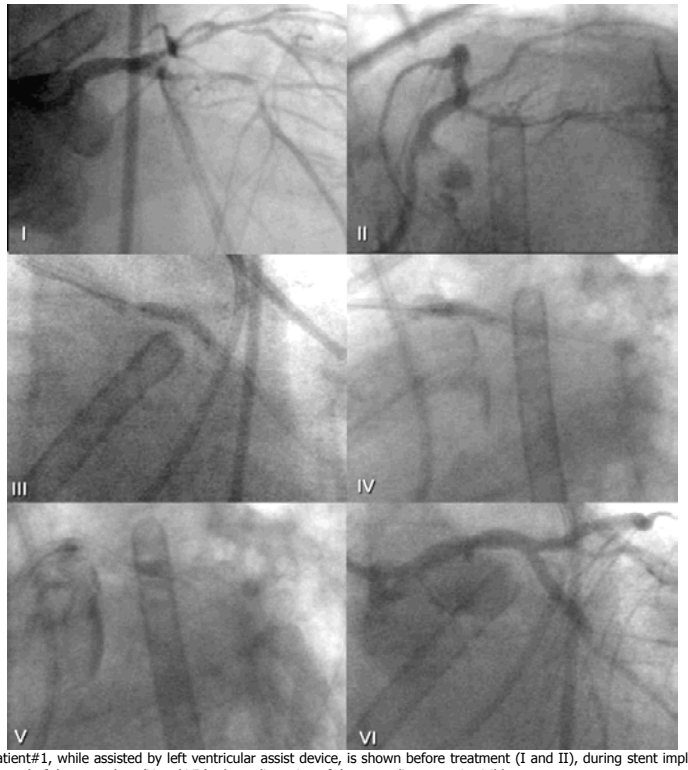
Discussion

With a total population of 340 patients, this report represents the biggest series of patients undergoing unprotected and elective LMCA intervention ever reported. In addition, by limiting our observations to only those patients undergoing DES-supported intervention, the current survey may represent a benchmark study for future randomized trials.

The main findings of this survey may be summarized as follows:

1) The overall mortality rate after LMCA intervention with unrestricted use of DES appears to be in the range of 4% at one year, which drops to 2.3% when the

Figure 1



Index procedure in patient#1, while assisted by left ventricular assist device, is shown before treatment (I and II), during stent implantation in the LMCA (III and IV) and at the end of the procedure (V and VI) where dissection of the ascending aorta is visible.

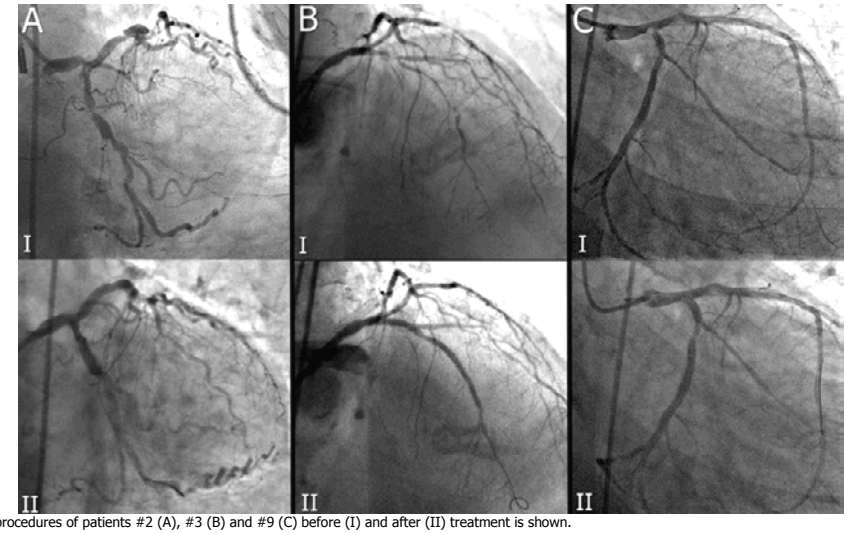
cardiac mortality alone is considered. The observations that non-cardiac mortality may significantrly contribute to total mortality is not an unexpected finding. Patients included in the current survey, in line with what is recommended by current guidelines, have major contraindications to surgery often due to the presence of relevant comorbities; they may play a role in explaining long-term survival in this patient population almost as much as LMCA disease does. This notion needs to be considered in planning future investigations comparing percutaneous versus surgical LMCA treatment, where patients with serious concomitant disease, in order to be eligible to both treatments, have necessarily to be excluded so that the overall and non-cardiac mortality might be correspondingly lower in such a setting.

2) The rate of sudden death in our series of patients was below 1%. Importantly, our data do not support the idea that SD may be causally connected to in-stent restenosis. One case of SD occurred 8 days after treatment, while the second case occurred 3 months after intervention immediately after the discontinuation of antiplatelet therapy. The temporal relationship with intervention in the first case and awareness that anti-platelet treatment discontinuation is the biggest predictor of early and late stent thrombosis in the DES era [7], argue in favor of stent thrombosis as the most likely mechanism of SD in our cohort of patients.

3) The rate of stent thrombosis appeared to be in the range of 1% in the worst possible scenario, where confirmed or suspected thrombotic events were pooled. This finding favorably compares to the rate of stent thrombosis in the BMS era and does not seem to differ from what was previously reported in consecutive series of patients undergoing liberal DES-supported intervention[7, 8].

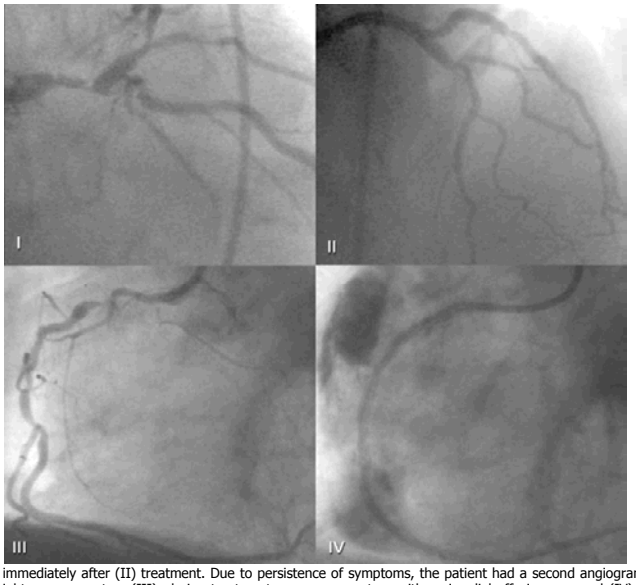
4) A clear clustering of fatal and non-fatal hard adverse events in the first three months after treatment was noted, with a 50% decrease in death or MI form 3 to 6 months, which appeared to stabilize thereafter, at least until 12 months. This drop of major adverse events after three months is in full agreement with what previously reported in the BMS era[2]. As previously discussed, this was interpreted as the hazard of developing in-stent restenosis after LMCA treatment. This speculation was supported by the notion that intimal hyperplasia after BMS is known to peak 14-16 weeks after intervention. The finding that after DES implantation the same

Figure 2.



Index procedures of patients #2 (A), #3 (B) and #9 (C) before (I) and after (II) treatment is shown.

Figure 3.

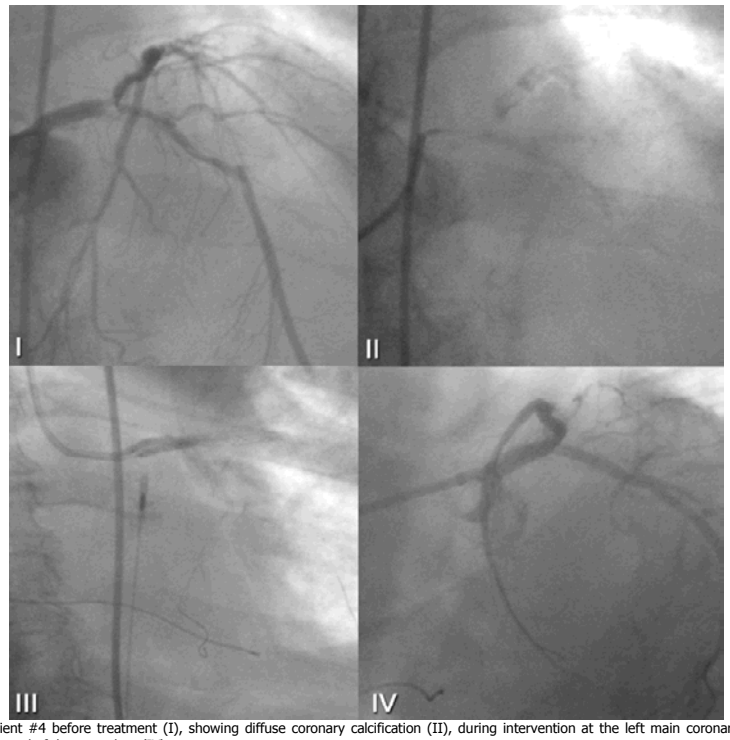


Patient #8 before (I) and immediately after (II) treatment. Due to persistence of symptoms, the patient had a second angiogram at follow-up showing a significant disease in the right coronary artery (III), during treatment a coronary rupture with pericardial effusion occurred (IV). The patient was sent to emergent surgery but died soon afterwards

clustering of adverse events persists in the first months after treatment, offers the unique possibility to challenge previous beliefs about the malignant role of intima hyperplasia in this cohort of patients. In the longest available angiographic follow-up after drug eluting stent implantation, neointimal growth has been shown to mildly non-significantly progress even beyond one year[9].

Recently, Wessely et al. reported on two patients treated with sirolimus-eluting stent in the left anterior descending artery and right coronary artery who presented at 13 and 19 months, respectively, with recurrence of symptoms and angiographically confirmed in-stent restenosis. Of note, both patients had undergone previous coronary angiogram at 7 –month which showed

Figure 4.



Angiogram of patient #4 before treatment (I), showing diffuse coronary calcification (II), during intervention at the left main coronary artery (III) and immediately at the end of the procedure (IV).

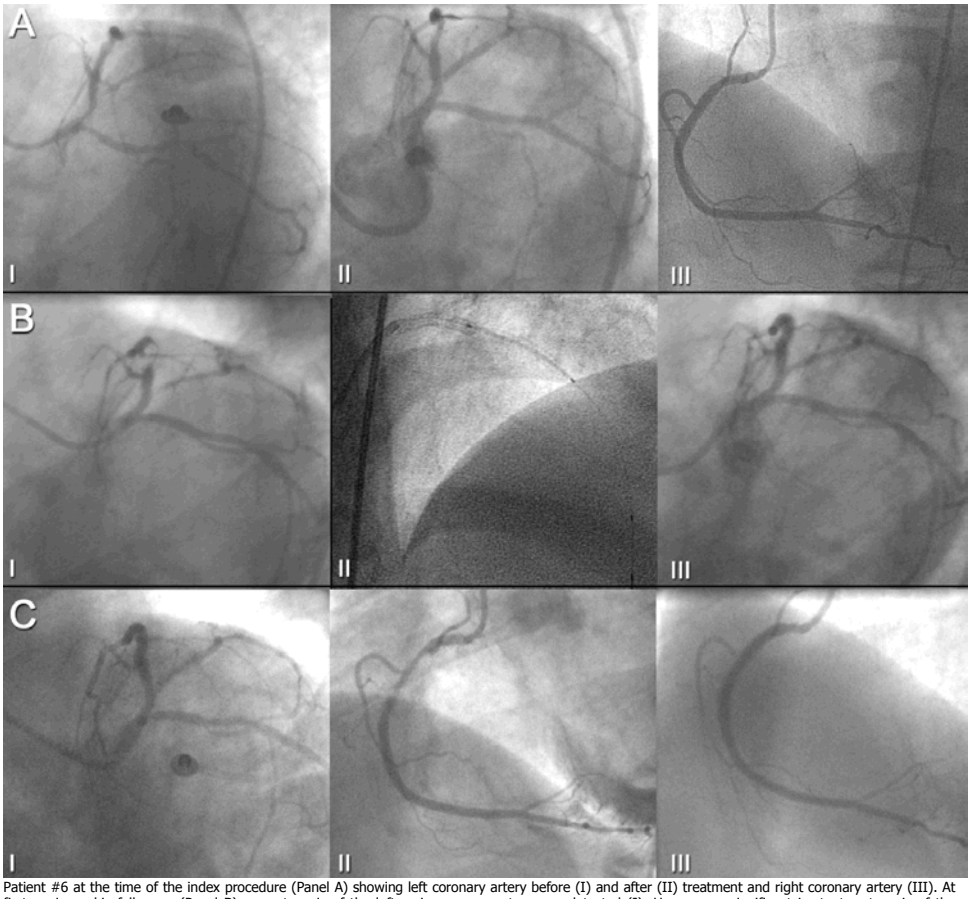
no evidence of intima growth at that stage[10]. Finally, in 15 patients who underwent treatment with DES for LMCA disease at the thoraxcenter, serial angiographic follow-up at 6 and 12 months after the index procedure was recently carried out. Of note, the late loss which was observed at 6 months [median (IQR): 0.29 (0.07-0.4] doubled at 1 year [0.63 (0.37-0.76), p<0.001], with two patients presenting with mild intima hyperplasia at 6 months who developed late in stent restenosis at 1 year (*JACC, in press*).

Thus, current evidence confirms the notion that intimal hyperplasia after DES implantation may be much more delayed with respect to what was observed in the BMS era. Of note, even after LMCA intervention with DES, the same clustering of adverse events in the first few months afterwards, as it has previously reported in BMS treated patients, seems to occur according to the present survey. Thus, when taken together, available data may argue in favor of mechanisms different from intimal hyperplasia as putative explanation for the different rate of death or MI over time in this patient population.

5) In those patients who refused to undergo angiographic follow-up (n=65), no increase of adverse events was noted in the current survey. Notably, no fatal or non fatal major adverse event occurred in this group of patients. We cannot rule out the possibility that these findings may be subject to a considerable selection bias. Ideally, a randomized prospective study allocating consecutive LMCA treated patients to protocol-mandated angiographic surveillance versus conservative management would be in demand to evaluate the safety of avoiding systematic angiographic examination in this cohort of patients. However, the present study does not support the previous recommendation that routine angiographic surveillance seems to be mandatory in LMCA patients undergoing percutaneous treatment. The fact that early angiographic control may underestimate the real incidence of in-stent restenosis, coupled with the potential hazard to undergo multiple angiographic examinations over time should not be neglected if current recommendation to obtain multiple early angiograms in this patient population is followed.

In conclusion, based on the largest series of patients undergoing unprotected and elective LMCA intervention ever reported, current study shows that in this cohort of patients i) the rate of SD, cardiac death and stent thrombosis favorably compares to what reported in patients receiving treatment for non-LMCA lesions, ii) in this patient population at high surgical risk, the contribution of non-cardiac death to overall mortality may be substantial, iii) a clustering of adverse events in the first months after treatment, as was in the BMS era, could be confirmed in patients receiving DES implantation. This finding, coupled with the rising notion that the peak of intima hyperplasia may be much delayed

Figure 5.



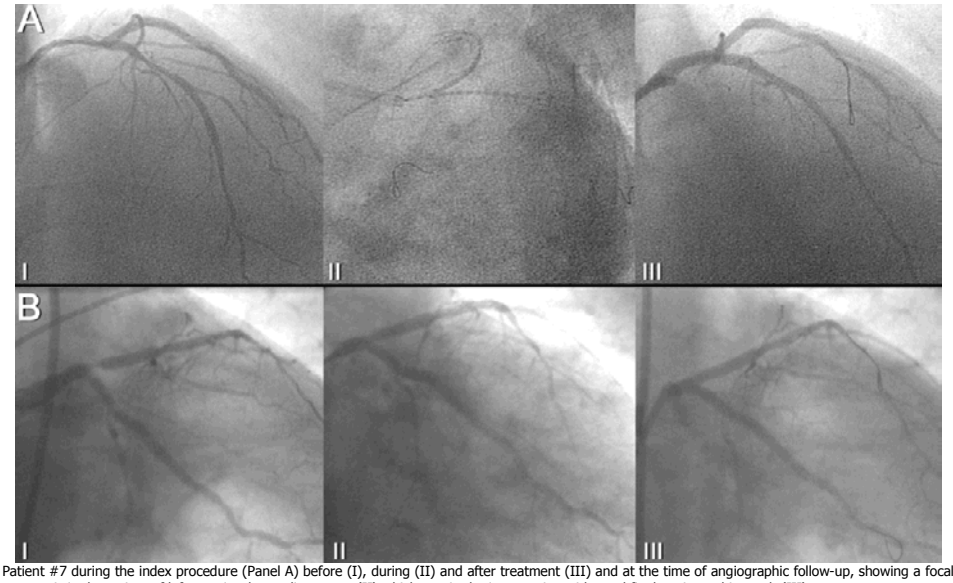
Patient #6 at the time of the index procedure (Panel A) showing left coronary artery before (I) and after (II) treatment and right coronary artery (III). At first angiographic follow-up (Panel B) no restenosis of the left main coronary artery was detected (I). However, a significant in-stent restenosis of the proximal left anterior descending artery required reintervention (II) with excellent final angiographic result (III). At the second angiographic follow-up (Panel C), there was not detectable restenosis in the left coronary artery (I) while a progression of disease in the mid tract of the right coronary artery (II) required reintervention (III).

after DES with respect to BMS and that no safety concern emerged in the current analysis in those patients refusing to undergo angiographic control, may suggest that postponing angiographic follow-up beyond the conventional 6 months does not affect the outcome of these patients, while this would allow to monitor the vessel status when the intimal growth has more probably ceased and the net lumen gain is likely to be maintained over time.

There remains considerable uncertainty, however, around the need to perform or not a mandatory angiographic control in patients undergoing LMCA intervention. Thus, no clear recommendation can be made in this setting. We cannot exclude the possibility that in selected patient subsets "malignant" early intimal hyperplasia takes place which may contribute to explain the clustering of adverse events in the first few months after treatment.

In conclusion, our survey shows that in patients undergoing elective intervention with DES for unprotected LMCA stenosis, the short and mid-term outcome is favourable. The great majority of major observed cardiac events occurred in the first few months after treatment, while at the time when intima hyperplasia is expected to peak (beyond 6 months) there was no detectable increase of death or myocardial infarction. Prospective randomized controlled investigations are in demand in order to evaluate the safety to avoid systematic angiographic surveillance in this group of patients.

Figure 6.



Patient #7 during the index procedure (Panel A) before (I), during (II) and after treatment (III) and at the time of angiographic follow-up, showing a focal restenosis in the ostium of left anterior descending artery (II) which required reintervention with good final angiographic result (III).

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Chapter 8. Distal left main coronary disease is a major predictor of outcome in patients undergoing percutaneous intervention in the drug eluting stent era. An integrated clinical and angiographic analysis based on the RESEARCH and T-SEARCH registries

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Distal Left Main Coronary Disease Is a Major Predictor of Outcome in Patients Undergoing Percutaneous Intervention in the Drug-Eluting Stent Era

An Integrated Clinical and Angiographic Analysis Based on the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) and Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) Registries

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OBJECTIVES This study sought to investigate whether the anatomical location of the disease carries prognostic implications in patients undergoing drug-eluting stent (DES) implantation for the left main coronary artery (LMCA) stenosis.

BACKGROUND Liberal use of DES, compared with a bare metal stent (BMS), has resulted in an improved outcome in patients undergoing LMCA intervention. However, the overall event rate in this subset of patients remains high, and alternative tools to risk-stratify this population beyond conventional surgical risk status would be desirable.

METHODS From April 2002 to June 2004, 130 patients received DES as part of the percutaneous intervention for LMCA stenoses in our institution. Distal LMCA disease (DLMD) was present in 94 patients. They were at higher surgical risk and presented with a greater coronary disease extent compared with patients without DLMD.

RESULTS After a median of 587 days (range 368 to 1,179 days), the cumulative incidence of major adverse cardiac events (MACE) was significantly higher in patients with DLMD at 30% versus 11% in those without DLMD (hazard ratio [HR] 3.42, 95% confidence interval [CI] 1.34 to 9.7; p = 0.007), mainly driven by the different rate of target vessel revascularization (13% and 3%; HR 6, 95% CI 1.2 to 29; p = 0.02). After adjustment for confounders, DLMD (HR 2.79,95% CI 1.17 to 8.9; p = 0.032) and surgical risk status (HR 2.18,95% CI 1.06 to 4.5; p = 0.038) remained independent and complementary predictors of MACE.

CONCLUSIONS Distal LMCA disease carries independent prognostic implications, and it may help in selecting the most appropriate patient subset for LMCA intervention beyond the conventional surgical risk status in the DES era. (J Am Coll Cardiol 2006;47:1530–7) © 2006 by the American College of Cardiology Foundation

Routine implantation of drug-eluting stents (DES), by reducing the need for target vessel revascularization (TVR) and angiographic restenosis, recently has been shown to favorably affect outcome compared with bare-metal stents (BMS) in patients undergoing percutaneous left main coronary artery (LMCA) intervention (1–3). However, the rate of major cardiovascular events in the DES era remains high in the first series of patients reported (1,3). Catheter-based LMCA treatment is today mainly reserved for poor surgical candidates, which may at least partially explain the high rate of adverse events observed in this patient population. This hypothesis is based on the ability of surgical risk scores to predict both short-term and long-term outcomes in this subset of patients (1,4).

The identification of novel independent predictors of outcome beyond surgical risk status would further expand our capability to risk-stratify this patient population.

In particular, a clinical or angiographic parameter able to differentiate outcomes between percutaneous LMCA treatment and surgical revascularization would be highly desirable. This might help in selecting the appropriate subset of patients with LMCA disease in whom catheter-based treatment would be indicated, independent of surgical risk status (5).

Observational studies in the BMS era identified the distal location of the disease within the LMCA anatomy as a possible determinant of restenosis in patients undergoing

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Abbreviations and Acronyms

BMS = bare-metal stent
DES = drug-eluting stent
DLMD = distal left main disease
LMCA = left main coronary artery
MACE = major adverse cardiac events
MI = myocardial infarction
MLD = minimal luminal diameter
SES = sirolimus-eluting stent
TIMI = Thrombolysis In Myocardial Infarction
TVR = target vessel revascularization

percutaneous treatment of the LMCA (6). However, other investigators have not confirmed this observation (7,8), and whether this holds true in the DES era remains largely unknown.

The treatment of distal left main disease (DLMD) is offset by the need to handle the bifurcation between LMCA and the main proximal left coronary branches. The treatment of such a lesion, even with the use of DES, may remain challenging (9).

Therefore, the purpose of the present study was to investigate the clinical and angiographic outcomes of DLMD treatment in patients undergoing percutaneous revascularization in the DES era.

METHODS

Study design and patient population. Since April 16, 2002, sirolimus-eluting stent (SES) implantation (Cypher, Johnson & Johnson-Cordis unit, Warren, New Jersey) have been used as a default strategy for every percutaneous coronary intervention at our institution as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. From the first quarter of 2003, paclitaxel-eluting stents (Taxus, Boston Scientific, Natick, Massachusetts) became commercially available, replacing SES as the stent of choice in every percutaneous coronary intervention, as part of the Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registry. As a policy, all elective patients presenting with significant (>50% by visual estimation) LMCA disease referred to our institution for coronary revascularization are evaluated both by interventional cardiologists and by cardiac surgeons, and the decision to opt for percutaneous coronary intervention or surgery is reached by consensus, as previously described (1).

From April 16, 2002, to June 28, 2004, a total of 130 consecutive patients were treated exclusively with one or more DES in the LMCA as part of an elective or nonelective revascularization procedure and constitute the patient population of the present report. Fifty-five patients in the first cohort received exclusively SES, which were available at that time in diameters from 2.25 to 3.00 mm, whereas in the next group of 75 patients, paclitaxel-eluting stents—available in diameters from 2.25 to 3.5 mm—were implanted.

To stratify the study population into high surgical risk and low surgical risk groups, the Parsonnet surgical risk score was calculated for each patient (10). A score of >15 was used to identify patients at high risk as previously suggested (4,11). Protected LMCA segment was defined by the presence of at least one patent arterial or venous conduit to at least one left coronary segment. Nonelective treatment was defined as a procedure carried out on referral before the beginning of the next working day (12).

This protocol was approved by the hospital ethics committee and is in accordance with the Declaration of Helsinki. Written informed consent was obtained from every patient.

Procedures and post-intervention medications. All interventions were performed according to current standard guidelines. The final interventional strategy, including the use of glycoprotein IIb/IIIa inhibitors, was entirely left to the discretion of the operator, except for the stent use. 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. Angiographic success was defined as residual stenosis <30% by visual analysis and the presence of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3. All patients were advised to maintain aspirin

Table 1. Baseline Characteristics of the Study Population

Variables	Distal LMCA Disease (n = 94)	Nondistal LMCA Disease (n = 36)	p Value
Age (yrs)*	65 ± 12	61 ± 12	0.09
Male (%)*	63	72	0.64
Body mass index*	24 ± 4	24 ± 3	0.50
Diabetes (%)*	27	22	0.83
Hypertension (%)*	63	47	0.41
Hypercholesterolemia (%)	65	61	0.87
Current smokers (%)	19	25	0.64
Creatinine (μmol/l)*	101 ± 72	89 ± 25	0.32
LV ejection fraction (%)*	44 ± 16	46 ± 14	0.42
Medical history (%)			
Protected left main	14	14	>0.99
PCI	31	22	0.53
Myocardial infarction	39	47	0.60
TIA/stroke	10	8	>0.99
Heart failure*	15	17	>0.99
COPD severe*†	7	5	>0.99
Peripheral arterial disease*	22	16	0.63
Carotid artery disease*	9	5	0.71
Clinical presentation (%)			
Stable angina	53	47	0.86
Unstable angina	32	36	0.90
Acute myocardial infarction*	15	17	0.95
Cardiogenic shock at entry*	7	8	>0.99
Parsonnet score	18 ± 13	14 ± 10	0.048

*Parameters included in the Parsonnet classification. †Resulting in functional disability, hospitalization, requiring chronic bronchodilator therapy or FEV1 <75% of predicted (10).

COPD = chronic obstructive pulmonary disease; LMCA = left main coronary artery disease; LV = left ventricular; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

lifelong, and clopidogrel was prescribed for 6 months in both groups.

End point definitions and clinical follow-up. Distal LMCA disease was defined as significant lumen obstruction (>50%) at visual estimation occupying the third distal area of the LMCA shaft with the entire lesion or part of it either directly involving the ostium of the left anterior descending and/or circumflex artery or in close contact with at least one of them. The primary outcome was the occurrence of major adverse cardiac events, defined as: 1) death, 2) nonfatal myocardial infarction, or 3) target vessel revascularization. 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. Target vessel revascularization was defined as a repeat intervention (surgical or percutaneous) to treat a luminal stenosis in the stent or within the adjacent 5-mm segments adjacent to the stent, including the ostium of the left anterior descending artery and/or circumflex artery. Information about in-hospital outcomes was obtained from an electronic clinical database for patients maintained at our institution and by review of hospital records for those discharged to referring hospitals (patients were referred from a total of 14 local hospitals). Post-discharge survival status was obtained from the Municipal Civil Registries. Data on occurrence of myocardial infarction (MI) or repeat interventions at follow-up were collected by consultation of our institutional electronic database, by contacting referring institutions, and from all living patients.

Quantitative angiographic analysis. Quantitative analyses of all angiographic data were performed with the use of edge-detection techniques (CAAS II, Pie Medical, Maastricht, the Netherlands). A value of 0 mm was assigned for the minimum luminal diameter (MLD) in cases of total occlusion at baseline or follow-up. Binary restenosis was defined as stenosis of more than 50% of the luminal diameter in the target lesion. Acute luminal gain was defined as the MLD after the index procedure minus the MLD at baseline angiography. Late loss was defined as the MLD immediately after the index procedure minus the MLD at angiographic follow-up. Net luminal gain was defined as the difference between MLD at follow-up and MLD before the procedure. Quantitative angiographic measurements of the target lesion were obtained in-stent and in-lesion (including the stented segment as well as the margins 5 mm proximal and distal to the stent).

Statistical analysis. Because the T-SEARCH is an ongoing registry at out institution, the selection of the cohort of

Table 2. Procedural and Angiographic Characteristics of the Study Population

Variables	Distal LMCA Disease (n = 94)	Nondistal LMCA Disease (n = 36)	p Value
Pure LMCA disease (%)	0	19	0.0002
LMCA plus 1-vessel disease (%)	12	25	0.12
LMCA plus 2-vessel disease (%)	20	22	0.82
LMCA plus 3-vessel disease (%)	54	33	0.22
Bifurcation lesion classification (%)			
Isolate distal LMCA stenosis	11	–	–
Distal LMCA plus ostial LAD or CFX	40	–	–
Distal LMCA plus both LAD/CFX ostia	49	–	–
Right coronary artery >70% stenosis (%)	69	64	0.21
Right coronary artery occlusion (%)	17	22	0.63
Number of implanted stents	1.65 ± 0.65	1.22 ± 0.42	0.0003
Main branch/bifurcation stenting (%)	51/49	89/11	0.005
Culotte/T-stent/Crush/V-stent (%)*	37/33/17/13	50/25/25/0	0.29
Nominal stent diameter (mm)	3.19 ± 0.28	3.26 ± 0.37	0.22
Total stent length per patient (mm)	29 ± 13	18 ± 13	<0.0001
SES/PES (%)	37/63	42/58	0.63
Pre-dilation (%)	73	70	>0.99
Cutting balloon (%)	3	14	0.05
Rotational atherectomy (%)	0	5	0.08
Post-dilation (%)	79	75	0.88
Bigger balloon inflated (mm)	3.66 ± 0.46	3.87 ± 0.47	0.025
Maximal pressure (atm)	18 ± 3	17.8 ± 3	0.67
Intravascular ultrasonography (%)	20	47	0.045
Glycoprotein IIb/IIIa inhibitors (%)	34	36	0.85
Intra-aortic balloon pump (%)	20	18	>0.99
Left ventricle assist device (%)	2	6	0.32
Temporary pacing during procedure (%)	7	9	>0.99

*Referred to the total number of patients treated with bifurcation stenting.

CFX = circumflex artery; LAD = left anterior descending artery; PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent; other abbreviations as in Table 1.

patients for the present report was based on the following criteria: a minimum follow-up time of 1 year, and an expected major adverse cardiac events (MACE) rate of 10% in the group of patients without DLMD with a 3× event rate increase in the DLMD, based on previous findings (1), with alpha and beta errors of 5% and 20%, respectively.

Continuous variables are shown as mean ± SD and were compared using the Student unpaired *t* test. Categorical variables are presented as counts and percentages and are compared with the Fisher Exact test. Survival curves were generated by the Kaplan-Meier method, and survival among groups was compared using the log-rank test. Cox proportional hazards models were used to assess risk reduction of adverse events. Multivariable analysis, considering all variables reported in Tables 1 and 2 with a p value of <0.10, was performed to adjust for possible confounders and to identify whether DLMD was an independent predictor of adverse events. Probability was significant at a level of <0.05. All statistical tests were two-tailed. Statistical analysis was performed on Statistica 6.1 (Statsoft Inc., Tulsa, Oklahoma).

RESULTS

Baseline and procedural characteristics. Baseline and procedural characteristics of the patient population, stratified into LMCA disease location, are shown in Tables 1 and 2. Patients with DLMD tended to be older and presented with an overall higher Parsonnet surgical risk score compared with those without DLMD. Similarly, coronary artery disease extent, number of stents, and total stent length were greater and the use of intravascular ultrasound was less than in DLMD patients. In one patient per group, both presenting with acute myocardial infarction, procedural success was not obtained because of TIMI flow grade <3 after stenting.

Clinical outcome based on left main disease location. At 30 days, there was no difference in clinical outcome between patients with and without DLMD, considering either the whole population, those receiving an elective intervention, or those at low surgical risk according to the Parsonnet score (Table 3). Overall, no documented thrombotic stent occlusion occurred in the first 30 days or thereafter.

After a median follow-up of 587 days (range 368 to 1,179 days; 577 days [range 368 to 1,156 days] in the DLMD group vs. 598 days [range 398 to 1,179 days] in the group without DLMD, p = 0.56), the cumulative incidence of MACE (death, MI, or TVR) was significantly higher in patients with DLMD (30% vs. 11% in those without DLMD; hazard ratio [HR] 3.42, 95% confidence interval [CI] 1.34 to 9.7; p = 0.007) (Fig. 1A). The composite death/MI was 17% in the DLMD group and 8% in patients without DLMD (HR 2.11, 95% CI 0.45 to 10; p = 0.34), whereas the cumulative incidence of TVR was 13% versus 3% in patients with and without DLMD (HR 6, 95% CI 1.2 to 29; p = 0.02) (Fig. 1B).

Table 3. 30-Day Outcomes

Variables	Distal LMCA Disease	Nondistal LMCA Disease	p Value*
Whole population	(n = 94)	(n = 36)	
Death, n (%)	7 (7)	3 (8)	>0.99
Nonfatal MI, n (%)	4 (4)	0 (0)	0.57
Death or nonfatal MI, n (%)	11 (12)	3 (8)	0.76
TVR, n (%)	0 (0)	1 (3)‡	0.28
Any event, n (%)	11 (12)	4 (11)	>0.99
Stent thrombosis, n (%)†	0 (0)	0 (0)	>0.99
Elective population	(n = 71)	(n = 33)	
Death, n (%)	1 (1)	2 (6)	0.25
Nonfatal MI, n (%)	4 (6)	0 (0)	0.32
Death or nonfatal MI, n (%)	4 (6)	2 (6)	0.11
TVR, n (%)	0 (0)	1 (3)‡	0.31
Any event, n (%)	4 (6)	3 (9)	0.68
Stent thrombosis, n (%)†	0 (0)	0 (0)	>0.99
Low-surgical-risk population	(n = 47)	(n = 22)	
Death, n (%)	0 (0)	0 (0)	>0.99
Nonfatal MI, n (%)	1 (2)	0 (0)	>0.99
Death or nonfatal MI, n (%)	1 (2)	0 (0)	>0.99
TVR, n (%)	0 (0)	1 (4)‡	0.32
Any event, n (%)	1 (2)	1 (4)	0.54
Stent thrombosis, n (%)†	0 (0)	0 (0)	>0.99

*By Fisher exact test. †Angiographically documented. ‡In a patient with calcified ostium of the left main coronary artery (LMCA), a residual ≈50% stenosis despite use of cutting balloon and rotablator justified elective surgical revascularization.
MI = myocardial infarction; TVR = target vessel revascularization.

In the elective patient population (106 patients overall, 73 in the DLMD group), the cumulative incidence of MACE remained greater in the DLMD subgroup (26%) compared with those without DLMD (9%; HR 3.59, 95% CI 1.23 to 12.1; p = 0.01) (Fig. 1C). The composite of death/MI was 11% in patients with and 6% in those without DLMD (HR 2.48, 95% CI 0.7 to 8.5; p = 0.35), whereas the need for TVR was 15% and 3% in the two groups, respectively (HR 6.1, 95% CI 1.6 to 21; p = 0.02) (Fig. 1C). Even after excluding patients receiving protected intervention, the MACE rate remained higher in patients with compared with those without DLMD (HR 3.1, 95% CI 1.08 to 9.1; p = 0.01).

Complex bifurcation stenting was more common in the DLMD subgroup. However, the technique of stent deployment in itself failed to affect outcome, with a MACE rate of 31% in DLMD patients undergoing stenting of the main branch versus 28% in those treated with bifurcation stenting (HR 0.96, 95% CI 0.46 to 1.49; p = 0.92).

Patients at high surgical risk according to the Parsonnet score had a higher MACE rate compared with those at low risk, confirming previous findings (Fig. 2A).

To explore the additive prognostic value of combining the anatomical location of LMCA disease and surgical risk status, Kaplan-Meier curves were constructed according to the four combinations generated by having distal or nondistal LMCA disease and being at high or low surgical risk. As shown in Figure 2, the cumulative event rate in the group of patients affected by nondistal LMCA disease with low surgical risk was 10-fold lower (4%) than that observed in surgical high-risk patients with DLMD (40%, p = 0.002).

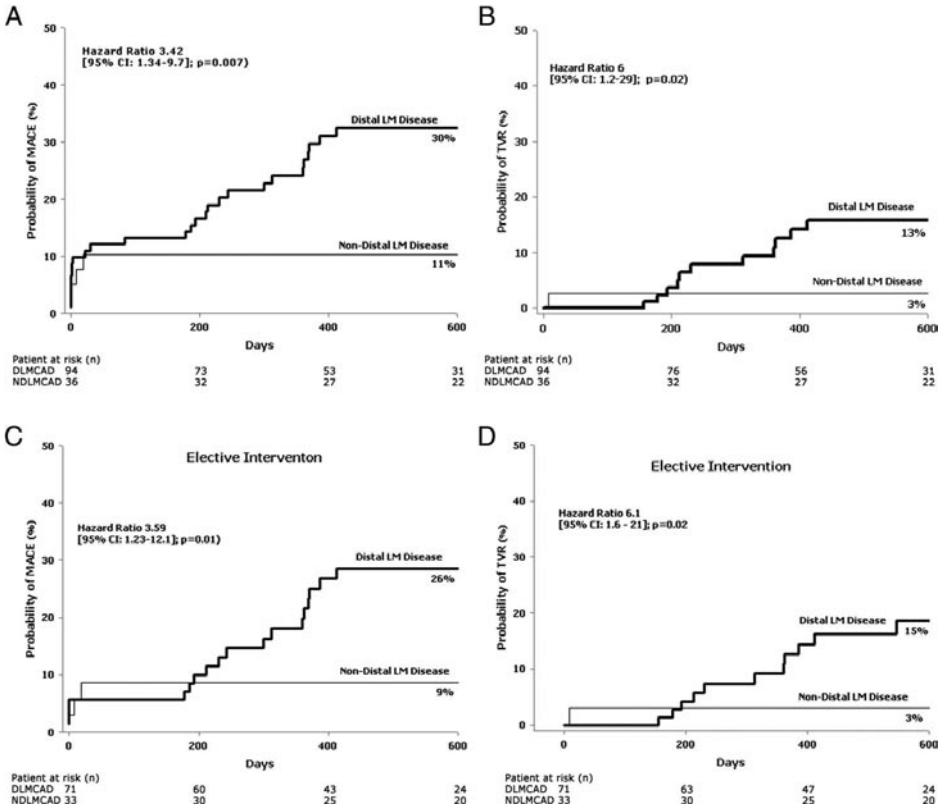

Figure 1. Adverse events in patients treated for distal left main coronary artery (LMCA) disease (DLMD) as compared with patients treated for nondistal LMCA disease (NDLMD). Cumulative risk of major adverse cardiac events (MACE) **(A)** and target vessel revascularization (TVR) **(B)** in the whole population, and cumulative risk of MACE **(C)** and TVR **(D)** in the elective population.

Surgical high-risk status seemed to stratify patients at greater probability of early events independent of the anatomical location of LMCA disease, whereas DLMD identified patients at higher risk for late events irrespective of surgical risk.

Multivariable analysis. After adjustment for Parsonnet risk score (which includes age), the extent of coronary disease, number of deployed stents, post-procedural minimal lumen diameter, bigger balloon inflated, and use of intravascular ultrasound at multivariable Cox regression analysis, DLMD remained an independent predictor of MACE (HR 2.79, 95% CI 1.17 to 8.9; p = 0.032) independent of surgical risk status (assessed as high risk versus low risk; HR 2.18, 95% CI 1.06 to 4.5; p = 0.038). The estimates of these two covariates remained unchanged if: 1) treatment technique (main branch vs. bifurcation stenting) or 2) treatment technique but not number of deployed stents—to check for possible colinearity between these two variables—were introduced in the model.

No statistical interaction emerged between the anatomical location of LMCA disease and the surgical risk with respect to MACE (p = 0.3).

Quantitative angiographic analysis. Seventy-one patients in the DLMD group (84% of eligible patients) and 28 patients without DLMD (85% of eligible patients) underwent eight-month angiographic follow-up (p > 0.99). Quantitative coronary angiography analysis is reported in Table 4. As shown, despite a similar LMCA reference vessel diameter, patients with DLMD location tended to have a longer lesion length and a slightly smaller MLD. In-stent and in-segment acute luminal gain seemed to be similar in the two groups, whereas late loss was almost double in the DLMD group. Thus, in-stent and in-segment

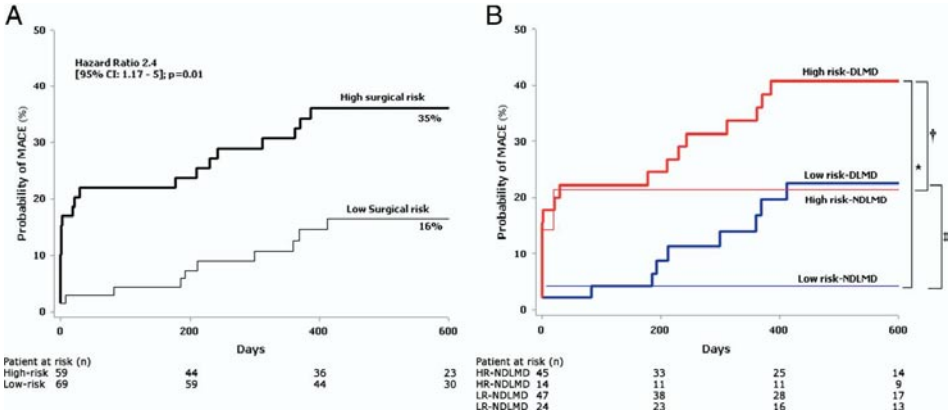

Figure 2. Cumulative risk of major adverse events in patients with high surgical risk (Parsonnet score >15) as compared with that of patients at low surgical risk (Parsonnet score <15) **(A)**, and in patients at high surgical risk affected by DLMD as compared with that of patients at high surgical risk and NDLMD, low surgical risk and DLMD, and low surgical risk and NDLMD **(B)**. *p = 0.002; †p = 0.048; ‡p = 0.066. Abbreviations as in Figure 1.

net luminal gain was significantly lower in patients with as compared with those without DLMD.

DISCUSSION

The percutaneous treatment of LMCA disease is a challenging task, with historical event rates often reported to be unacceptably high (4,13,14). The advent of BMS has not been regarded as a major breakthrough in the percutaneous treatment of such lesions (15) because the occurrence of in-stent restenosis was believed to be associated with fatalities (4,13). Recently, the liberal use of DES to treat LMCA has been shown to favorably affect outcome compared with the use of BMS (1–3). However, the rate of major cardiovascular events in the DES era remains high in some of the first series of patients reported (1,3).

Whether the percutaneous treatment of LMCA should be strictly reserved for poor surgical candidates or offered with less restriction to patients known to be at low risk for future MACE remains highly debated (5). Ideally, risk factors able to differentiate outcomes between those undergoing catheter-based LMCA treatment and those receiving surgical revascularization might help in selecting the most appropriate revascularization strategy. Anatomical characteristics of the LMCA lesion have great potential in this regard because they may theoretically influence the percutaneous but not the surgical revascularization technique. Some early observational studies in the BMS era identified distal location of the disease with respect to LMCA anatomy as a major determinant of restenosis in patients receiving percutaneous treatment of the LMCA (6). Similarly, we and other groups have reported that the great majority of lesions, which undergo TVR at follow-up, are located in the distal tract of the LMCA (1,3,16).

The main finding of our investigation is that the long-term outcome of patients undergoing percutaneous treatment for DLMD is significantly worse compared with that of patients treated for LMCA lesions not located in the distal tract. Interestingly, this remained true in both elective and low-surgical-risk groups. The procedural success rate along with the short-term (30 days) outcome was remarkably similar between the two groups, whereas the difference between patients with and without DLMD emerged at long-term follow-up, mainly driven by a higher need for TVR in the former group. Despite the lack of statistical significance, the composite of death and nonfatal MI was consistently two times higher in the DLMD group, both in the total cohort of patients (17% vs. 8% in the non-DLMD group, p = 0.34) and after selection for elective cases only (11% vs. 6.% in the non-DLMD group, p = 0.35). Whether these results on death and MI reflect a type II error or a chance finding remains unclear.

Our multivariable model, based on all possible confounders of clinical outcome, showed that DLMD is an independent predictor of poor outcome in this subset of patients, with an adjusted risk for MACE of almost three-fold higher than that for non-DLMD at long-term follow-up.

To further rule out the possibility that treatment technique, more than the anatomical location of the disease, was responsible for the difference in long-term outcomes between patients with and without DLMD, the MACE rate in patients receiving bifurcation stenting was compared with that in patients undergoing single-vessel stenting in the DLMD subgroup. The MACE rate was remarkably similar between these two groups of patients, supporting the hypothesis that the anatomical location of the LMCA disease more than the techniques

Table 4. Quantitative Coronary Angiography in the Main Stented Branch

Variables	Distal LMCA Disease (n = 71)	Nondistal LMCA Disease (n = 28)	p Value
Before procedure			
RVD (mm)	3.10 ± 0.59	3.29 ± 0.71	0.52
MLD (mm)	1.18 ± 0.62	1.38 ± 0.65	0.17
Diameter stenosis (%)	61 ± 21	56 ± 17	0.35
Lesion length (mm)	9.8 ± 3.8	8.5 ± 5.3	0.18
After procedure			
In-stent			
RVD (mm)	3.00 ± 0.58	3.17 ± 0.56	0.25
MLD (mm)	2.63 ± 0.46	2.89 ± 0.54	0.028
Acute luminal gain (mm)*	1.46 ± 0.7	1.5 ± 0.89	0.80
Diameter stenosis (%)	12 ± 9.5	8.3 ± 8	0.12
In-lesion			
RVD (mm)	2.88 ± 0.6	2.99 ± 0.55	0.25
MLD (mm)	2.27 ± 0.51	2.68 ± 0.61	0.0021
Acute luminal gain (mm)*	1.11 ± 0.79	1.28 ± 0.9	0.37
Diameter stenosis (%)	12.87 ± 9.9	10.8 ± 9.3	0.35
Follow-up			
In-stent			
RVD (mm)	2.99 ± 0.66	3.08 ± 0.58	0.54
MLD (mm)	2.20 ± 0.71	2.65 ± 0.62	0.007
Diameter stenosis (%)	24 ± 22	14 ± 12	0.03
Late loss (mm)†	0.42 ± 48	0.23 ± 0.28	0.01
Net luminal gain (mm)§	1.03 ± 53	1.27 ± 0.61	0.032
Binary restenosis, no. (%)‡	9 (13)	0 (0)	0.18
In-lesion			
RVD (mm)	2.93 ± 0.63	3.00 ± 0.69	0.69
MLD (mm)	2.01 ± 0.68	2.51 ± 0.62	0.00237
Diameter stenosis (%)	24 ± 22	16 ± 12	0.089
Late loss (mm)†	0.25 ± 0.52	0.15 ± 0.34	0.09
Net luminal gain (mm)§	0.85 ± 0.58	1.13 ± 0.6	0.02
Binary restenosis, no. (%)‡	8 (11)	0 (0)	0.19

*Difference between MLD after procedure and MLD before procedure. †Difference between MLD at follow-up and MLD after procedure. ‡All restenoses were focal (length <10 mm). §Difference between MLD at follow-up and MLD before the procedure.

LMCA = left main coronary artery; MLD = minimal lumen diameter; RVD = reference vessel diameter.

used to treat it was responsible for the higher overall event rate in the DLMD group.

In the quantitative angiographic analysis, the late loss was higher, the acute luminal gain was lower, and the binary restenosis rate also tended to be higher in the DLMD group, which provides a possible mechanistic explanation for our clinical findings.

Finally, to investigate the prognostic power of DLMD in relation to surgical risk status, Kaplan-Meier curves were constructed according to the four combinations generated by having distal or nondistal LMCA disease and being at high or low surgical risk. Surgical risk status seemed to stratify patients at a greater probability of events independent of the anatomical location of LMCA disease, whereas DLMD identified patients at a higher risk for poor prognosis irrespective of surgical risk. Of note is that the surgical risk status seemed to better risk-stratify patients according to early events, with survival curves running parallel after the first month of treatment. Conversely, DLMD identified patients with a higher event rate at follow-up, with the two survival curves diverging at around 180 days after the procedure. Interestingly, we failed to identify a statistical interaction between surgical risk status and the location of LMCA disease in our patient population, which implies that the risk associated with DLMD is additive—not multiplicative—with respect to that of being at high surgical risk status. This further confirms that the two currently used approaches for risk stratification, namely surgical risk status and anatomical location of the disease, are independent and possibly complementary to each other.

As a potential corollary to our findings, the extremely low event rate in patients at low surgical risk undergoing LMCA intervention for nondistal LMCA disease should not go unnoticed. This subset of patients with excellent long-term outcome after catheter-based treatment should be ideally selected to prospectively test whether percutaneous intervention is a valuable alternative to surgical revascularization in future trials.

Study limitations. A limitation of proposing distal location of LMCA disease as a risk-stratifying tool lies in the recognition that the distal site is the most prevalent site of disease in LMCA patients undergoing catheter-based intervention in the DES era. Whether this partially reflects the fact that patients with DLMD are more likely to be at higher surgical risk or tend to be older, as in our present series, and consequently are more likely to undergo percutaneous instead of surgical revascularization, remains to be addressed.

The results of our study are encouraging, but they cannot be conclusive. Studies with larger sample sizes and more prolonged clinical follow-up are clearly in demand to confirm our findings and extend our capability to risk-stratify this challenging subset of patients.

Conclusions. The percutaneous treatment of DLMD emerged as a major predictor of poor long-term outcome, independent of the type of procedure (elective versus nonelective) and the overall surgical risk status. Conversely, the event rate after treatment for non-DLMD seemed to be remarkably low, with an excellent short-term and long-term prognosis, especially in the low surgical risk population. Our current findings extend the previous knowledge about risk stratification for patients undergoing catheter-based treatment of LMCA, and may help in identifying the most appropriate LMCA population, in which catheter-based intervention may be indicated beyond surgical risk status in the DES era.

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Part. 2. Change in plaque composition in relation to distance from the coronary ostia

Chapter 9. Distance from the Ostium as an Independent Determinant of Coronary Plaque Composition *In Vivo*. An Intravascular Ultrasound Study Based Radiofrequency Data Analysis In Humans

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Distance from the ostium as an independent determinant of coronary plaque composition *in vivo*: an intravascular ultrasound study based radiofrequency data analysis in humans

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KEYWORDS
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Aims Relative plaque composition, more than its morphology alone, is thought to play a pivotal role in determining propensity to vulnerability. Thus, we investigated *in vivo* whether the distance from coronary ostium to plaque location independently affects plaque composition in humans. This may help explaining the recently reported non-uniform distribution of culprit lesions along the vessel in acute coronary syndromes.

Methods and results In 51 consecutive patients (45 men), aged 38–76 years (mean age: 58 $\pm$ 10), a non-culprit vessel was investigated through spectral analysis of IVUS radiofrequency data (IVUS-Virtual Histology^{TM}). The study vessel was the left anterior descending artery in 23 (45%) patients; the circumflex artery in nine (18%), and right coronary artery in 19 (37%). The overall length of the region of interest, subsequently divided into 10 mm segments, was 41.5 $\pm$ 13 mm long (range: 30.2–78.4). No significant change was observed in terms of relative plaque composition along the vessel with respect to fibrous, fibrolipidic, and calcified tissue, whereas the percentage of lipid core resulted to be increased in the first (median: 8.75%; IQR: 5.7–18) vs. the third (median: 6.1%; IQR: 3.2–12) ($P = 0.036$) and fourth (median: 4.5%; IQR: 2.4–7.9) ($P = 0.006$) segment. At multivariable regression analysis, distance from the ostium resulted to be an independent predictor of relative lipid content [$\beta = -0.28$ (95%CI: -0.15, -0.41)], together with older age, unstable presentation, no use of statin, and presence of diabetes mellitus.

Conclusion Plaque distance from the coronary ostium, as an independent determinant of relative lipid content, is potentially associated to plaque vulnerability in humans.

Coronary plaque rupture or erosion, by triggering local thrombosis is thought to play a pivotal role in the genesis of acute coronary syndromes (ACS) and sudden death.[1,2]

A series of landmark angiographic studies in the mid-1980s demonstrated that nearly two-thirds of all myocardial infarction originate from non-flow limiting atherosclerotic lesions and prior angiographic studies focusing on plaque morphology alone failed to identify quiescent plaques prone to rapidly progress or rupture.[3–7]

Consequently, the mechanical and biological properties of coronary plaques, which overall reflect plaque composition, along with systemic inflammation has mainly been targeted for the diagnosis and treatment of plaque instability.[8]

Epidemiological studies in patients with ST-segment elevation myocardial infarction (STEMI) report that sites of occlusion are not uniformly distributed throughout each of the major epicardial coronary arteries but tended to cluster within the proximal third of each of the vessels.[9,10] Accordingly, despite the recognition that several factors involved in the pathogenesis of plaque vulnerability are widespread,[11–14] local trigger(s) should be also targeted to explain the presence of high-risk coronary spots.[15]

Plaque composition, favouring propensity to vulnerability, might also be non-uniformly distributed along each coronary vessel. This might explain the higher likelihood for plaque erosion or rupture to occur proximally in the coronary tree.

To investigate this hypothesis, the non-culprit, non-treated vessel containing angiographically non-obstructive ($<$50%) lesions was systematically investigated to assess plaque composition through spectral analysis of IVUS radiofrequency data [IVUS-Virtual Histology^{TM} (IVUS-VH)] in consecutive patients referred to our institution for percutaneous coronary intervention (PCI).

Our findings support for the first time to the best of our knowledge *in vivo* the hypothesis that plaque composition

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in humans may differ in relation to plaque localization along the coronary tree.

Methods

Study protocol and patients enrolment

This was a single-center, investigators-driven, observational prospective study aimed to evaluate the distribution of plaque composition along the coronary vessel in consecutive patients referred to our institution for elective or urgent PCI, in whom the non-culprit, non-treated vessel was judged suitable for a safe IVUS 30 mm-pullback or more, based on angiographic (absence of the following: >50% stenotic disease, extensive calcification, severe vessel tortuosity) and clinical (haemodynamic stability) findings. According to the protocol, not more than one vessel-per patient could be evaluated and the region of interest (ROI), subsequently divided into 10 mm segments, had to start from the coronary ostium. Thus, an analysable interrogated vessel length of at least 30 mm, starting from coronary ostium, was the main selection criterion, once the patient was included in the study.

In the group of patients presenting with an ACS, the culprit lesion has been categorized as complex or non-complex, based on angiographic findings as previously described.[12]

This protocol was approved by the Hospital Ethics Committee and is in accordance with the declaration of Helsinki. Written informed consent was obtained from every patient.

IVUS-VH acquisition and analysis

Details regarding the validation of the technique, on explanted human coronary segments, have previously been reported.[16] Briefly, IVUS-VH uses spectral analysis of IVUS radiofrequency data to construct tissue maps that classify plaque into four major components. In preliminary *in vitro* studies, four histological plaque components (fibrous, fibro-lipid, lipid core, and calcium) were correlated with a specific spectrum of the radiofrequency signal.[16] These different plaque components were assigned colour codes. Calcified, fibrous, fibrolipidic, and lipid-necrotic regions were labelled white, green, greenish-yellow, and red, respectively.[17]

IVUS-VH data was acquired after intracoronary administration of nitrates using a continuous pullback (0.5 mm/s) with a commercially available mechanical sector scanner (Ultracross™ 2.9F 30 MHz catheter, Boston Scientific, Santa Clara, CA), by a dedicated IVUS-VH console (Volcano Therapeutics, Rancho Cordova, CA). The IVUS-VH data were stored on a CD-ROM and sent to the imaging core lab for offline analysis. IVUS B-mode images were reconstructed from the RF data by customized software (IVUSLab, Volcano Therapeutics, Rancho Cordova, CA).[17] Manual contour detection of both the lumen and the media-adventitia interface was performed and the RF data was normalized using a technique known as 'Blind Deconvolution', an iterative algorithm that deconvolves the catheter transfer function from the backscatter, thus accounting for catheter-to-catheter variability.[18,19]

Statistical analysis

The sample size was calculated on the assumption that plaques located in the proximal segment of the coronary artery, defined as the first 10 mm coronary segment, would display a mean lipid content of around 40%, with a sigma of around 35% based on previous findings,[20] with a lipid content of 10% in the distal plaques, defined as those located beyond the first 20 mm from the coronary ostium. To detect this effect size with 80% power and a type-I error (alpha) of 0.05, 48 patients were required. Four main models were constructed based on the number of 10 mm segments that were included.

Model 1 comprised three 10 mm segments available in all patients included.
Model 2 comprised four 10 mm segments available in 43 patients.
Models 3 and **4**, composed of five and six 10 mm segments in 20 and 11 patients, respectively, were considered as exploratory analysis because of limited sample size.

Values are expressed as mean $\pm$ SD and median and inter-quartile range (IQR) as appropriate.

As all cross-sectional areas (CSA) provided by IVUS analysis, were shown to have a non-normal distribution at Kolmogorov–Smirnov goodness-of-fit test, they were log-transformed before analysis. Similarly, to all percentages relative to stenosis rate and plaque composition were applied an arcsin transformation.[21] Comparisons between the two groups were performed with the Student's *t*-test. Fisher's exact test was used for categorical variables. Comparisons among 10 mm segments were accomplished through a general linear mixed model with a compound symmetry correlation structure and the intercept as only random effect. Maximum likelihood method was adopted to estimate parameters in the models. Linear contrasts were applied to evaluate effects of distance, analysed as dummy variable, on the studied parameters. *Post hoc* comparisons were systematically performed by Turkey honest significance difference test.[22]

Because of limited statistical power in models 3 and 4, the multivariable analysis regarding both clinical presentation and plaque location along the vessel, along with the interaction between the two was restricted to models 1 and 2.

In order to establish the determinants of lipid relative content in the plaques in our model and confirm distance from the coronary ostium as an independent predictor of relative lipid content, a univariate (including age, sex, history of hypertension, hypercholesterolaemia, cardiovascular disorders in the family, diabetes mellitus, levels of LDL, HDL, and triglycerides, use of statin, coronary vessel analysed, clinical presentation, and distance for the ostium stratified into 10 mm segments) and multivariable (with all variables showing a *P*-value of $\leq$0.1 at univariate analysis) linear mixed model using percentage of lipid content in all 10 mm segments, analysed as outcome variable, was also applied.

All statistical tests were two-tailed. Probability was significant at a level of $<$0.05. Statistical analysis was performed using Statistica 6.1 Software (Statsoft Inc.) and R-language (R Foundation).

Results

From 16 April 2003 to 10 September 2004, 67 patients were prospectively included in the protocol. Sixteen patients were subsequently excluded from the final analysis because of short ($<$30 mm) IVUS pullback in 10, poor IVUS quality in two and lack of coronary plaque at IVUS investigation in four patients. Thus, 51 patients (45 men), aged 38–76 years (mean age: 58 $\pm$ 10) constituted the final patient population. Their baseline characteristics are provided in *Table 1*. Overall, 33 patients were affected by stable angina (SA), whereas the remaining 18 patients were admitted to hospital because of a non-ST-elevation ACS. In the SA group, the mean Cardiovascular Canadian Score was 2 $\pm$ 1, whereas the TIMI risk score, the percentage of patients with troponin T above upper limit of normal (0.02 μg/L) and the delay from symptoms onset to PCI were 4 $\pm$ 2, 56% and 4$\pm$3 days in the ACS group, respectively. In the ACS group, the culprit lesion was located in the proximal coronary segments in 13 (72%) patients, including 6 (33%) in the left anterior descending artery (LAD), four (22%) in the circumflex artery (CFX), and three (17%) in the right coronary artery (RCA), while in the remaining five (28%) patients the culprit lesion was located in the mid or distal segment of the coronary vessels. Overall, 11 out of 18 identified culprit lesions in the ACS group satisfied the criteria for complex lesions

Table 1 Study population

Variables	Patients		
	All ($n = 51$)	SA Group ($n = 33$)	ACS Group ($n = 18$)
Age (years)	58 ± 10	56 ± 12	59 ± 9
Males, no. (%)	45 (88)	28 (85)	16 (94)
Weight (kg)	80 ± 9	80 ± 8	81 ± 9
Height (cm)	174 ± 7	174 ± 7	175 ± 8
BMI (kg/m^2)	27 ± 4	27 ± 3	28 ± 5
Diabetes, no. (%)	12 (23)	8 (24)	4 (22)
Hypertension, no. (%)	20 (39)	14 (42)	6 (33)
Current smokers, no. (%)	19 (37)	13 (39)	6 (33)
Previous smoker, no. (%)	16 (31)	9 (27)	7 (39)
Medical history, no. (%)			
CABG	3 (6)	2 (6)	1 (6)
PCI	11 (22)	8 (24)	3 (17)
ACS	23 (45)	18 (54)	5 (28)
Medical treatment at entry, no. (%)[a]			
Aspirin	51 (100)	33 (100)	18 (100)
Clopidogrel	51 (100)	51 (100)	18 (100)
Statin	38 (75)	25 (76)	13 (72)
ACE-inhibitor	40 (78)	30 (91)	10 (56)
β-Blocker	48 (94)	32 (97)	16 (89)

Plus–minus values are means ± SD. BMI, Body mass index; CABG, coronary artery bypass grafting; ACE, angiotensin converting enzyme.

The SA group was well matched (P-value >0.3) with the ACS group with respect to all variables reported earlier.

[a]For this analysis we considered all medications administered in the previous 4 or more days. At discharge all patients except one were taking statins.

based on angiographic findings. The study vessel was the LAD artery in 23 (45%) patients, the CFX in nine (18%), and RCA in 19 (37%). The overall length of the ROI was 41.5 ± 13 mm long [(range: 30.2–78.4) (41 ± 13 in SA group vs. 42 ± 13 in ACS group, $P = 0.6$)]. The results regarding quantitative coronary IVUS analysis in the whole population, stratified into 10 mm vessel length (paired-segment analysis), are reported in *Table 2*. Lumen CSA significantly decreased every 10 mm in model 1, whereas this happened starting from the third segment, as compared with first coronary tract, in model 2.

As compared with ostial 10 mm segment, vessel CSA resulted to be decreased in the third and fourth segment in models 1 and 2, respectively, whereas plaque CSA reduction reached statistical significance only in the fourth segment of model 2. Distance from the coronary ostium did not affect the percentage of stenosis. The third and fourth models, restricted to a progressively lower number of patients but based on a longer vessel length, mainly confirmed the trends observed in the first two models.

Change in plaque composition along the study vessel

The results regarding quantitative coronary plaque composition analysis are reported in *Table 3*.

Fibrous tissue was the most prevalent component of plaque composition in each 10 mm segment throughout the four models considered, followed by fibrolipidic tissue, lipidic core, and calcium.

No significant change was observed in terms of relative plaque composition passing from the most proximal to those progressively more distally located segments along the vessel with respect to fibrous, fibrolipidic, and calcified tissue. Conversely, the percentage of lipid core resulted to be increased in the first [(mean: 13%; 95%CI: 10, 16), (median: 8.75%; IQR: 5.7, 18)] with respect to the third segment [(mean: 8.7%; 95%CI: 6.5, 11), (median: 6.2%; IQR: 2.6, 12.1)] in model 1 ($P < 0.05$; primary endpoint) and to third [(mean: 8.4%; 95%CI: 6, 11), (median: 6.1%; IQR: 3.2–12)] ($P < 0.05$) and fourth [(mean: 6.8%; 95%CI: 4, 9.6), (median: 4.5%; IQR: 2.4–7.9)] ($P < 0.01$) segment in model 2 (*Figure 3*). A similar shift in relative plaque composition along the vessel was observed in models 3 and 4. Interestingly, ACS patients presenting with the culprit lesion located in the proximal segment of the coronary artery did not differ in terms of relative plaque distribution along the vessel with respect to those with culprit lesion sited in the mid of distal tract.

Clinical presentation and change in plaque composition along the study vessel

No significant change in calcium content with respect to clinical presentation (stable vs. unstable) was observed (data not shown). In model 1, fibrous plaque content was overall significantly increased in stable (68%) [95%CI: 65%, 71%] vs. unstable (63%) [95%CI: 59%, 64.7%] group, whereas a decrease in stable (17%) [95%CI: 16%, 19%] vs. unstable (22%) [95%CI: 20%, 24%] patients was observed for

Table 2 Quantitative vessel analysis at IVUS

Coronary segments	Mean cross-sectional areas (mm^2)			Stenosis (%)
	Lumen	Vessel	Plaque	
Model 1; $n = 51$				
1° (0–10 mm)	9.4 ± 3.6	17.1 ± 8.1	7.3 ± 3.7	41.4 ± 10.5
2° (10–20 mm)	7.8 ± 2.9†	15.7 ± 7.8	7.2 ± 3.4	46 ± 12
3° (20–30 mm)	7.1 ± 2.8‡	14.2 ± 8‡	6.2 ± 2.7	45 ± 11
P-value	0.002	0.01	0.12	0.08
Model 2; $n = 43$				
1° (0–10 mm)	9.3 ± 3.6	17.4 ± 8.6	7.6 ± 3.9	42 ± 11
2° (10–20 mm)	7.7 ± 2.7	15.9 ± 8.2	7.3 ± 3.5	46 ± 12
3° (20–30 mm)	7 ± 2.6*	14.5 ± 8.7	6.3 ± 2.8	45 ± 11.2
4° (30–40 mm)	6.4 ± 2.7‡	13.5 ± 9.7‡	6 ± 3.4†	45.3 ± 12.4
P-value	0.0002	0.001	0.02	0.4
Model 3; $n = 20$				
1° (0–10 mm)	10.4 ± 4.3	20.5 ± 11.5	9 ± 5.2	39.8 ± 10.5
2° (10–20 mm)	8.8 ± 2.8	19 ± 11	8.2 ± 4.7	41.7 ± 12
3° (20–30 mm)	8 ± 2.9	17.4 ± 12	6.9 ± 3	42 ± 10
4° (30–40 mm)	7.3 ± 3.2	16.5 ± 13.3	6.8 ± 4.2	42 ± 12
5° (40–50 mm)	7 ± 2.9	16.2 ± 15	5.7 ± 2.3	41 ± 11.4
P-value	0.07	0.12	0.054	0.98
Model 4; $n = 11$				
1° (0–10 mm)	10.7 ± 2.8	19.3 ± 2.7	8.6 ± 2.1	45 ± 7.8
2° (10–20 mm)	9.3 ± 3.7	18 ± 4	8.6 ± 2.4	49 ± 10
3° (20–30 mm)	8.6 ± 2.3	16.8 ± 4.6	8.2 ± 2.4	48 ± 8.3
4° (30–40 mm)	8.3 ± 2.2	17.1 ± 5	8.8 ± 2.8	51 ± 5.7
5° (40–50 mm)	7.5 ± 2.5	15.3 ± 4.9	7.8 ± 2.6	51.3 ± 4.8
6° (50–60 mm)	6.7 ± 2.6†	13 ± 4	6.2 ± 2	48.2 ± 9.7
P-value	0.023	0.06	0.063	0.4

*$P < 0.01$; †$P < 0.05$; ‡$P < 0.001$ as compared with segment 1 at *post hoc* analysis.
Results are given as mean ± SD.

fibrolipid content when all 227 segments were pooled together ($P = 0.03$ and $P = 0.006$, respectively). However, when distance from the ostium, stratified into 10 mm segments, was also inserted into the model, only trends towards increase in fibrous and decrease in fibrolipidic content in stable vs. unstable patients were observed, which did not reach statistical significance. This was confirmed in model 2. In contrary, even when analysed simultaneously, both plaque location along the vessel ($P = 0.044$ and $P = 0.002$ for models 1 and 2, respectively) and clinical presentation (stable vs. unstable) ($P = 0.01$ and $P = 0.004$ for models 1 and 2, respectively) resulted to be independent predictors of lipid content (*Figures 1B* and *2B*) after adjustment for age, sex, diabetic status, type of coronary artery analysed, and use of statin. Finally, in order to evaluate whether the shift in lipid content along the vessel was influenced by clinical presentation, the interplay between these two main determinants of lipid content was investigated, but no statistical interaction emerged between plaque location and lipid core content ($P = 0.8$ and $P = 0.49$ for models 1 and 2, respectively).

Distance from the ostium as an independent predictor of lipid content

In *Table 4* the variables found to be associated to the relative lipid content along the vessel are shown. The lipid core in the most distally located coronary segment (segment 3) in model 1 was significantly lower compared with segment 1, taken as a reference, independently from all other identified predictors. When all 227 segments were included in the model, distance from the ostium, stratified into 10 mm segments, resulted to be an independent predictor of relative lipid content along vessel wall, together with older age, unstable presentation, no use of statin, and the presence of diabetes mellitus. In keeping with the results obtained at the *post hoc* analysis, after adjusting for clinical presentation, relative lipid content in segment 1 did not differ from segment 2 [β −0.08 (95%CI: −0.28, 0.116)], while it did so starting from segment 3 [β −0.22 (95%CI: β 0.39, β 0.05)], with a progressively lower β-value for segment 4 [β −0.34 (95%CI: −0.39, −0.05)] and 5 [β −0.38 (95%CI: −0.55, −0.21)].

Discussion

Several lines of research in the last decades have clearly pointed out how factors involved in pathogenesis and progression of atherosclerotic lesions are widespread throughout the circulatory bed.[8,11,12,14,23,24]

As a corollary to this, evidence that a single pharmacological or mechanical treatment, when applied locally, is able to affect progression of coronary atherosclerosis is weak and not conclusive.[25] On the other hand, systemic

Table 3 Plaque composition stratified into 10 mm segments

Coronary segments	Plaque composition (%)			
	Calcium	Fibrous	Fibrolipidic	Lipid core
Model 1; $n = 51$				
1° (0–10 mm)	0.69 (0.26–1.98)	67.1 (60–74.4)	16.86 (11.2–24)	8.8 (5.7–18)
2° (10–20 mm)	0.67 (0.3–1.58)	68.3 (60–77)	18.1 (12.7–23.1)	9.6 (4.3–15.1)
3° (20–30 mm)	0.79 (0.37–1.82)	69 (64–78)	18.7 (13.4–25.3)	6.2 (2.6–12.1)*
P-value	0.67	0.40	0.84	0.039
Model 2; $n = 43$				
1° (0–10 mm)	0.76 (0.28–2.3)	64.7 (59.3–74)	17.7 (13.4–24.5)	8.01 (5.7–18)
2° (10–20 mm)	0.70 (0.4–1.58)	66.9 (57.9–77)	18.6 (14–24.4)	10 (4.2–16.7)
3° (20–30 mm)	0.75 (0.37–1.82)	69 (63.9–77.8)	19.8 (14.3–25.4)	6.1 (3.5–12)*
4° (30–40 mm)	0.48 (0.09–1.5)	68.7 (60.8–75)	21.1 (17–28.2)	4.5 (2.4–8)†
P-value	0.36	0.55	0.63	0.0058
Model 3; $n = 20$				
1° (0–10 mm)	0.77 (0.5–2.6)	71.4 (49.7–76.4)	17.3 (13.4–23.7)	8 (6–25)
2° (10–20 mm)	0.49 (0.18–1.15)	72.3 (57.9–79.59)	17.2 (100–22.7)	9.3 (4.1–14.6)
3° (20–30 mm)	0.87 (0.1–2.4)	69.3 (61.1–79.6)	17.4 (13.1–25.3)	6.8 (4.1–12)
4° (30–40 mm)	0.9 (0.2–2.6)	67.8 (57.1–77.6)	19.1 (17.4–30)	6.1 (3–8.3)
5° (40–50 mm)	0.65 (0–1)	75.3 (60.6–81.4)	16.4 (14.5–32.6)	3.5 (0.7–5.8)*
P-value	0.14	0.8	0.71	0.039
Model 4; $n = 11$				
1° (0–10 mm)	0.3(0.2–1.6)	74.1 (61–79)	20.8 (16–28)	5.97 (2.25–12)
2° (10–20 mm)	0.8 (0.4–1)	74 (64–79)	20.5 (18–22)	5.7 (3–13)
3° (20–30 mm)	0.54 (0.13–1.6)	75.1 (70–80)	18.5 (16.8–22)	5 (2.8–6.5)
4° (30–40 mm)	0.63 (0.1–1.8)	75.7 (66–77)	21 (20–27)	3.4 (92.4–5.7)
5° (40–50 mm)	0.38 (0.1–1.3)	73.1 (67–81)	21.2 (15–27)	3.2 (2.7–5.3)
6° (50–60 mm)	0.37 (0–0.8)	77.3 (66–79)	24 (19–28)	2.7 (1–4.3)*
P-value	0.65	0.78	0.98	0.036

* $P < 0.05$; † $P < 0.01$ as compared with segment 1 at *post hoc* analysis.
Results are given as median (IQR).

therapy, such as an intensive lipid-lowering treatment, has been convincingly shown to be able to stop atherosclerotic disease progression and even induce coronary lesions regression in some studies.[26–30] The same paradigm is thought to be true for factors involved in atherosclerotic lesions vulnerability, albeit probably in a more elusive way.[25]

These findings should be combined, however, with the evidence provided by recent epidemiological studies, which corroborate the hypothesis according to which sites of occlusions are not uniformly distributed throughout the coronary tree, rather they show a tendency to cluster in partially predictable hot spots located within the proximal third of each coronary vessels.[9,10]

Thus, the interplay among systemic and local factors able to promote progression and vulnerability of atherosclerotic coronary lesions should be probably both targeted in the attempt to control the chronic and acute consequences of coronary atherosclerosis.[15]

Among local factors known to affect genesis and progression of coronary atherosclerotic lesions, shear stress (SS) has been extensively investigated.

Fluid SS, acting on genes 'sensitive' to local haemodynamic forces, is known to elicit a large number of humoural, metabolic, and structural responses in endothelial cells (EC).[31] Low SS on ECs partially explains the local arterial susceptibility to atherosclerosis, as low SS enhances the oxidation of lipids and their accumulation in the intima.[31,32]

Moreover, fluid turbulence in itself is able to directly activate platelets, thus possibly playing a pivotal role in thrombogenesis as well.[33]

It is tempting to speculate that other local factors could play additional roles in modulating progression and instability of atherosclerotic lesions in coronary arteries. Among them, pathological studies have suggested that the distribution of thin-cap atheromas, which are lipid rich core plaques known to be at particularly high-risk for rupture, are not uniformly distributed along the coronary vessels in post-mortem examinations.[34] Rather, they cluster in the proximal segments of the three main coronary arteries, which is in keeping with the longitudinal distribution of both ruptured and healed plaques.[34]

This non-uniform distribution of vulnerable plaques in humans could partially explain the clustering of occlusive culprit lesion in the proximal or middle tract of coronary arteries. In this regard, we hypothesized that plaque composition was also not uniformly distributed *in vivo* in humans in patients with symptomatic coronary disease. Thanks to a recently developed technology based on spectral analysis of IVUS radiofrequency data (IVUS-VH),[16,17] we prospectively evaluated whether plaque composition is independently affected by the distance from coronary ostium in a

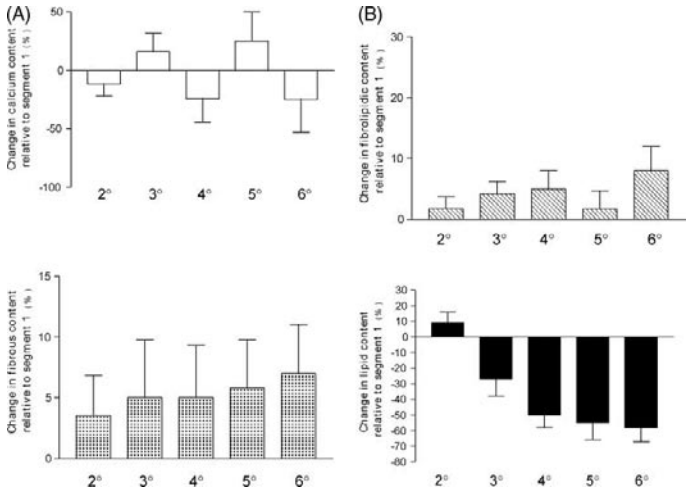

Figure 1 Relative change in plaque composition with respect to segment 1. Starting from segment 3, relative lipid content showed a progressive decrease with respect to ostial segment (segment 1) taken as a reference. Relative changes in segments 2 and 3 were calculated using model 1, whereas for the relative change in segments 4, 5, and 6, models 2, 3, and 4 were employed, respectively. All relative changes are expressed as mean value and standard deviation.

consecutive series of patients. Our findings support the concept that coronary plaques located in the proximal tract (≈20 mm) of coronary vessels are relatively richer in lipid content with respect to those more distally located, independently from clinical presentation. In this regard, the magnitude of lipid content appeared to be relatively higher in patients presenting with clinical instability but no interaction emerged in our model between clinical presentation and lipid content, suggesting that the relative change in plaque composition along the vessel is a well-preserved phenotype in both groups of patients. Moreover, distance from the coronary ostium resulted to be an independent predictor of relative lipid content along the vessel wall in our regression model, together with age, unstable presentation, presence of diabetes mellitus, and no use of statin.

Our current findings should be regarded as an attempt to extend the pathophysiological knowledge on plaque vulnerability, mainly because of the well-known linkage between plaque composition and risk of plaque rupture or erosion.[34–36] Thus, this might contribute to explain the higher likelihood for plaque erosion or rupture to occur proximally in the coronary tree. Moreover, the finding that coronary plaques show a relatively higher lipid content if proximally located along the longitudinal axis of the vessel with respect to those more distally located might elicit new methodological issues in future investigations. In particular, hypothesizing that plaque progression/regression studies accomplished through aggressive lipid-lowering regimen would mainly affect the lipid content in the plaque, it seems reasonable to believe that the relative effect of the tested medication observed at IVUS investigation in terms of overall plaque CSA, could differ in relation to the localization of ROI with respect to the coronary ostium. This could bear special hazard particularly in those studies having limited ROI length.[37]

An interesting finding of our study was that the percentage of stenosis did not differ in relation to the distance from the ostium, whereas plaque area was progressively smaller moving form proximal to distal segments. This might be explained by the interplay between the physiological proximal–distal tapering of the coronary vessel and the higher propensity of the proximal segments to undergo positive remodelling with respect to those located more distally. This seems to be in keeping with our recent findings that positive remodelling is indeed more pronounced in lipid-rich coronary segments.[38]

Limitations of the study

As exploratory-pilot investigation, our current findings should be regarded as provisional. In particular, to assess relatively minor changes in plaque composition along longitudinal vessel axis, such as that observed for fibrous tissue, or for highly dispersed data such as for relative calcium content, a bigger, properly powered, sample size is clearly needed. Similarly, the observed insignificant trends for fibrous tissue to be increased and fibrolipidic content to be decreased in stable vs. unstable patients may reflect a type-II error. Our results mainly apply to the first 40 mm of the three main coronary arteries, whereas the longitudinal pattern of shift in coronary plaque composition in coronary segments more distally located or in left main coronary artery should be evaluated in studies specifically designed for such an aim. In particular, in keeping with our primary endpoint, the only comparison for which this study was properly powered for is the one between the first and the

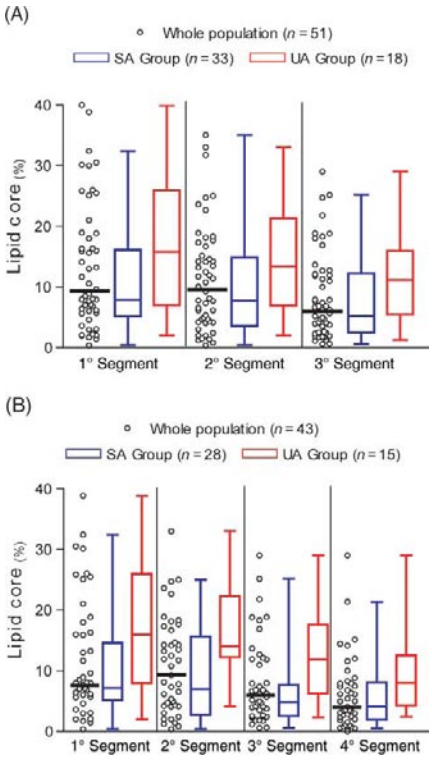

Figure 2 Per-segment distribution of relative lipid content in the study population. Per-segment distribution of relative lipid contents both in the whole population and stable vs. unstable patients in model 1 (*A*) and 2 (*B*). Bars indicate median values in the whole population. As shown in *Table 3*, relative lipid content significantly decreased in the whole population in segment 3 in model 1 and in segments 3 and 4 in model 2 with respect to segment 1 at *post hoc* analysis.

third segment in model 1. All other analyses, including the tests for four models and all *post hoc* comparisons should be regarded as exploratory. Despite careful examination of all angiograms, we cannot completely rule out the possibility that patients with a higher number of IVUS interrogated 10 mm segments had a more favourable coronary anatomy as compared with those in whom a long pull-back could not been obtained.

Relevant to this point, it is the fact that: (i) plaque composition in the first three coronary segments did not differ in patients with 30 mm pull back length as compared with those in whom a longer IVUS pull back was obtained; and (ii) the change in plaque composition along the study vessel was remarkably consistent in all the four models analysed.

We failed to find sex-related differences in the proximal–distal pattern of plaque composition. However, the great majority (88%) of patients enrolled were males, which

Table 4 Predictors of plaque lipid content at uni- and multivariate analysis in model 1

Variables	Beta-values (95% CI)		*P*-values
Univariate analysis			
Age (years)	−0.12	−0.25, 0.008	0.069
Sex (M vs. F)	0.029	−0.101, 0.16	0.66
Smoking status	0.022	−0.108, 0.15	0.7
Previous history of			
Hypertension	0.048	−0.08, 0.16	0.48
CVD in the family	−0.038	−0.16, 0.082	0.56
Hypercholesterolaemia	0.08	−0.032, 0.197	0.21
Diabetes mellitus	0.14	0.023, 0.257	0.041
ACS	0.044	−0.086, 0.174	0.50
Coronary revascularization	−0.15	−0.2, −0.028	0.02
Coronary vessel[a]	0.038	−1.93, 2.008	0.5
ACS at presentation	0.25	0.11, 0.39	0.0032
LDL (mg/dL)	0.09	−0.04, 0.22	0.42
HDL (mg/dL)	−0.12	−0.25, 0.01	0.067
Triglycerides (mg/dL)	0.04	−0.09, 0.17	0.78
Use of statin	−0.25	−0.37, −0.12	0.0001
Distance from ostium[b]	−0.32	−0.45, −0.30	<0.0001
Multivariable analysis[c]			
Distance from ostium[b]	−0.28	−0.15, −41	<0.0001
Age (years)	−0.26	−0.12, −40	0.0004
ACS at presentation	0.16	0.03, 0.29	0.005
Use of statin	−0.18	−0.36, 0.004	0.057
Diabetes mellitus	0.21	0.07, 0.34	0.003
Coronary revascularization	−0.07	−0.02, 0.12	0.46
HDL (mg/dL)	−0.02	−0.05, 0.21	0.84

CVD, cardiovascular disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
[a]Analysed as left anterior descending vs. circumflex vs. right coronary artery
[b]Analysed as segment 1 taken as a reference vs. segment 3.
[c]Adjusted $R^2 = 0.36$ for the model.

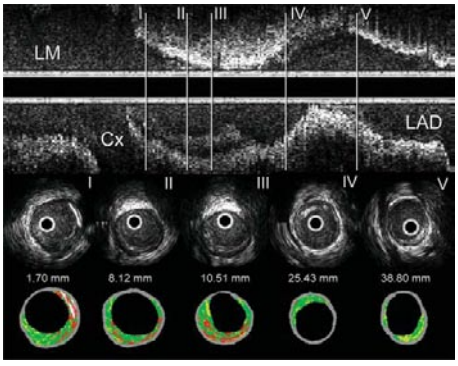

Figure 3 IVUS-VH CSA along a coronary vessel. IVUS-VH cross-sectional areas in a representative patient showing the change in plaque composition (calcium: white; fibrous: green; fibrolipidic: greenish-yellow; and lipid core: red) along the longitudinal axis of the vessel. LM, left main coronary artery; CFX, circumflex artery; LAD, left anterior descending artery. The distance between the cross-sectional area and the ostium of the vessel is reported in millimetres (mm).

calls for future studies with more balanced sex-distribution to properly address this gender issue.

Finally, it should not undergo unnoticed that the proportion of lipid core content predicted by our multivariable regression model, despite highly significant, was far from being optimal. This means that future investigations should probably aim to increase the capability to predict relative lipid content in coronary plaques taking a broader set of possible independent predictors into account.

Conclusion

Our study provides proof of concept for a non-uniform longitudinal distribution of plaque composition mainly in terms of lipid core content along the main coronary arteries *in vivo* in humans. The clinical and pathophysiological meaning of this observation and whether it could help explaining the non-uniform distribution of vulnerable plaques along the coronary vessel remains unclear. Future studies are needed to extend and possibly confirm our current findings.

Conflict of interest: none declared.

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Chapter 10 Plaque Composition in the Left Main Stem Mimics the Distal but not the Proximal Tract of the Left Coronary Artery. Influence of Clinical Presentation, Length of the Left Main Trunk, Lipid Profile and Systemic Inflammatory Status

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Plaque Composition in the Left Main Stem Mimics the Distal but not the Proximal Tract of the Left Coronary Artery

Influence of Clinical Presentation, Length of the Left Main Trunk, Lipid Profile and Systemic levels of C-Reactive Protein

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Objective: To investigate whether plaques located in the left main stem (LMS) differ in terms of necrotic core content from those sited in the proximal tract of the left coronary artery.
Background: Plaque composition, favoring propensity to vulnerability, might be non-uniformly distributed along the vessel. This might explain the higher likelihood for plaque erosion or rupture to occur in the proximal but not in the distal tracts of the coronary artery or in LMS.
Methods: 72 patients were prospectively included: 48 (32 men; mean age: 57±11), [25 with stable angina (SA); 23 affected by acute coronary syndromes (ACS)] underwent a satisfactory non-culprit vessel investigation through spectral analysis of IVUS radiofrequency data (IVUS-Virtual Histology™). The region of interest was subsequently divided into LMS and LMS carina, followed by six consecutive non-overlapping 6 mm-segments in left anterior descending (LAD) artery in 34 or in circumflex artery (CFX) in 14 patients.
Results: Necrotic core content (%) i) was minimal in LMS [median (IQR): 4.6 (2-7)]; peaked in the first 6-mm coronary segment [11.8 (8-16); p<0.01], while it then progressively decreased distally; ii) was overall higher in ACS [11.4 (5.5-19.8) than SA patients [7.3 (3.2-12.9)]; (p<0.001); iii) was largely independent from plaque size and iv) did not correlate to systemic levels of CRP or lipid profile.
Conclusions: Plaques located in the LMS carry minimal necrotic content. Thus, they mimic the distal but not the proximal tract of the left coronary artery where plaque rupture or vessel occlusion occurs more frequently.

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INTRODUCTION

The distribution of ruptured or prone to rupture plaques is known to be non-uniform throughout the coronary tree(1-5). Pathological studies have suggested the so called "thin-cap atheromas" –necrotic rich core plaques at high risk for rupture– are infrequent in the left main stem (LMS) and in the distal tracts of the coronary vessels, while they group together with ruptured and healed plaques in the proximal segments of the three main coronary arteries(1).

Similarly i) angiographic studies in patients with ST-segment elevation myocardial infarction (STEMI) have recently shown that sites of occlusion are clustered within the proximal third of each of the vessels(2,3) and ii) intravascular ultrasound (IVUS) analyses have observed that plaque rupture rarely occurs in the LMS or the distal part of the coronary arteries, whereas it is far more common in the proximal part of the coronary vessels(4), especially in the left anterior descending artery (5).

The reasons why vulnerable or ruptured plaques tend to spare the LMS and distal segments of the left coronary vessels remain poorly understood. Plaque composition, favoring propensity to vulnerability(6-8), might also be non-uniformly distributed along the coronary arteries.

We sought to investigate whether the plaques located in the LMS, which are known to be at low probability of rupture, differ in terms of composition from those sited in the proximal tract of left anterior descending or circumflex artery, where rupture or occlusion occurs more frequently. This may contribute establishing *in vivo* the role of plaque composition as key determinant of vulnerability in humans. In this context, the role of clinical presentation, length of LMS, lipid profile and systemic level of C-reactive protein were also investigated.

METHODS

Study Protocol and Patients Enrolment

This was a single-centre, investigators-driven, observational study aimed to evaluate the distribution of plaque composition along the left coronary artery in consecutive patients referred to our institution for elective or urgent PCI, in whom the non-culprit, non-treated vessel was judged suitable for a safe IVUS 35 mm-pullback or more, based on angiographic (absence of the following: >50% stenotic disease, extensive calcification, severe vessel tortuosity) and clinical (haemodynamic stability) findings.

According to the protocol, not more than one vessel-per patient could be evaluated and the region of interest (ROI) was subsequently divided into the following coronary segments: LMS and LMS carina, based on anatomical landmarks, followed by six consecutive non-overlapping 6 mm-segments, with the first one to be started at the coronary ostium of either left anterior descending or circumflex artery. The length chosen for those coronary segments located distally to the LMS carina was based on the median length of LMS in the study population.

To ensure that the ostial-proximal part of the LMS was included in the IVUS pullback and to rule out the occurrence of deep intubation by the guiding catheter, the last part of the pullback was filmed and each angiogram carefully inspected before patient inclusion. An analyzable interrogated vessel length of at least 35 mm beyond LMS carina, starting from coronary ostium, was the main selection criterion, once the patient was included in the study. This protocol was approved by the hospital ethics committee and is in accordance with the

declaration of Helsinki. Written informed consent was obtained from every patient.

IVUS-VH Acquisition and Analysis

Details regarding the validation of the technique, on explanted human coronary segments, have previously been reported (9). Briefly, IVUS radiofrequency data (IVUS-Virtual Histology™) uses spectral analysis of IVUS radiofrequency data to construct tissue maps that classify plaque into four major components. In preliminary *in vitro* studies, four histological plaque components (fibrous, fibro-lipid, necrotic core and calcium) were correlated with a specific spectrum of the radiofrequency signal (9). These different plaque components were assigned color codes. Calcified, fibrous, fibrolipidic and necrotic core regions were labeled white, green, greenish-yellow and red respectively(10).

IVUS-VH data was acquired after intracoronary administration of nitrates using a continuous pullback (0.5 mm per second) with commercially available mechanical sector scanners (Ultracross™ 30 MHz catheter, Boston Scientific, Santa Clara, CA-USA- or Eagle Eye™ 20 MHz catheter, Volcano Corporation, Rancho Cordova, USA), by a dedicated IVUS-VH console (Volcano Therapeutics, Rancho Cordova, CA). The IVUS VH data were stored on a CD-ROM/DVD and sent to the imaging core lab for offline analysis (Cardialysis). IVUS B-mode images were reconstructed from the RF data by customized software and contour detection was performed using cross-sectional views with a semi-automatic contour detection software to provide geometrical and compositional output (IvusLab 3.0 for 30 MHz acquisitions and IvusLab 4.4 for 20 MHz acquisitions respectively; Volcano Corporation, Rancho Cordova, USA)(10).

The contours of the external elastic membrane (EEM) and the lumen-intima interface enclosed an area that was defined as the coronary plaque plus media area. Plaque burden was calculated as [(EEM_{area} - $Lumen_{area}$ / EEM_{area}) X 100]. Plaque eccentricity was defined as minimum plaque thickness divided by maximum plaque thickness. Geometrical and compositional data were obtained for each cross-sectional area (CSA) and an average was calculated for each coronary and for the total coronary tree. RF data was normalized using a technique known as "Blind Deconvolution", an iterative algorithm that deconvolves the catheter transfer function from the backscatter, thus accounting for catheter-to-catheter variability (11,12).

Biochemical measures

Antecubital venous blood was collected from all patients at entry, left in ice for 45 min, centrifuged at 1700×g at 4°C for 15 min and serum obtained finally stored at –80°C. High-sensitive (hs) C-reactive protein (CRP) was measured in serum using a commercially available kit (N High Sensitivity CRP, Dade Behring, Marburg, Germany). Plasma concentrations of total cholesterol, high-density lipoprotein cholesterol (HDL), and triglycerides were measured in the local laboratory. The Friedewald formula was used to derive low-density lipoprotein cholesterol (LDL) levels.

Statistical Analysis

The sample size was calculated on the assumption that plaques located in the most proximal 6-mm segment of the LAD or CFX, would display a mean necrotic core content of approximately 10% and a standard deviation of 10%, based on previous findings(13), with a relative necrotic core content of around 5% in plaques located in the LMS. To detect this effect size with 80% power and a type I error (alpha) of 0.05, at least 46 patients were required (model 1). Model 2 was also created to explore whether in patients with LMS length beyond median value (long LMS cohort) plaque composition differs in the proximal compared to the distal tract of the LMS. No formal sample size was calculated for model 2 as it was meant to be a hypothesis generating analysis.

Values are expressed as mean±SD and median and interquartile range (IQR) whenever appropriate. Since all cross sectional areas, provided by IVUS analysis, were shown to have a non-normal distribution at Kolmogorov-Smirnov goodness-of-fit test, they were log-transformed before analysis. Similarly, to all percentages relative to stenosis rate and plaque composition an arcsin transformation was applied (14). Assumptions for normality were checked after transformation based on a p-value >0.20 at Kolmogorov-Smirnov test and on visual assessment of Q-Q plots of residuals.

Comparisons between the two groups were performed with the Student's *t*-test. Fisher's exact test was used for categorical variables. Comparisons among coronary segments were accomplished through a general linear mixed model and *post hoc* comparisons by Tukey honest significance difference test(15). Spearman's correlation coefficients were used to detect any association between variables. Probability was significant at a level of <0.05. Statistical analysis was performed using Statistica 6.1 Software (Statsoft Inc.) and R-language (R Foundation).

RESULTS

From 11 December 2003 to 27 July 2005, seventy-two patients were prospectively included in the protocol. Twenty-four patients were subsequently excluded from the final analysis due to short (< 36 mm) IVUS pullback in 16, uncertainty regarding the true interface lumen-vessel wall based on IVUS grey-scale in 4 and occurrence of angiographically confirmed deep intubation of the guiding catheter during the pullback in 4 patients. Thus, 48 patients (32 men), aged 30 to 75 years (mean age: 57±11) constituted the final patient population. Their baseline characteristics are provided in below.

Table 1. Study Population

Variables	Patients			
	All (N=48)	SA Group (N=25)	ACS Group (N=23)	P-Value*
Age (ys)	57±11	58±11	57±12	0.81
Males, no. (%)	32 (67)	16 (64)	16 (65)	>0.99
Weight (kg)	82±12	81±12	84±12	0.36
Height (cm)	174±9	173±8	176±10	0.28
BMI (kg/m^2)	27±3	27±4	27±2	0.81
Diabetes, no. (%)	11 (23)	5 (20)	6 (26)	0.75
Hypertension, no. (%)	37 (77)	20 (80)	17 (74)	>0.99
Current Smokers,no. (%)	19 (40)	8 (32)	11 (48)	0.32
Previous Smoker, no. (%)	16 (33)	9 (36)	7 (30)	0.50
C-reactive protein (mg/l)	29±48	12.7±15	38±58	0.19
Low density lipoprotein (mmol/l)	3.09±1.22	3.26±1.3	2.9±1.3	0.44
High density lipoprotein (mmol/l)	1.22±0.5	1.30±0.6	1.14±0.4	0.39
Cholesterol/HDL ratio	4.26±1.49	4.26±1.5	4.25±1.2	0.99
Medical History, no. (%)				
CABG	2(4)	2 (6)	0 (0)	0.29
PCI	11 (23)	8 (32)	3 (13)	0.32
ACS	18 (37)	10 (40)	8 (35)	>0.99
Medical Treatment, no. (%)				
Aspirin	48 (100)	25 (100)	23 (100)	>0.99
Clopidogrel	48 (100)	25 (100)	23 (100)	>0.99
Statin	42 (88)	23(92)	19 (83)	0.84
ACE-inhibitor	40 (83)	25 (100)	15 (65)	0.39
β-Blocker	42 (88)	23 (92)	19 (83)	0.84

Plus-minus values are means±SD. BMI: Body mass index, SA: Stable angina, ACS: acute coronary syndrome. CABG: coronary artery bypass grafting, PCI: percutaneous coronary intervention, ACE: angiotensin converting enzyme

Table 2: Quantitative Vessel Analysis at IVUS stratified into coronary segments

	Cross Sectional Areas (mm^2)			Plaque Eccentricity Index	Plaque Burden (%)
	Lumen	Vessel	Plaque		
MODEL 1 N=48					
CORONARY SEGMENTS					
LMS	15.2 (12-17)	24.5 (19-26)	8 (6-9)	0.11 (0.05-0.18)	34.3 (29-38)
LMS Carina	12.2 (11-15)	20.4 (16-24)	6.7 (6-8)	0.03 (0.01-0.06)†	33.8 (31-39)
1° (0-6 mm)	9.9 (7-11) †	16.2 (14-18) †	6.4 (5-7)	0.09 (0.07-0.14)	38.6 (36-46)
2° (6-12 mm)	9.1 (7-10) †	16 (14-18) †	6.8 (5-8)	0.11 (0.06-0.16)	40 (39-45)
3° (12-18 mm)	8.6 (7-10) †	15 (13-17) †	6.9 (5-8)	0.10 (0.08-0.15)	41 (40-46)
4° (18-24 mm)	8.2 (7-10) †	14 (13-16) †	6.3 (5-7)	0.13 (0.06-0.17)	41 (37-51)
5° (24-30 mm)	7.5 (6-9) †	13.2 (12-15) †	5.6 (5-6)	0.16 (0.10-0.20)	40 (38-54)
6° (30-36 mm)	7.2 (6-8) †	12.3 (11-14) †	4.9 (4-6)†	0.12 (0.08-0.21)	42 (36-47)
P-VALUE	<0.0001	<0.0001	0.0006	0.0001	0.16
MODEL 2 N=24					
CORONARY SEGMENTS					
PROX. LMS	16.1 (13-19)	23.4 (21-27)	7.5 (5-9)	0.11 (0.07-0.15)	32 (29-39)
DIST. LMS	14.6 (12-17)	25.8 (20-27)†	8.9 (7-10)	0.11 (0.07-0.25)	38 (33-43)
LMS CARINA	13.1 (11-15)†	21.2 (18-25)	7.7 (7-8)	0.05 (0.02-0.08)	37 (31-43)
1° (0-6 mm)	9.9 (8-11)†	16.3 (15-19)†	7.1 (6-8)	0.13 (0.09-0.14)	43 (37-48)
2° (6-12 mm)	9.1 (7-11)†	16.6 (14-19)†	7.7 (6-9)	0.15 (0.08-0.17)	47 (45-50)*
3° (12-18 mm)	8.6 (7-10)†	15.7 (14-18)†	7.4 (6-8)	0.11 (0.09-0.21)	50 (45-53)*
4° (18-24 mm)	8.2 (7-10)†	14.5 (13-16)†	7.0 (5-8)	0.14 (0.09-0.17)	48 (38-51)*
5° (24-30 mm)	8.2 (6-10)†	14.0 (12-17)†	5.7 (5-7)	0.19 (13-24)	45 (34-54)
6° (30-36 mm)	7.0 (6-8)†	12.0 (11-14)†	5.1 (4-7)*	0.19 (0.11-0.30)	45 (39-51)
P-VALUE	<0.001	<0.0001	0.002	0.019	0.0093

P-values refer to results for the whole model at general linear analysis. *: p<0.05; †: p<0.01 at adjusted-post-hoc comparison as compared to left main stem (LMS) in model 1 and to Prox. LMS in model 2. Results are given as median (IQR); Prox.: proximal; Dist.: distal

The study vessel was the LMS and left anterior descending (LAD) artery in 34 (71%) patients and LMS and circumflex artery (CFX) in 14 (29%). The overall LMS length was 7.49±4 mm [median (IQR): 6 (4.8-9.3); range: 3.4-20]; (7.3±4 in SA group vs. 7.8±5 in ACS group, p=0.64). Lumen and vessel cross sectional area (CSA) decreased significantly starting from the first 6-mm segment of the coronary artery as compared to LMS (table 2). Plaque CSA in the LMS was significantly increased only compared to the most distal 6-mm segment. The degree of plaque eccentricity was relatively constant throughout the vessel except in the LMS carina, where it resulted to be higher compared to both the LMS and the coronary segments distal to the first one. Plaque burden did not change along the vessel in model 1, despite a trend being progressively increased from proximal to distal.

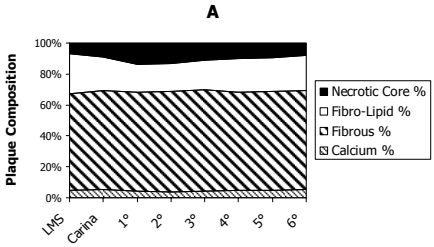
Model 2 (Table 2), in which LMS has been stratified into the proximal and distal segment after selection of those patients (n=24) with long LMS (length >6 mm), mainly confirmed the trends observed along the vessels in model 1.

Change in plaque composition along the study vessel

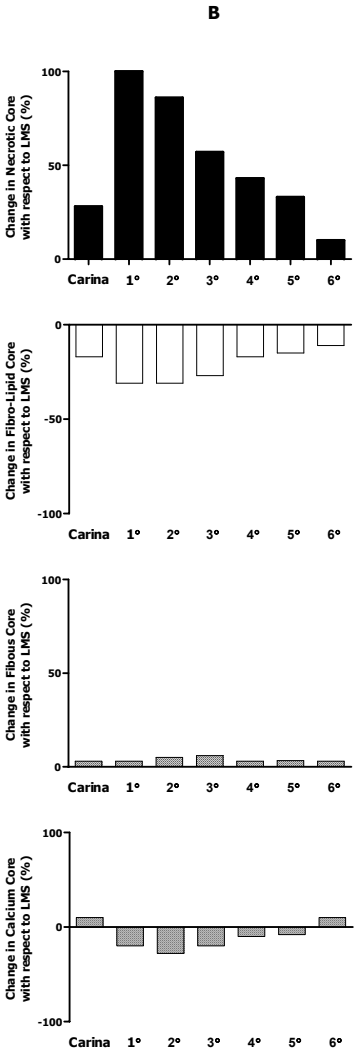
Fibrous tissue was the most prevalent component of plaque composition in each analyzed segment throughout the two models, followed by fibrolipidic tissue, necrotic core and calcium (table 3). No significant change was observed in terms of relative plaque composition throughout the study vessel with respect to fibrous and calcified tissue content. The percentage of fibrolipidic tissue decreased in the second and third 6-mm segment when contrasted to the LMS. When compared to the 6th coronary segment, however, no difference emerged among the vessel tracts in terms of fibrolipidic content at post-hoc analysis.

The necrotic core increased significantly in the first, second and third 6-mm segment compared to the LMS. When the most distal segment of the study vessel was taken as reference, the necrotic core remained greater in both the first and second 6-mm segment at post-hoc analysis. As shown in figure 1, the necrotic core was the plaque component with the highest relative change along the vessel (Figure 1). Changes in terms of plaque composition in model 2 are shown in table 3.

Figure 1. Change in plaque composition along the left coronary artery



A: plaque composition in terms of median necrotic, fibro-lipid, fibrous and calcium core content expressed in absolute values along the left coronary vessel



B. The percentage of each plaque components are reported with respect to left main coronary artery (LMS) taken as reference. All analyses are based on model 1.

Table 3. Plaque Composition along the left coronary artery stratified into coronary segments

	Plaque Composition (%)			
	Calcium Core	**Fibrous Core**	**Fibrolipidic Core**	**Necrotic core**
MODEL 1; N=48				
Coronary Segments				
LMS	0.65 (0.2-1.7)	63.5 (57-68)	24.9 (20-29)	4.6 (2-7)
LMS CARINA	1.1 (0.3-1.6)	63.6 (62-71)	23.0 (15-28)	7.2 (4-9)
1° (0-6 mm)	2.1 (0.8-3.8)	61.6 (59-70)	19.8 (8-24)	11.8 (7.8-16)†
2° (6-12 mm)	2.2 (1.1-3.3)	62.4 (59-68)	15 (10-24)*	10.8 (7-16)*
3° (12-18mm)	1.9 (1.0-3)	64.4 (60-70)	17.4 (10-21)*	9.5 (6.5-13.3)*
4° (18-24 mm)	1.6 (1-3)	61.7 (57-70)	17.6 (11-23)	8.7 (6-10)
5° (24-30 mm)	1.2 (1-3)	63.4 (58-66)	18.7 (13-26)	7 (4-11)
6° (30-36 mm)	1.4 (0.6-2.4)	61.5 (57-67)	18.4 (11-25)	6.1 (3-9)
P-VALUE	P=0.32	P=0.88	P=0.01	P=0.0001
MODEL 2; N=24				
Coronary Segments				
PROX. LMS	0.85 (0.08-1.5)	62.8 (55-69)	24.6 (20-30)	3.8 (2.3-6.8)
DIST. LMS	1.0 (0.3-2.1)	64.1 (59-69)	25 (22-28)	6.5 (4.5-8.8)
LMS CARINA	1.3 (0.3-1.6)	64 (61-71)	28.8 (20-29)	7.3 (4.2-8)
1° (0-6 mm)	2.3 (1-3.4)	62.9 (60-71)	20.9 (13.1-25)	11.3 (8-16)†
2° (6-12 mm)	2.3 (1.2-5.0)	62.6 (55-69)	18.8 (13-27)	9.1 (7-13)*
3° (12-18 mm)	2.2 (0.98-4.3)	64.2 (60-70)	20 (16-23)	8.7 (6.7-13.3)*
4° (18-24 mm)	1.2 (0.9-4.5)	64.4 (57-71)	19.5 (11-26)	8.9 (8-10)*
5° (24-30 mm)	1.3 (0.3-4.8)	63.4 (58-68)	22.5 (13-27)	4.9 (4-8)
6° (30-36 mm)	1.2 (0.6-4)	59.9 (52-66)	22.2 (13-29)	3.5 (1.8-6)
P-VALUE	0.36	0.89	0.19	<0.0001

P-values refer to results for the whole model at general linear analysis. *: p<0.05; †: p<0.01 at adjusted-post-hoc comparison as compared to left main stem (LMS) in model 1 and to Prox. LMS in model 2. Results are given as median (IQR). Prox.: proximal; Dist.: distal.

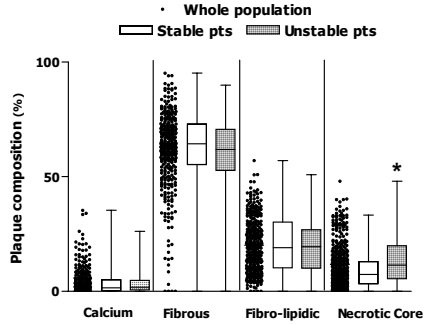
Change in plaque composition according to clinical presentation

No significant change in calcium, fibrous and fibrolipidic content with respect to clinical presentation (stable vs. unstable) was observed when all 384 coronary segments were pooled together (Figure 2). Necrotic core (%) was significantly increased in patients with [median (IQR): 11.4 (5.5-19.8)] as compared to those [median (IQR): 7.3 (3.2-12.9)] without ACS (p<0.001) (Figure 2). After introducing anatomical location stratified into eight coronary segments in the model, the increase in necrotic core in ACS patients was mainly confined to the LMS [6.9 (2.6-9.4) vs. 3.5 (1.4-6.2) in stable patients; p=0.02], in the first [14.9 (7.7-19.6) vs. 11.5 (4.9-17.3) in stable patients; p=0.03], second [12.2 (5.5-16.1) vs. 9.4 (5.1-20.6) in stable patients; p=0.03] and third 6-mm coronary segment [11.4 (5.4-15) vs. 8 (3.6-14.4) in stable patients; p=0.04]. However, the statistical interaction between necrotic core and the anatomical location of the segments did not reach the significance (p=0.12).

LMS length as a predictor of plaque composition along the study vessel

Patients were stratified into two groups based on median LMS length (short LMS ≤ 6 mm and long LMS >6 mm). These two groups did not differ in terms of baseline and procedural characteristics. When each coronary segment was separately analyzed, no difference emerged between the two groups for IVUS-derived quantitative vessel analysis. The same held true if all 384

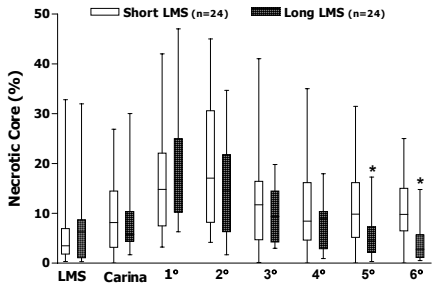
Figure 2. Plaque composition in relation to clinical presentation



Plaque composition on a per segment based analysis in patients with stable angina (stable pts) or with acute coronary syndromes (ACS) (unstable pts). The necrotic core (%) was significantly increased in patients with [median (IQR): 11.4 (5.5-19.8)] as compared to those [median (IQR): 7.3 (3.2-12.9)] without ACS.
*: p<0.001 vs. stable pts.

coronary segments were cumulatively considered independently from their anatomical location. Calcium, fibrous and fibrolipid content did not differ between the two groups (data not shown). The pattern of necrotic distribution in relation to LMS length is shown in figure 3.

Figure 3. Necrotic core distribution along the left coronary artery according to the length of LMS

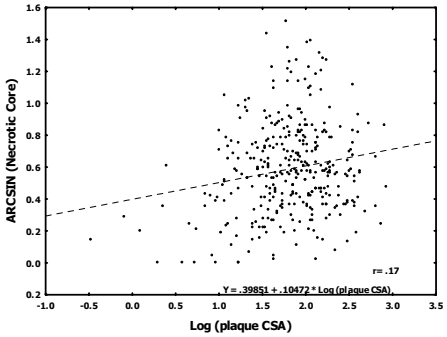


The necrotic core peaked in the first and in the second 6-mm segment in patients with long (above median value) and short left main coronary artery (LMS), respectively. After the peak, the necrotic core decrease was more pronounced in the long than in the short LMS group. As a consequence, the necrotic core content resulted to be significantly increased in the fifth and sixth 6-mm segments in the short as compared to the long LMS group.
*: p<0.05 vs. short LMS.

Correlations

In a segment-based analysis, necrotic core was largely independent from plaque area (r=0.17; p=0.06; R^2=0.09). Similarly, we failed to find an association between necrotic core content and C-reactive protein levels (r=0.09, p=0.8), level of LDL (p=0.11, p=0.23) or HDL (r=-0.2, p=0.4) at entry. However, there was a significant, although weak, direct correlation between necrotic core and cholesterol/HDL ratio (r=0.18, p=0.01; R^2=0.1).

Figure 4. Correlation between arcsin transformed plaque cross sectional area (CSA) and log transformed necrotic core content



CSA: cross sectional area.

DISCUSSION

There is increasing evidence that the distribution of ruptured or prone to ruptured plaques is not uniform along the coronary vessel: they cluster in the proximal tract of the three major coronary vessels while they tend to spare both the LMS and distal segments of coronary arteries(4,16).
These findings have been recently confirmed by mapping the distribution of angiographic sites of occlusive or non-occlusive culprit lesions along the coronary arteries in patients with ST segment elevation acute coronary syndromes(2,3).

The reason why vulnerable plaques show a tendency to cluster in partially predictable *hot spots* located within the proximal tracts of coronary vessel is largely unknown. Atherosclerotic plaques also cluster within the proximal portions of the three major coronaries(17-20). Thus, the risk to undergo rupture may be identical for each coronary plaque independently from its anatomical location, being rupture simply more likely to occur where atherosclerotic plaques are more frequently clustered(21). This may easily explain the non-uniform distribution of ruptured or prone to rupture plaques without calling into question the idea that plaque rupture is partially a site-specific phenomenon.

Alternatively, plaques located within the proximal third of each coronary may harbour some specific hallmark of vulnerability which makes them *individually* more likely to undergo rupture.
To gain some insights into this topic of debate, we hypothesized that plaque necrotic core content, which is a well-known determinant of vulnerability(7,8,22), may differ along the coronary vessel, being greater at the spots where plaque rupture is known to be more frequent.
Our main findings can be summarized as follows:
1) The plaque necrotic content was minimal in the LMS, particularly in the most proximal tract, while it peaked in the first 6-mm segments after the ostium of the two major left coronaries, progressively decreasing towards the more distal segments.
2) The plaque CSA was largely unrelated to necrotic core content throughout the left coronary vessel. This statement is supported by the absence of correlation between necrotic content in plaques and plaque CSA at

the segment-based analysis and by the observation that plaque CSA showed a progressive increase in the distal-proximal direction along the vessel whereas plaque necrotic content did not.

3) The necrotic core was higher in patients with clinical instability, presenting with ACS compared to those affected by stable atherosclerotic disease.

4) The necrotic content was not related to systemic inflammatory status, as measured by a well recognized prognostic marker of inflammation such as C-reactive protein nor LDL or HDL alone, while it showed a significant although weak correlation to cholesterol/HDL ratio.

5) The length of left main trunk was shown to affect the distribution of necrotic core along the vessel. In patients with long LMS, necrotic core content peaked immediately in the first coronary segment after LMS and rapidly decreased distally. Conversely, the necrotic core content peaked in the second 6-mm segment in patients with short LMS and it resulted to be increased in the two most distally analyzed segments compared to the long LMS group.

It is tempting to speculate that the observed clustering of ruptured or prone to rupture plaques in the proximal segment of each coronary artery is not just a simple reflection of the non-uniform distribution of atherosclerosis along the coronary vessel. The necrotic content of those plaques located in these proximal segments, independent of their size, was higher, both compared to the LMS and to those segments which are more distally located. The plaques located within the proximal segments of the left coronary artery, being relatively richer in necrotic content, may undergo rupture more easily than those located in the LMS or in the distal tracts of the vessel.

Some preliminary unpublished findings by our group suggest that plaque necrotic core content, as assessed through IVUS-VH, may be the only independent predictor for mechanically deformable regions (high-strain spots)(23) throughout the coronary arteries in humans. Thus, when our findings are put in perspective of current evidence, they support the idea that vulnerability may cluster in necro-lipid-rich regions throughout the vessel.

Necrotic core content in the present study was higher in patients with ACS, suggesting again that plaque composition in itself may play a pivotal role in determining vulnerability. Interestingly, it was recently reported that when rupture of coronary plaques occurs in the LMS, the distal half of LMS is more likely to be involved (24). Our findings that the distal LMS tends to harbour a greater necrotic core content compared to proximal half, together with the well established role of shear stress in bifurcated lesions(25), may contribute to explain the non-uniform distribution of plaque rupture even within the LMS.

The reasons why the plaque necrotic core seems to exceed in the proximal as compared to the distal tracts of the coronary vessel or the LMS remain speculative at the present time. Low-oscillatory shear stress is known to induce a loss of the physiological flow-oriented alignment of the endothelial cells, an enhancement of the expression of adhesion molecules and a weakening of cell junctions, ultimately leading to an increase in permeability to lipids and macrophages(25). The segments located in the first few centimetres of the coronary arteries, due to flow turbulence generated by high velocity blood impacting against anatomical flow dividers(26), may be more exposed to low-oscillatory shear stress compared to the most proximal (i.e. LMS) or more distal coronary segments, thus possibly explaining our present findings(27). Concomitant quantitative measurement of shear stress and plaque composition along coronary vessels in vivo would be pivotal in corroborating this working hypothesis.

Limitations of the Study

Based on previous findings and the well known role of necrotic core content in determining vulnerability(6-8,22), our investigation was primarily focused on the distribution of necrotic core content along the left coronary artery. In order to assess relatively minor changes in plaque composition along the longitudinal artery axis, such as that observed for fibrous tissue, a bigger properly powered sample size is clearly needed. In keeping with previous considerations, all other analyses and comparisons performed in the current manuscript should be regarded as exploratory and hypothesis-generating since we cannot rule out the possibility that inflation of type I error due to multiple comparisons may have confounded our results.

In our study the operators were left free to wire the most suitable vessel for the IVUS pullback, provided it was supplying a major left ventricle territory. This resulted in the predominance of LAD as region of interest, while the CFX artery was mainly investigated in those patients presenting with small or tortuous LAD. The distribution of necrotic core along the vessel did not differ in LAD as compared to CFX. The same held true for other studied plaque components. However, the applied selection process may have biased this comparison. Thus, whether the distribution of plaque composition may differ in relation to the studied vessel remains to be tested. Similarly, in order to maximize patients' safety and avoid potential IVUS-related complications, individuals with severe angiographic calcification were excluded. Despite this decision may have clearly contributed to generate some selection bias, the distribution of calcium along the coronary vessel intriguingly mirrored the one observed for the necrotic core. Further studies are needed to investigate the specific role of calcium content in determining plaque vulnerability.

Patients with proximal occlusions have bigger MI and thus they are more likely to present to hospital and be referred for angioplasty. Similarly, myocardial infarction due to LMS as culprit artery may often result in immediate death. Thus, it may be argued that a selection bias might have artificially increased the prevalence of patients with culprit lesions located in the proximal compared to distal tracts of coronaries or LMS. This is obviously theoretical possible. However, for the following reasons, we believe that this possibility is relatively unlikely:

A. The Necrotic core in our series clustered in the same coronary spots where previous studies, based on post-mortem examination, found a higher prevalence of ruptured or healed plaques.

B. Our results are based on the investigation of the non-culprit vessel. Thus, they are potentially less prone to suffer from clinical selection due to the location of the culprit lesion in the culprit vessel.

C. Although it seems to be exacerbated in patients presenting with clinical instability, the non-uniform distribution of plaque composition along the vessel has been observed also in patients with stable coronary disease, in whom the selection bias due to the importance of the culprit lesion is less obvious, at least for the comparison LMS vs. proximal tracts of LAD or CFX.

Thus, based on these considerations, we think that our findings, especially when put in the context of previous evidence(1-5), may help reinforcing the notion that there may be some hot spots along the coronary vessel which are per se more prone to develop vulnerable plaque and as such undergo plaque rupture.

Summary and Conclusions

Plaque composition was found to be not uniformly distributed along the left coronary artery with a progressive increase in necrotic core starting from the proximal half of the LMS to the most proximal segments of the LAD or CFX, followed by a steady decline towards those segments which are more distally located along the vessel. The necrotic core appeared to be increased in patients with ACS, especially in the LMS and in the three proximal coronary segments of LAD or CFX, while it did not correlate with the CRP or lipid profile. The relatively site-specificity of necrotic core content towards the proximal segment of the left coronary artery is in keeping with the increasing evidence that a clear clustering of ruptured or prone to rupture plaques occurs in humans within this region (2,3,5). Our findings i) reinforce the notion the plaque composition may be a major determinant for and subsequently a potential target of plaque vulnerability in humans and ii) call for prospective evaluation of the independent role of plaque composition on long-term outcome in patients with established coronary artery disease.

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Part. 3. Primary Intervention for acute myocardial infarction

Chapter 11 High-dose bolus tirofiban and sirolimus eluting stent versus abiciximab and bare metal stent in acute myocardial infarction (STRATEGY) study--protocol design and demography of the first 100 patients.

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High-Dose BoluS TiRofibAn and Sirolimus Eluting STEnt versus Abiciximab and Bare Metal Stent in Acute MYocardial Infarction (STRATEGY) Study—Protocol Design and Demography of the First 100 Patients

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Summary. Background: **Primary bare metal stenting and abciximab infusion are currently considered the best available reperfusion strategy for acute ST-segment elevation myocardial infarction (STEMI). Sirolimus eluting stents (SES), compared to bare metal stent (BMS), greatly reduce the incidence of binary restenosis and target vessel revascularisation (TVR), but their use on a routine basis results in a significant increase in medical costs. With current European list prices, the use of tirofiban instead of abciximab would save enough money to absorb the difference between SES and BMS.**

Aim: **To assess whether in patients with STEMI the combination of SES with high dose bolus (HDB) tirofiban results in a similar incidence of major cardiovascular events (MACE) but in a lower binary restenosis rate after six months compared to BMS and abciximab.**

Methods and Results: **160 patients are required to satisfy the primary composite end-point, including MACE and binary restenosis. The study is ongoing: the current paper focuses on the methodology and demography of the first 100 patients so far enrolled. Patients randomised to HDB tirofiban ($n = 50$, mean age: 62 ± 12, 40 males) and abciximab ($n = 50$, mean age: 63 ± 12, 38 males) do not differ for medical history, presentation profile, medications at discharge, angiographic profile and creatine-kinase MB-fraction at peak.**

Conclusions: **The results of the trial will be available by the end of 2004: they will be crucial for the cardiologists to know whether the gold standard for AMI treatment should be reconsidered after the introduction of SES into the clinical practice.**

Key Words. **Sirolimus eluting stents, high dose Bolus tirofiban, Abciximab, primary percutaneous coronary intervention**

Background

Primary angioplasty is the current preferred therapeutic option for patients with ST-segment elevation myocardial infarction (STEMI) [1]. The superiority of mechanical reperfusion in patients with acute myocardial infarction (AMI) reflects of the technological advances fulfilled by catheter-based coronary interventions in the last ten years, mainly consisting of widespread use of last generation stents and glycoprotein IIb/IIIa inhibitors.

Routine coronary stent implantation in patients with AMI decreases the need for target-vessel revascularization (TVR) [2,3], while the use of abciximab is associated to a lower incidence of subacute stent thrombosis and recurrent ischaemia during the first month after primary PCI [4,5]. Therefore, despite no clear data are available on the cost-effectiveness of the combination [6], stenting plus abciximab has been recently advocated as the gold standard for STEMI treatment [7].

Drug eluting stents (DES) are one of the most promising new fields of research in interventional cardiology. Sirolimus eluting stents (SES), compared to bare metal stent (BMS), greatly reduce the incidence of binary restenosis and clinically-driven TVR [8]. In

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a consecutive series of 96 AMI patients treated with SES, a good safety profile was also reported, suggesting that the long-term benefit of SES implantation could be duplicated in AMI patients, with low incidence of short-term complications [9].

However, the cost of combining only one single SES with abciximab infusion in an average-weight patient will much exceed 3000 Euros and this would result in a considerable increase of medical care costs.

The STRATEGY trial is a single-centre, single-blind randomised trial comparing the current recommended gold standard therapy for AMI, namely BMS plus abciximab, vs. a new combination based on the association of SES plus tirofiban with high-dose bolus (HDB).

The rationale behind the use of tirofiban is:

(i) With current European list prices, the combination of tirofiban with one SES leads to a comparable economical impact than one BMS plus abciximab;
(ii) HDB has recently replaced the RESTORE-regimen, showing promising results in elective and urgent PCI. Possibly, this revised tirofiban regimen will fill the gap with abciximab in the subset of patients undergoing urgent PCI, thus promoting allocation of the current economical resources to the emerging DES technology during primary PCI.

Methods

Patients

All consecutive patients older than 18 years, scheduled for primary PCI, presenting with ST-segment elevation AMI are being enrolled according to the following inclusion criteria: (i) chest pain persisting >30 min, associated with ST-segment elevation of at least 0.1 mV in two or more contiguous ECG leads; and (ii) admission either within 12 h from symptom onset or between 12 and 24 h if there was evidence of continuing ischaemia. The exclusion criteria included previous administration of fibrinolytic or any glycoprotein IIb/IIIa inhibitors, history of bleeding diathesis or allergy to the studies drug, major surgery within 15 days, active bleeding, previous stroke in the last six months and inability to obtain informed consent. According to the protocol, cardiogenic shock—defined as systolic blood pressure <90 mm Hg (without inotropic or intra-aortic balloon support) thought to be secondary to ventricular dysfunction and associated with signs of end-organ hypoperfusion such as: cold or diaphoretic extremities; altered mental status; or anuria—will not be considered an exclusion criterion.

Our local Ethics Committee on Human Research has approved the protocol in January 2003 and all participants are asked to give their informed consent before entering the study.

Randomisation

Patients who meet the eligibility criteria are being randomly assigned—with the use of computer-based 1:1 randomisation scheme—to HDB tirofiban (Aggrastat, Merck, West Point, Pa.) or abciximab (Reopro, ReoPro, Centocor, Malvern, Pennsylvania) on a single-blind basis. The study drug is started as soon as possible in the intensive cardiac care unit (CCU), and subsequently patients are transferred to the cath-lab.

All patients with a reference infarct related artery (IRA) diameter >2.25 mm at visual estimation are eligible for stenting.

Per protocol, patients randomised to tirofiban receive SES (Cypher; Johnson & Johnson, Cordis Corp.), and crossover to other types of stent is allowed only after failure of SES implantation attempt, or impossibility to match available stent size with coronary reference diameter.

Patients allocated in the abciximab arm are eligible only to BMS: the first choice is Sonic stent (Johnson & Johnson, Cordis Corp.), but any bare metal stent type approved by regulatory agency can be implanted. Coronary stenting is accomplished using a standard technique or directly, without pre-dilatation, at the discretion of the operator.

Analyses of the data will be based on the intention-to-treat principle.

Angiographic analysis

The angiographic images are acquired with a General Electrics Advantage CRS V 5.6.5 single-plane system at a cine rate of 25 frames/s. Basal TIMI flow and collateral circulation to the culprit vessel are evaluated on the first angiogram. TIMI flow, corrected TIMI frame count and myocardial blush (MB) is graded on the angiograms taken immediately after PTCA, as previously described [10–12]. Latero-lateral view for the left anterior descending coronary artery (LAD), right anterior oblique 45° view for the right coronary artery, and latero-lateral or right anterior oblique 45° views for the circumflex artery are used in most cases. Ten seconds of cine filming are required to allow some filling of the venous system to evaluate the washout phase of contrast dye. In order to facilitate the subjective grading of MB, angiograms are also digitised and a logarithmic non-magnified mask-mode background subtraction is applied to the image subset to eliminate non-contrast medium densities. The analysis are being carried out by two cardiologists who are blinded to the patient's identity and ECG findings. Blush is graded according to the dye density score: grade 0 to 1 was minimal to no MB or contrast density (relative to the dye density in uninvolved areas); grade 2 was moderate MB; and grade 3 was normal MB.

Quantitative coronary angiography on results obtained immediately at the end of PCI and at month 6 will include IRA reference diameter and minimum lumen diameter.

Medications and procedures

All patients will receive aspirin (160–325 mg orally as loading dose (LD) and then 80–125 mg orally indefinitely) and clopidogrel (300 mg orally as LD and then 75 mg/day for at least three months). Tirofiban is given as a bolus of 25 μg/Kg/3-min, followed by an infusion of 0.15 μg/Kg/min for 18–24 h. Heparin is adjusted as follows: all patients, at the time of study drug bolus infusion, receive 50–70 U/Kg heparin (maximum 7000 U) with additional boluses to achieve and maintain an activated clotting time of at least 200 secs.

IRA is the only target of the procedure. Intra-aortic counterpulsation is performed in case of haemodynamic instability. TIMI grade 3 coronary flow in the treated vessel with a residual stenosis <20% is considered successful PTCA.

A 12-lead ECG is recorded before and continuously 30 min after IRA recanalisation. Two observers, unaware of the clinical and angiographic data, perform the analysis. ST-segment changes are evaluated in the single lead with the most prominent ST-segment elevation as well as cumulative before and after mechanical intervention. ST-segment elevation is measured to the nearest 0.5 mm at 60 ms after the J point, with the aid of hand-held calipers. Creatine kinase (CK) measurements are systematically performed on hospital admission, every 3 h for the subsequent 24 h, and then every 12 h for two days. The peak CK value and the time to peak CK are evaluated in each patient.

The protocol anticipates to discontinue heparin after the procedure and remove arterial sheath when ACT is <180 secs with arteriotomy closure device or with external compression for haemostasis. Investigators can modify these guidelines at their discretion to meet the medical needs on a patient-by-patient basis. Patients will not be discharged before four days after revascularisation.

Angiographic follow-up

Complete angiographic follow-up at month 6 will be carried out unless patients die, undergone repeated revascularisation, have an occluded vessel at the end of the procedure or do not undergo a revascularization procedure after the initial coronary angiography (e.g., because the rate of flow in the target vessel was classified as grade 3 according to the classification of the Thrombolysis in Myocardial Infarction [10] trial and the stenosis was judged to be less than 50 percent), or refuse angiography at month 6.

Study end-points

The primary end-point is a composite of death, nonfatal MI, stroke and binary restenosis within a median follow-up of 180 days after index procedure. Patients with more than one event will be assigned the highest ranked event, according to the previous list.

Nonfatal MI is defined as recurrent chest pain with ST-segment or T-wave changes and recurrent elevation of cardiac enzymes. Stroke is defined as an acute neurologic defect that lasts >24 h and results in death or an inability to perform normal activities.

Angiographic binary restenosis, dichotomised in in-stent and in-segment (5 mm above and after the stent margins) is defined as a >50% diameter stenosis by quantitative coronary angiography.

Secondary end-points include the composite one at day 30 and month 6 of death, recurrent MI, stroke and clinically-driven target vessel revascularisation (TVR), defined as any coronary artery bypass graft surgery, or a second PCI of the original target vessel, performed on a non-elective basis for recurrent myocardial ischaemia, and degree of myocardial perfusion according to ST-segment resolution and MB analysis after the procedure. For an analysis of safety, the end-points of major and minor bleeding complications are defined according to the criteria of the Thrombolysis in Myocardial Infarction Trial [13].

Statistical analysis

The sample size was calculated on the assumption that incidence of death, reinfarction and stroke at six month would be around 5% in both groups and that the rate of binary restenosis would be 25% in the abciximab-BMS group and 8% in the tirofiban-SES group. To detect this effect size with 80% power and a type I error (alpha) of 0.05, 160 patients will be required, after augmenting to take in account of a 10% of drop-outs.

One single interim analysis is planned after the angiographic follow-up of the first 50 patients, applying the Lan-DeMets approach [14]. If necessary, the estimated sample size will be re-powered accordingly.

Discrete data will be summarized as frequencies, whereas continuous data will be expressed as mean $\pm$ SD. The chi-squared and Fisher's exact tests will be used for comparison of categorical variables. The Student's t-test and Mann-Whitney U test will be used to test differences among continuous variables. Multivariate logistic regression analysis will be performed to identify independent correlates of the primary end point, six-month mortality, and cumulative six-month mortality, reinfarction and urgent TVR. All analyses will be conducted according to the intention-to-treat principle. For exploratory purpose survival curves will be generated using the Kaplan-Meier method, and the difference between curves will be assessed by the log-rank test. A p value <0.05 was considered significant. Odds ratios (ORs) with 95% confidence intervals (CIs) will be calculated. Analyses will be performed using the package software STATISTICA version 6.1 (Statsoft Inc.).

Table 1. *Base-line characteristics of the patients*

Characteristics	Abciximab-BMS ($n = 50$)	HDB-Tirofiban-SES ($n = 50$)	P
Age (yr)	63 ± 12	62 ± 12	NS
Male sex (%)	76	80	NS
Weight (kg)	74 ± 13	78 ± 13	NS
Diabetes (%)	9	14	NS
Hypertension (%)	40	58	NS
Smoker (%)	42	38	NS
Creatinine (mg/dl)	1.13 ± 0.3	1.23 ± 0.4	NS
Creatinine Clearance ()	73	68	NS
Medical history (%)			
CABG	4	0	NS
PCI	2	0	NS
Acute myocardial infarction	10	14	NS
Cerebrovascular accident	6	4	NS
Presentation profile			
Systolic Pressure (mmHg)	132 ± 26	128 ± 23	NS
Heart Rate (beats/min)	76 ± 16	76 ± 18	NS
Anterior MI	48	58	NS
Killip class >1	14	10	NS
Medications (%)			
Aspirin	86	94	NS
Clopidogrel	84	90	NS
Statin	82	66	NS
ACE-inhibitor	78	88	NS
β-blocker	78	70	NS

Results

Study enrolment began on 6 March 2003, being the first 100 patients included in the trial in seven month time. Baseline clinical characteristics of the study population are shown in Table 1. Patients randomised to abciximab and BMS are balanced in respect to HDB tirofiban and SES group for baseline demography, medical history, presentation profile and medications at discharge. Angiographic and procedural data are shown in Table 2. Patients randomised to HDB tirofiban and SES do not differ in respect to abciximab and BMS group for location of culprit lesion, prevalence of multivessel disease, reference diameter of infarct related artery, door to balloon time, prevalence of stenting and number or total length of stents delivered, final minimal lumen diameter, prevalence of patients submitted to heparin infusion after sheath removal and creatine-kinase MB-fraction at peak.

STRATEGY sub-study

In a subset of patients ($n = 50$), platelet aggregation assay is conducted before (T_0), 5 (T_1), 10 (T_2) and 30 (T_3) min after the bolus dose with the PFA-100 device (Dade-Behring).

The PFA-100 analyser is a new, rapid and standardised assay that reflects the extent of platelet adhesion and aggregation blockade, and that might be helpful in monitoring antiplatelet drug therapy and in guiding dose adjustment in order to achieve optimal clinical benefit [15,16].

The PFA-100 device (Dade-Behring) is used to measure platelet adhesion and aggregation at high shear conditions, in some way mimicking an *in vivo* bleeding time [17,18].

Blood is forced to flow through a synthetic capillary, with a collagen and ADP-coated membrane with a central hole at its end. When a haemostatic platelet plug completely obliterates the central hole, the blood flow will stop. The time necessary to stop the flow is called "closure time" and is related to platelet function.

This sub-study will give additional information on the degree of platelet inhibition in patients treated with HDB tirofiban as compared with those treated with abciximab standard regimen. Any adverse clinical events recorded in this subset of patients will be correlated to the degree of platelet inhibition before and after treatment.

Table 2. *Procedural data*

Characteristic	Abciximab-BMS ($n = 50$)	HDB-Tirofiban-SES ($n = 50$)	P
Infarct-related artery (%)			
LAD	58	48	NS
RCA	32	28	NS
LCx	20	12	NS
Multivessel Disease (%)	34	50	NS
Reference diameter (mm)	3 ± 0.52	2.94 ± 0.6	NS
Door-to-Balloon (min)	82 ± 36	74 ± 33	NS
Delivery of at least 1 stent (%)	96	92	NS
>1 stent implanted (%)	8	8	NS
Stent length (mm)	20 ± 5	22 ± 7	NS
Final minimal lumen diameter (mm)	2.83 ± 0.6	3 ± 0.4	NS
Heparin after sheath removal (%)	18	10	NS
CK-MB at peak (ng/ml)	245 ± 237	240 ± 205	NS

Discussion

In the last years, many new catheter-based devices have been developed for percutaneous treatment of elective and urgent coronary interventions [19–23]. However, due to exponential growing of the costs, their use in the cath-lab if often regarded as competitive; even if their simultaneous use has been regarded as promising [24], they are very rarely combined in clinical practice. The potential risk of this attitude is to progressively create a dangerous divergence between evidenced-based medicine and clinical practice.

It has been recently shown that the unrestricted utilization of sirolimus-eluting stents in the "real world" is safe and effective in reducing repeat revascularization at 1 year compared with bare stent implantation [25].

However, the cost-effectiveness of this policy has been also recently questioned [26]. The main argumentation is that the use of DES would not probably result in a final reduction of death and MI. Accordingly, the routine use of DES in the clinical arena will be justified only if a significant cost-reduction is provided. An alternative and attractive approach—that is the aim of the current ongoing clinical study—is to combine DES with a less expensive adjunctive therapy and directly compare this new interventional strategy with the current golden standard.

The philosophy behind the study design is that, by simply re-allocating the current economical resources for the treatment of AMI, a better clinical/angiographic outcome can be reached, thus improving the cost-effectiveness for medical interventions in this setting.

The STRATEGY trial is based on the assumption that the two combination therapies will be equally effective in terms of death, myocardial re-infarction and stroke, with the 6-month angiographic follow-up showing a superiority in terms of in-segment late-loss and binary restenosis rate in the tirofiban plus SES study arm.

The choice to start the administration of glycoprotein IIb/IIIa inhibitors in the CCU is peculiar of the STRATEGY trial and should be further discussed.

In the ADMIRAL study, it was clearly shown that the earlier the administration of abciximab, the bigger the benefit in respect to placebo therapy was [5]. This has prompted the idea—currently being tested in randomised clinical trials—that facilitated primary PCI could be superior to PCI even if glycoprotein IIb/IIIa inhibitors are given at the time of the procedure.

Moreover, by administering the study drug before assessing the coronary anatomy, the patient is enrolled in the trial regardless the complexity of the culprit lesion(s), thus avoiding the selection bias that was claimed to be responsible for the neutral effect of abciximab vs. placebo in the CADILLAC trial [7].

In the TARGET trial, tirofiban at RESTORE regimen was shown to offer less protection in from MACE in respect to abciximab in unstable patients [27].

The reasons for these results are currently speculative and possibly due to an inadequate early platelet inhibition of tirofiban at RESTORE regimen in the trials.

Platelet reactivity is pivotal in the pathogenesis of complications after PCI and the degree of platelet inhibition with the use of glycoprotein (GP) IIb/IIIa inhibitors during PCI is critical for the protection from ischaemic events [28].

In the randomised comparison of platelet inhibition with abciximab, tirofiban and eptifibatide during PCI in ACS (COMPARE) trial, platelet aggregation 15 and 30 min after drug infusion was significantly less inhibited with the tirofiban-RESTORE regimen compared to with abciximab and eptifibatide and, at 30 min, also compared with the tirofiban-PRISM-PLUS regimen [29].

Accordingly, the bolus of tirofiban regimen has been revised and increased from 10 μg/kg to 25 μg/kg (HDB tirofiban) [30]. From preliminary uncontrolled findings, this new regimen appears safe [31] and in a recently completed double-blind placebo controlled trial, the use of HDB tirofiban was shown to be superior to placebo in both stable and unstable high-risk patients.

The STRATEGY trial will be the first head-to-head comparison between HDB tirofiban and abciximab and its results will probably give some new insights into the unexpected results of the TARGET trial.

Finally, the clinical impact of reduced restenosis rate on prognosis is out of the scope of the present phase II study, but preliminary data would possibly allow shaping the sample size for future studies in this field.

In case the interim analysis confirms the prespecified sample size, the results of the STRATEGY trial will be available by the end of 2004. By that time, three main questions will be answered:

(i) What is the rate of MACE if HDB tirofiban, combined to SES, is used instead of abciximab and BMS?
(ii) What is the net gain in terms of binary restenosis and late-loss when SES is implanted during primary PCI instead of a BMS?
(iii) Is the combination between HDB tirofiban and SES superior to abciximab and BMS in terms of composite of MACE and binary restenosis?

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Chapter 12 Tirofiban and sirolimus-eluting stent vs abciximab and bare-metal stent for acute myocardial infarction: a randomized trial.

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Tirofiban and Sirolimus-Eluting Stent vs Abciximab and Bare-Metal Stent for Acute Myocardial Infarction

A Randomized Trial

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Context Bare-metal stenting with abciximab pretreatment is currently considered a reasonable reperfusion strategy for acute ST-segment elevation myocardial infarction (STEMI). Sirolimus-eluting stents significantly reduce the need for target-vessel revascularization (TVR) vs bare-metal stents but substantially increase procedural costs. At current European list prices, the use of tirofiban instead of abciximab would absorb the difference in cost between stenting with sirolimus-eluting vs bare-metal stents.

Objective To evaluate the clinical and angiographic impact of single high-dose bolus tirofiban plus sirolimus-eluting stenting vs abciximab plus bare-metal stenting in patients with STEMI.

Design, Setting, and Patients Prospective, single-blind, randomized controlled study (Single High Dose Bolus Tirofiban and Sirolimus Eluting Stent vs Abciximab and Bare Metal Stent in Myocardial Infarction [STRATEGY]) of 175 patients (median age, 63 [interquartile range, 55-72] years) presenting to a single referral center in Italy with STEMI or presumed new left bundle-branch block and randomized between March 6, 2003, and April 23, 2004.

Intervention Single high-dose bolus tirofiban regimen plus sirolimus-eluting stenting (n=87) vs standard-dose abciximab plus bare-metal stenting (n=88).

Main Outcome Measures The primary end point was a composite of death, nonfatal myocardial infarction, stroke, or binary restenosis at 8 months. Secondary outcomes included freedom, at day 30 and month 8, from major cardiac or cerebrovascular adverse events (composite of death, reinfarction, stroke, and repeat TVR).

Results Cumulatively, 14 of 74 patients (19%; 95% confidence interval [CI], 10%-28%) in the tirofiban plus sirolimus-eluting stent group and 37 of 74 patients (50%; 95% CI, 44%-56%) in the abciximab plus bare-metal stent group reached the primary end point (hazard ratio, 0.33; 95% CI, 0.18-0.60; $P<.001$ [$P<.001$ by Fischer exact test]). The cumulative incidence of death, reinfarction, stroke, or TVR was significantly lower in the tirofiban plus sirolimus-eluting stent group (18%) vs the abciximab plus bare-metal stent group (32%) (hazard ratio, 0.53; 95% CI, 0.28-0.92; $P=.04$), predominantly reflecting a reduction in the need for TVR. Binary restenosis was present in 6 of 67 (9%; 95% CI, 2%-16%) and 24 of 66 (36%; 95% CI, 26%-46%) patients in the tirofiban plus sirolimus-eluting stent and abciximab plus bare-metal stent groups, respectively ($P=.002$).

Conclusion Tirofiban-supported sirolimus-eluting stenting of infarcted arteries holds promise for improving outcomes while limiting health care expenditure in patients with myocardial infarction undergoing primary intervention.

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BARE-METAL STENTING, BY DECREASING the rate for target-vessel revascularization (TVR),[1,2] has been endorsed as a class I indication in the treatment of acute ST-segment elevation myocardial infarction (STEMI).[3] Abciximab, by virtue of its salutary effect on tissue perfusion and coronary artery patency, has also been recommended as part of a reasonable treatment strategy.[3,4]

Sirolimus-eluting stents greatly reduce the need for TVR compared with bare-metal stents and thus have the potential to further improve long-term clinical outcome after primary percutane-

For editorial comment see p 2154.

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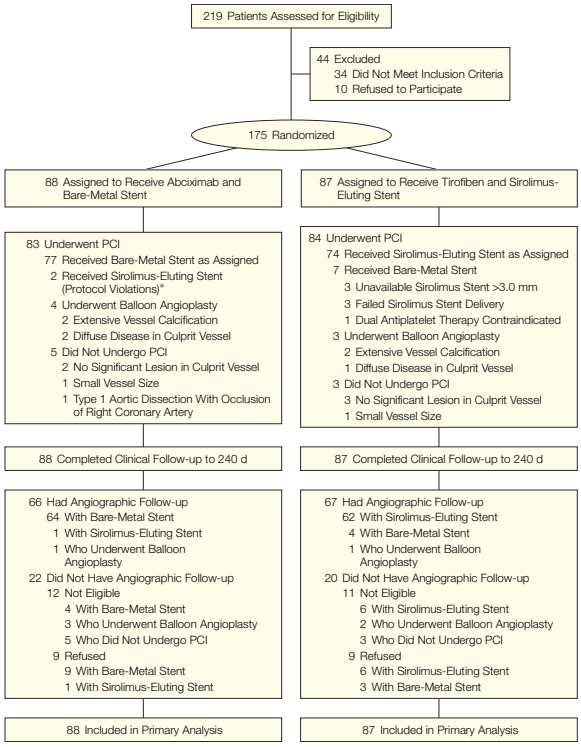
ous coronary intervention (PCI).[5] However, the lack of randomized trials to assess the safety and long-term efficacy of sirolimus-eluting stent implantation in patients with STEMI, in conjunction with the financial consequences of replacing bare-metal stenting with sirolimus-eluting stenting, currently limit use of sirolimus-eluting stents in this setting.[6] Furthermore, in the first tertiary referral center to adopt unrestricted use of sirolimus-eluting stents, a concomitant decrease in the use of abciximab has been reported.[7] This may indicate a reluctance to use glycoprotein (Gp) IIb/IIIa inhibitors and drug-eluting stents simultaneously for economic reasons.

Current clinical guidelines specifically recommend abciximab during primary PCI,[3]and recent additional evidence strongly supports the value of Gp IIb/IIIa inhibitors in this setting.[8] Replacing abciximab with tirofiban, administered as a single high-dose bolus (SHDB) regimen, is a promising strategy that could preserve financial resources. At current European market prices (approximately 580 € [$742] for tirofiban vs approximately 1900 € [$2432] for abciximab), this would absorb the additional cost of sirolimus-eluting stenting vs bare-metal stenting (European list price: approximately 1800 € [$2304] for sirolimus-eluting vs approximately 600 € [$768] for bare-metal stenting).

Thus, in an attempt to further improve outcome after myocardial infarction (MI) without affecting overall costs, we compared a strategy of tirofiban-supported infarct artery sirolimus-eluting stent implantation with a current preferred strategy for STEMI treatment in terms of angiographic and clinical outcome.[4]

Figure 1. Study Profile



PCI indicates percutaneous coronary intervention.
*Unjustified protocol violations in patients with diabetes and left anterior descending lesions.

METHODS

Protocol and Randomization

The Single High Dose Bolus Tirofiban and Sirolimus Eluting Stent vs Abciximab and Bare Metal Stent in Myocardial Infarction (STRATEGY) trial was a prospective, single-center, randomized trial of 2 strategies: SHDB tirofiban plus sirolimus-eluting stent implantation vs standard abciximab regimen plus bare-metal stent implantation, in patients undergoing primary angioplasty for acute STEMI. The design of the study has been described in detail.[9]

Individuals eligible for enrollment were consecutive patients presenting with STEMI who fulfilled the following inclusion criteria: (1) chest pain for more than 30 minutes with ST-segment elevation of 1 mm or more in 2 or more contiguous electrocardiograph leads or with presumably new left bundle-branch block and (2) admission either within 12 hours of symptom onset or between 12 and 24 hours with evidence of continuing ischemia. Exclusion criteria included administration of fibrinolytic agents in the previous 30 days, history of bleeding diathesis or allergy to the study drugs, major surgery within 15 days, and active bleeding or previous stroke in the last 6 months. The University of Ferrara institutional review board approved the protocol in January 2003, and all patients gave written informed consent.

Open-label randomization was performed in the coronary care unit by the treating physician immediately after eli-

gibility criteria were met. A 1:1 computer-generated random sequence supplied by an academic statistician, without blocking or stratification, was used. Sealed envelopes indicated the treatment group to which the patients were assigned: SHDB tirofiban (Aggrastat; Merck, West Point, Pa [Europe]/Guilford Pharmaceuticals, Baltimore, Md [United States]) or abciximab (ReoPro; Centocor, Malvern, Pa). The study drug was started in the coronary care unit and subsequently patients were transferred to the cardiac catheterization laboratory. Per protocol, patients allocated to the tirofiban group received sirolimus-eluting stenting (Cypher; Cordis Corp, Miami Lakes, Fla). Crossover to bare-metal stenting was allowed only when sirolimus-eluting stent implantation failed or when it was impossible to match sirolimus-eluting stent diameter with coronary reference diameter (sirolimus-eluting stents were only available in diameters from 2.25-3.00 mm during the enrollment period). Patients allocated to the abciximab group received bare-metal stenting: the first choice was a Sonic stent (Cordis Corp), but any commercially available bare-metal stent could be implanted.

Medications

Tirofiban was given as a bolus of 25 µg/kg over 3 minutes, followed by an infusion of 0.15 µg/kg per minute for 18 to 24 hours. Abciximab was administered as a bolus of 0.25 mg/kg over 3 minutes, followed by a 12-hour infusion of 0.125 µg/kg per minute. All patients received aspirin (160-325 mg orally as a loading dose and then 80-125 mg/d orally indefinitely) and clopidogrel (300 mg orally as a loading dose and then 75 mg/d for at least 3 months). Heparin (50 U/kg) was administered before the procedure, with additional boluses administered to achieve and maintain an activated clotting time of at least 200 seconds.

Electrocardiographic and Platelet Measures

Cumulative ST-segment elevation, evaluated in all leads with any ST-segment elevation of 1 mm or greater, was measured to the nearest 0.5 mm at 60 milliseconds after the J point.

In a subset of 70 randomly selected patients, a platelet aggregation assay was conducted before and 10 minutes after the bolus dose of Gp IIb/IIIa inhibitors using a platelet function analyzer (PFA-100; Dade Behring Inc, Deerfield, Ill), as previously described.[10] *Closure time*, ie, the time necessary to form a hemostatic platelet plug and to stop blood flow when the sample is aspirated at high shear rate (5000-6000 seconds^{-1}) through a collagen- and adenosine diphosphate–coated capillary (147 µm diameter), inversely reflects platelet reactivity in the sample evaluated.

Angiographic Analysis

Thrombolysis in Myocardial Infarction (TIMI) grade 3 coronary flow in the treated vessel and a residual stenosis less than 30% were the criteria used to define a successful PCI. Quantitative angiographic analyses, using a validated edge-detection system (CAAS II; Pie Medical, Maastricht, the Netherlands), were performed by an experienced cardiologist who was unaware of treat-

Table 1. Baseline Characteristics and Medications of the Patients

Characteristic	SHDB Tirofiban + Sirolimus-Eluting Stent (n = 87)	Abciximab + Bare-Metal Stent (n = 88)	*P* Value
Age, median (IQR), y	62 (54-72)	63 (55-72)	.69
Men, No. (%)	67 (77)	61 (69)	.72
Body mass index, median (IQR)*	26 (24-29)	26 (24-29)	.79
Diabetes, No. (%)†	15 (17)	11 (12)	.53
Hypertension, No. (%)†	48 (55)	44 (50)	.79
Smoker, No. (%)†	34 (39)	36 (41)	.88
Creatinine clearance, median (IQR), mL/min	74 (55-102)	70 (55-94)	.48
Medical history, No. (%)			
CABG surgery	2 (2)	2 (2)	>.99
PCI	4 (5)	2 (2)	.68
MI	11 (13)	8 (9)	.63
Cerebrovascular accident	5 (6)	4 (5)	.74
Presentation profile			
Systolic blood pressure, median (IQR), mm Hg	129 (110-150)	125 (115-145)	.71
Heart rate, median (IQR), beats/min	72 (64-85)	75 (62-90)	.34
Anterior MI, No. (%)	43 (49)	36 (41)	.50
Killip class ≥2, No. (%)	15 (17)	12 (14)	.68
Cardiogenic shock, No. (%)	5 (6)	5 (6)	>.99
Hours from symptom onset to intervention, No. (%)			
<3	43 (49)	43 (49)	>.99
3-6	32 (37)	36 (41)	.77
>6	12 (14)	9 (10)	.64
Median (IQR)	3 (1.8-4)	3 (2.2-4.3)	.18
Medications at discharge, No. (%)			
Aspirin	82 (94)	80 (91)	.91
Clopidogrel	68 (78)	68 (77)	>.99
Ticlopidine	16 (18)	15 (17)	>.99
Oral anticoagulant	2 (2)	3 (3)	>.99
Statin	63 (72)	70 (80)	.73
ACE inhibitor	74 (85)	69 (78)	.73
β-Blocker	64 (74)	67 (76)	.90

Abbreviations: ACE, angiotensin-converting enzyme; CABG, coronary artery bypass graft; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention; SHDB, single high-dose bolus.
*Calculated as weight in kilograms divided by square of height in meters.
†Patients were classified as having hypertension or diabetes based on history; patients with an active smoking habit within 7 days before hospital admission were classified as smokers.

ment assignment. *Acute luminal gain* was defined as the minimal luminal diameter (MLD) immediately after the procedure minus the MLD at baseline. *Late loss* was defined as the MLD immediately after the procedure minus the MLD at follow-up. The *target lesion* was defined as the stented segment plus the 5-mm segments immediately proximal and distal to the stent(s).

Study End Points and Definitions

The primary end point was freedom, at 8 months after randomization, from death, nonfatal MI, stroke, and binary restenosis. The data for all primary end point events were reviewed by an independent adjudication committee whose members were unaware of treatment assignment. Nonfatal MI was defined as recurrent chest pain with ST-segment or T-wave changes and recurrent elevation of cardiac enzyme levels. Patients were considered eligible for angiographic follow-up if protocol-mandated PCI had been attempted. Binary restenosis, dichotomized for in-stent and in-segment (5 mm proximal and distal to the stent margins) was defined as a greater than 50% diameter stenosis demonstrated by quantitative coronary angiography.

Secondary end points included freedom, at day 30 and month 8, from major cardiac or cerebrovascular adverse events defined as the composite of death, reinfarction, stroke, and repeat TVR. Urgent TVR was defined as repeat PCI or coronary artery bypass graft surgery performed within 24 hours of severe recurrent ischemic symptoms. As a safety analysis, the end points of major or minor bleeding along with severe or mild thrombocytopenia were defined according to the criteria of the TIMI trial.[11]

Table 2. Procedural Data

Characteristic	SHDB Tirofiban + Sirolimus-Eluting Stent (n = 87)	Abciximab + Bare-Metal Stent (n = 88)	*P* Value
Infarct-related artery, No. (%)			
Left anterior descending	43 (49)	36 (41)	.50
Right coronary	29 (33)	33 (38)	.76
Circumflex	15 (17)	19 (21)	.57
No. of diseased vessels, No. (%)			
1	46 (53)	57 (65)	.45
2	28 (32)	20 (23)	.32
3	13 (15)	11 (12)	.82
Door-to-balloon time, median (IQR) [range], min	70 (55-90) [15-225]	67 (53-110) [15-210]	.54
Delivery of at least 1 stent, No. (%)	81 (93)	79 (90)	.91
Stent in culprit lesion, median (range)	1 (0-2)	1 (0-3)	.53
Total stent length, median (IQR), mm	23 (18-28)	23 (16-23)	.42
Nominal stent diameter, median (IQR), mm	3 (2.7-3)	3 (2.75-3.5)	.01
TIMI flow, No. (%)			
Preprocedure			
Grade 0 or 1	61 (70)	65 (74)	.90
Grade 2	15 (17)	13 (15)	.83
Grade 3	11 (13)	10 (11)	>.99
Postprocedure			
Grade 0 or 1	2 (2)	4 (4)	.68
Grade 2	1 (1)	2 (2)	>.99
Grade 3	84 (96)	82 (93)	.91
Cumulative ST-segment elevation, median (IQR), mm			
Preprocedure	10 (7-16)	9 (6-14)	.74
Postprocedure	3 (2-5)	3 (2-7)	.91
Cumulative ST-segment resolution, No. (%)			
>50	60 (69)	54 (63)*	.71
>70	43 (49)	34 (39)*	.49
CK-MB at peak, median (IQR), ng/mL	188 (95-350)	206 (102-392)	.55
Time to CK-MB peak, median (IQR), h	12 (9-15)	12 (9-15)	.64

Abbreviations: CK-MB, creatine kinase–MB; IQR, interquartile range; SHDB, single high-dose bolus; TIMI, Thrombolysis in Myocardial Infarction.
*Two patients presenting with left bundle-branch block were not included in this analysis.

Statistical Analysis

Sample size was calculated on the assumption that the incidence of death, reinfarction, stroke, and binary restenosis at 8 months would be 13% in the tirofiban plus sirolimus-eluting stent group and 30% in the abciximab plus bare-metal stent group. To detect this effect size with 80% power and a type I error (α) of .05, taking into account an expected 10% rate of dropouts, required 160 patients.

All analyses were conducted according to the intention-to-treat principle. Discrete data were summarized as frequencies, whereas continuous data were expressed as median and interquartile range (IQR). The Fisher exact test (categorical variables) and Mann-Whitney test (continuous variables) were used to analyze differences between the 2 study groups. Event-free survival curves were generated by the Kaplan-Meier method, and survival between groups was compared using the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using a Cox proportional hazards model. The proportional hazards assumption was confirmed by an academic statistician (E.B.). A 2-sided *P* value less than .05 was considered significant for all tests. All analyses were performed using STATISTICA version 6.1 (StatSoft Inc, Tulsa, Okla).

RESULTS

Patient Population

Between March 6, 2003, and April 23, 2004, 175 patients with STEMI were randomized. A trial flow diagram is shown in FIGURE 1. Baseline demographics and angiographic features (TABLE 1 and TABLE 2) were well matched between the 2 randomized cohorts. A single patient in either group had a time from symptom onset to intervention of

greater than 12 hours. Median time from Gp IIb/IIIa inhibitor bolus to intervention was 33 (IQR, 22-42) minutes in the tirofiban plus sirolimus-eluting stent group vs 35 (IQR, 23-41) minutes in the abciximab plus bare-metal stent group ($P=.73$). Total median duration of study drug infusion was 20 (IQR, 14-28) hours in the tirofiban plus sirolimus-eluting stent group vs 12 (IQR, 11-13) hours in the abciximab plus bare-metal stent group ($P<.001$).

Procedural Results

Based on initial angiographic findings, 3 patients (3%) in the tirofiban plus sirolimus-eluting stent group and 5 patients (6%) in the abciximab plus bare-metal stent group did not receive PCI (Figure 1). In 5 patients (2 tirofiban plus sirolimus-eluting stent, 3 abciximab plus bare-metal stent), no significant lesion was present in the culprit vessel on angiography, and anterograde flow was normal. In 2 patients (1 per group) the small size of the occluded vessel precluded intervention. Finally, 1 patient in the abciximab plus bare-metal stent group was found to have a type I aortic dissection with occlusion of the right coronary artery. Where angioplasty was attempted, procedural success did not differ significantly between the tirofiban plus sirolimus-eluting stent group (82/84 patients [98%]) and the abciximab plus bare-metal stent (79/83 patients [95%]) group ($P=.91$). Nominal stent diameter was smaller in the tirofiban plus sirolimus-eluting stent group, reflecting the limited available range of sirolimus-eluting stent diameters.

Overall, 74 patients (85%) in the tirofiban plus sirolimus-eluting stent group and 77 (88%) in the abciximab plus bare-metal stent group received the protocol-mandated treatment combination (Figure 1). The extent of ST-segment resolution (Table 2) and the TIMI flow grade postintervention (Table 2) did not differ between treatment groups, nor did quantitative angiographic parameters at baseline or immediately after intervention (TABLE 3).

Median platelet aggregation, evaluated in 70 patients as closure time, was similar at baseline in the tirofiban plus sirolimus-eluting stent group (77 [IQR, 68-86] seconds) and the abciximab plus bare-metal stent (74 [IQR, 69-83] seconds) group ($P=.71$). Ten minutes after the start of drug infusion, 30 of 35 patients (86%) receiving abciximab vs 31 of 35 (89%) treated with tirofiban reached full platelet inhibition (closure time, >300 seconds). In the remaining 9 patients, closure time was 298 (IQR, 297-299) seconds in the 4 who received tirofiban and 295 (IQR, 292-296) seconds in the 5 who received abciximab ($P=.07$).

30-Day Outcomes

There were no significant differences between the tirofiban plus sirolimus-eluting stent group and the abciximab plus bare-metal stent group in the incidence of major adverse cardiac or cerebrovascular events during the first 30 days (TABLE 4). Five fatal events occurred: 2 (1 due to left ventricular free wall rupture, another to cardiogenic shock) in the tirofiban plus sirolimus-eluting stent group and 3 (as a consequence of aortic dissection, cardiogenic shock, and left ventricular free wall rupture) in the abciximab plus bare-metal stent group. Among patients receiving abciximab, 2 had reinfarction due to angiographically confirmed stent thrombosis requiring urgent TVR. In 1 patient with diabetes, a sirolimus-eluting stent had been implanted as a protocol violation. In the tirofiban plus sirolimus-eluting stent group, 1 patient with diffuse 3-vessel disease and cardiogenic shock at entry satisfied the criteria for reinfarction while mechanically ventilated 3 days after the index procedure. Coronary angiography performed thereafter excluded new changes in coronary anatomy. Finally, in 1 patient per group, urgent TVR was required due to re-

Table 3. Quantitative Coronary Analysis

Variable	SHDB Tirofiban + Sirolimus-Eluting Stent (n = 87)	Abciximab + Bare-Metal Stent (n = 88)	*P* Value
Preprocedure, median (IQR)			
RVD, mm	2.27 (1.95 to 2.59)	2.33 (2 to 2.7)	.34
MLD, mm	0 (0 to 0.2)	0 (0 to 0.18)	.67
Diameter stenosis, %	100 (90 to 100)	100 (93 to 100)	.49
Lesion length, mm	13 (9.6 to 18)	13.1 (10 to 18)	.91
Postprocedure, median (IQR)			
RVD, mm	2.18 (1.9 to 2.6)	2.33 (2 to 2.7)	.24
MLD, mm	1.92 (1.6 to 2.2)	1.98 (1.6 to 2.3)	.53
Acute luminal gain, mm*	1.85 (1.36 to 2.08)	1.9 (1.45 to 2.2)	.36
Diameter stenosis, %	13 (6.5 to 20.5)	16 (5 to 26)	.30
Follow-up, median (IQR)			
RVD, mm	2.53 (2.1 to 2.9)	2.63 (2.2 to 3)	.34
MLD, mm	1.98 (1.6 to 2.4)	1.48 (0.9 to 2)	<.001
Diameter stenosis, %	15 (5.5 to 24)	42 (28 to 70)	<.001
Late loss, mm†	–0.22 (–0.39 to 0.19)	0.6 (0.12 to 0.96)	<.001
Binary restenosis, No. (%)	**(n = 66)**	**(n = 67)**	
In-stent	5 (7.5)	19 (28)	.01
Proximal edge‡	1 (1.5)	4 (6)	.36
Distal edge‡	0	1 (1.5)	>.99
Target vessel	7 (11)	24 (36)	.008
Focal restenosis, No./total (%)§	5/6 (83)	7/24 (29)	.24
Reocclusion, No. (%)	0	5 (7)‖	>.99

Abbreviations: IQR, interquartile range; MLD, minimal lumen diameter; RVD, reference-vessel diameter; SHDB, single high-dose bolus.
*Postprocedure MLD minus baseline MLD.
†Postprocedure MLD minus MLD at follow-up.
‡Restenosis within the 5-mm segment proximal or distal to the stent edge.
§Length <10 mm. Percentages given refer to patients presenting with binary restenosis at follow-up.
‖Two patients had subacute stent thrombosis during hospitalization, while the remaining 3 patients presented with reocclusion at follow-up due to occlusive in-stent restenosis.

sidual infarct-related artery dissection threatening vessel closure. No cerebrovascular accident occurred. The incidence of any thrombocytopenia was significantly lower in the tirofiban plus sirolimus-eluting stent group vs the abciximab plus bare-metal stent group (Table 4).

Clinical and Angiographic Outcomes

Complete follow-up information up to 240 days was available for all patients. Eight patients in the tirofiban plus sirolimus-eluting stent group and 8 in the abciximab plus bare-metal stent group refused to undergo angiographic follow-up performed after a median of 209 days (range, 148-267). In 1 additional patient per group, follow-up coronary angiography was not performed due to a severe allergic reaction to contrast media during the index procedure and transfusion-dependent chronic anemia. None of these patients experienced major adverse cardiac or cerebrovascular events; all were asymptomatic and none had inducible myocardial ischemia on stress testing. Their baseline characteristics did not differ with respect to patients who underwent follow-up angiography.

Cumulatively, 14 of 74 (19%; 95% CI, 10%-28%) patients in the tirofiban plus sirolimus-eluting stent group and 37 of 74 (50%; 95% CI, 44%-56%) in the abciximab plus bare-metal stent group fulfilled the criteria for the 8-month primary end point (death, MI, stroke, or binary restenosis) (HR, 0.33; 95% CI, 0.18-0.60; $P<.001$ [$P<.001$ by Fischer exact test]).

The cumulative incidence of major adverse cardiac or cerebrovascular events (death, reinfarction, stroke, or TVR) was significantly lower in the tirofiban plus sirolimus-eluting stent group vs the abciximab plus bare-metal stent group (18% vs 32%, respectively; HR, 0.53; 95% CI, 0.28-0.92; $P=.04$) (FIGURE 2). Overall, the composite of death or reinfarction was similar in the tirofiban plus sirolimus-eluting stent group (13%) vs the abciximab plus bare-metal stent group (17%) (HR, 0.71; 95% CI, 0.34-1.5; $P=.39$) (Figure 2), while there was a significant reduction in the need for TVR (7% vs 20%, respectively; HR, 0.30; 95% CI, 0.12-0.77; $P=.01$) in the tirofiban plus sirolimus-eluting stent group.

The results of quantitative coronary analyses are shown in Table 3. Cumulative distribution curves (paired-lesion analysis) for the difference of MLD before and immediately after the intervention and at follow-up in the 2 groups are shown in FIGURE 3. In-lesion binary restenosis—assessed in 67 and 66 patients in the tirofiban plus sirolimus-eluting stent and abciximab plus bare-metal stent groups (87% and 88% of those eligible, respectively)—was present in 6 (9%; 95% CI, 2%-16%) and 24 (36%; 95% CI, 26%-46%) patients, respectively ($P=.002$).

Table 4. 30-Day and 8-Month Outcomes and Safety Profile

Variable	No. (%) SHDB Tirofiban + Sirolimus-Eluting Stent (n = 87)	No. (%) Abciximab + Bare-Metal Stent (n = 88)	*P* Value*
Outcomes			
30-d			
Death	2 (2)	3 (3)	>.99
Reinfarction	1 (1)	3 (3)	.62
Urgent TVR	1 (1)	3 (3)	.62
Stroke	0	0	>.99
Subacute stent thrombosis†	0	2 (3)	.24
Death/reinfarction	3 (3)	6 (7)	.49
Death/reinfarction/stroke/urgent TVR	3 (3)	7 (8)	.33
8-mo			
Death	7 (8)	8 (9)	.78
Reinfarction	6 (7)	8 (9)	.60
TVR	6 (7)	18 (20)	.01
TLR	5 (6)	18 (20)	.006
Stroke	0	0	>.99
Late stent thrombosis†	0	0	>.99
Death/reinfarction	11 (13)	15 (17)	.39
Death/reinfarction/TVR	16 (18)	28 (32)	.04
Death/reinfarction/stroke/TVR	16 (18)	28 (32)	.04
Safety Profile			
Bleeding			
Major	1 (1)	2 (2)	>.99
Blood loss with no site identified	0	3 (3)	.24
Minor	7 (8)	8 (9)	>.99
Any bleeding events	8 (9)	14 (16)	.26
Red blood cell transfusion	2 (2)	4 (4)	.68
Any femoral hematoma	2 (2)	4 (4)	.68
Femoral hematoma requiring surgery	1 (1)	1 (1)	>.99
Thrombocytopenia‡			
Severe thrombocytopenia	0	2 (2)	.49
Mild thrombocytopenia	1 (1)	6 (7)	.11
Any thrombocytopenia	1 (1)	8 (9)	.03
Platelet transfusion	0	2 (2)	.49

Abbreviations: SHDB, single high-dose bolus; TLR, target-lesion revascularization; TVR, target-vessel revascularization.
*By Fischer exact test (log-rank test for 8-month outcomes).
†Angiographically documented.
‡Severe, mild, and any thrombocytopenia were defined by TIMI classification (see "Methods" section).

COMMENT

In the United States, the Food and Drug Administration approved the first drug-eluting stent (the sirolimus-eluting stent)

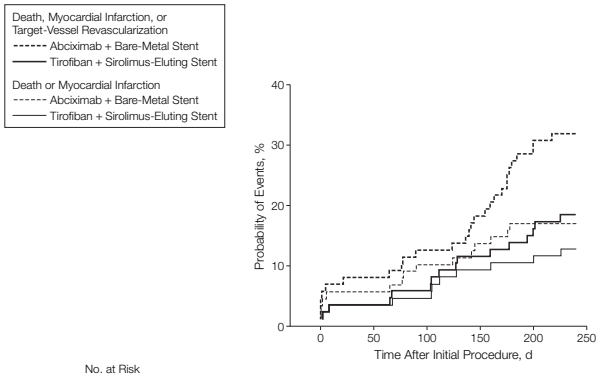
in April 2003. Since then, penetration of drug-eluting stenting has rapidly increased, replacing bare-metal stenting in more than 80% of PCI procedures.[12] This rapid transition has been facilitated by the presence of specific reimbursement for drug-eluting stenting. However, evidence for the efficacy and safety of drug-eluting stents has been obtained only for highly selected patient or lesion subgroups,[13-15] and concerns regarding the safety and economic consequences of liberal use of these devices have also been raised.[12,15-20]

In Europe, sirolimus-eluting stents became available 1 year previous (April 2002). Nevertheless, overall use of drug-eluting stents remains limited, with penetration rates as low as 6% in some countries.[6] This may be related to their high cost in conjunction with the almost universal lack of specific reimbursement. Thus, their short-term costs are currently playing a major role in clinical decision making.

To the best of our knowledge, no randomized trial has specifically examined the safety and efficacy of drug-eluting stents in the setting of primary intervention for STEMI. Abciximab and drug-eluting stent implantation have potentially complementary effects on death or MI and the need for reintervention in the setting of acute MI,[5,8,21-23] providing the rationale for testing their combination in this setting.[24] However, both therapies are expensive. The average cost of combining abciximab treatment with a single sirolimus-eluting stent exceeds 50% of current reimbursement for acute MI in some European countries.[25] Thus, financial pressure may lead to competitive use between drug-eluting stents and abciximab on the basis of their high cost.[7]

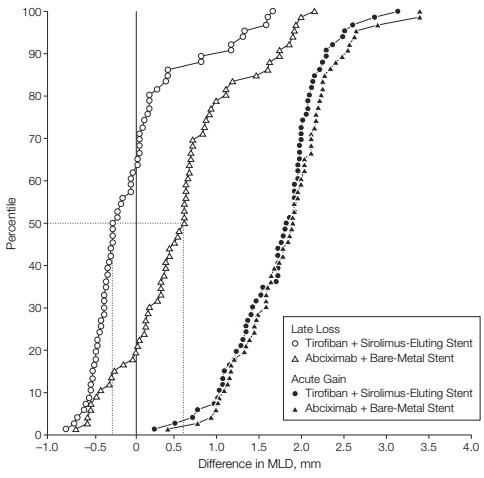
Our results demonstrate that a lower-cost strategy of tirofiban-supported sirolimus-eluting stent implantation during primary PCI was safe and resulted in improved clinical (ie, decreased need for TVR) and angiographic (ie, decreased restenosis) outcomes with respect to a strategy of abciximab-supported bare-metal stent implantation. Moreover, such a strategy was associated with an im-

Figure 2. Cumulative Risk of Events at 240 Days in the Tirofiban Plus Sirolimus-Eluting Stent and Abciximab Plus Bare-Metal Stent Groups



No. at Risk						
Death, Myocardial Infarction, or Target-Vessel Revascularization						
Abciximab + Bare-Metal Stent	88	81	77	72	63	60
Tirofiban + Sirolimus-Eluting Stent	87	84	82	77	74	71
Death, Myocardial Infarction						
Abciximab + Bare-Metal Stent	88	83	79	76	73	73
Tirofiban + Sirolimus-Eluting Stent	87	84	83	79	78	76

Figure 3. Cumulative Distribution Curves (Paired-Lesion Analysis) for Acute Luminal Gain and Late Loss in the Tirofiban Plus Sirolimus-Eluting Stent and Abciximab Plus Bare-Metal Stent Groups



See text for definitions of acute luminal gain and late loss. MLD indicates minimal luminal diameter.

proved safety profile with respect to thrombocytopenia.

Two specific aspects of our study protocol deserve emphasis. First, all consecutive patients with acute MI referred to a single referral center for intended primary intervention were prospectively enrolled provided they had no contraindication to the use of Gp IIb/IIIa inhibitors, thus substantially reducing any potential bias related to clinical presentation or angiographic findings. Second, Gp IIb/IIIa inhibitors were started at admission at a median interval of more than 30 minutes before coronary intervention. In a recent trial of patients with STEMI referred for intended bare-metal stenting, a similar approach to abciximab administration showed a benefit on total and cardiovascular mortality.[8] Furthermore, a recent meta-analysis supports the hypothesis that early administration of Gp IIb/IIIa inhibitors to patients with STEMI is associated with consistent trends toward a reduction in mortality and other major adverse cardiac events.[26]

In a previously reported head-to-head comparison between abciximab and tirofiban in patients undergoing PCI, abciximab was superior to tirofiban with respect to the prespecified combined end point.[27] The superiority of abciximab was driven by a higher rate of periprocedural MI in the tirofiban group, suggesting inadequate early platelet inhibition with the bolus regimen used (10 µg/kg). Subsequent dose-ranging studies showed that increasing the tirofiban bolus dose from 10 to 25 µg/kg was necessary to obtain an optimal level of platelet inhibition,[28] and initial clinical trials with the high bolus appear promising.[29,30] In the present study, evaluation of platelet function before and soon after administration of the Gp IIb/IIIa inhibitor showed that in the primary PCI setting, SHDB tirofiban resulted in a degree of early platelet inhibition similar to that observed with abciximab. Similarly, TIMI flow patterns and ST-segment resolution—both surrogates of long-term mortality that have been consistently improved by abciximab treatment even in relatively small studies[21,22]—did not differ between treatment groups. A large-scale noninferiority trial comparing a SHDB tirofiban regimen with abciximab is currently enrolling patients. The results of this trial will complement and extend our present findings.

Our study has several important limitations. First, it was underpowered to assess the effect of tirofiban-supported sirolimus-eluting stent implantation on the rate of major adverse cardiac or cerebrovascular events, implying that the benefit of treatment observed here was greater than expected but also that larger studies are needed to confirm our preliminary observations. Second, in keeping with the design of our investigation, no conclusion can be drawn regarding the relative contribution of a specific Gp IIb/IIIa inhibitor or stent type with respect to the other. This would have required a factorial study design. Third, despite careful avoidance of the "oculo-stenotic" reflex, we cannot rule out the possibility that protocol-mandated angiographic follow-up has not increased the magnitude of clinical benefit of study treatment. Finally, a formal cost-effectiveness analysis, which would have complemented our clinical and angiographic results, was not performed in this trial.

In conclusion, our study provides proof of concept for a new treatment strategy in STEMI that incorporates unrestricted use of sirolimus-eluting stenting but results in no (European market) or only a modest (US market) increase in medical expenditure.

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What I had always loved was a kind of foursquareness about the utterance, a feeling of living inside a constantly indicative mood, in the presence of an understanding that assumes you share an awareness of the perilous nature of life and are yet capable of seeing it steadily and, when necessary, sternly.
—Seamus Heaney (1939-)

Chapter 13 Value of Platelet Reactivity in Predicting Response to Treatment and Clinical Outcome in Patients Undergoing Primary Coronary Intervention. Insights into the Single High-Dose BoluS TiRofibAn and Sirolimus Eluting STEnt versus Abciximab and Bare Metal Stent in Acute MYocardial Infarction (STRATEGY) Study

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Value of Platelet Reactivity in Predicting Response to Treatment and Clinical Outcome in Patients Undergoing Primary Coronary Intervention

Insights into the Single High-Dose BoluS TiRofibAn and Sirolimus Eluting STEnt versus Abciximab and Bare Metal Stent in Acute MYocardial Infarction (STRATEGY) Study

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Objectives:
To evaluate the value of platelet reactivity (PR) in predicting the response to treatment and outcome in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention assisted by glycoprotein (GP) IIb/IIIa inhibition.
Background: There is limited prognostic information on the role of spontaneous or drug-modulated PR in STEMI patients.
Methods: PR was measured with Platelet Function Analyzer (PFA) 100 and light transmission aggregometry (LTA) using adenosine diphosphate as agonist in 70 consecutive STEMI patients -at entry (PRT_0), 10 min after GP IIb/IIIa bolus (PRT_1), at discharge (PRT_2)- and in 30 stable angina (SA) patients (PR_{SA}). Complete platelet inhibition (CPI) was based on closure time >300 sec at PFA-100 and percent inhibition of platelet aggregation >95% at LTA. Clinical, electrocardiographic and angiographic responses to treatment during 1-year follow-up were collected.
Results: According to both techniques, PRT_0 was higher than i) PRT_2 and PR_{SA}; ii) in those without CPI at T_1; iii) in patients with final Thrombolysis In Myocardial Infarction (TIMI) flow grade <3. PRT_0 assessed with PFA-100 correlated with i) corrected TIMI frame count ($r=-0.6$, $p<0.001$), ii) ST-segment resolution ($r=45$, $p<0.001$) and iii) CK-MB ($r=-0.47$, $p<0.001$). At 1 year, patients with high PRT_0 showed an adjusted 5 to_11-fold increase in the risk of death, re-infarction and target vessel revascularization (HR 11; [95%CI 1.5-78]; p=0.02 at PFA-100 and HR 5.2; [95%CI 1.1-23]; p=0.03 at LTA).
Conclusions: PR at entry affects response to GP IIb/IIIa inhibition, mechanical treatment and long-term outcome in STEMI patients undergoing primary intervention.

J Am Coll Cardiol 2006*, in press*

INTRODUCTION

Platelet activation, by favoring thrombus formation and coronary artery occlusion, is thought to play a key pathogenetic role in acute myocardial infarction. Percutaneous coronary intervention (PCI) is currently considered the preferred reperfusion strategy for patient with ST-segment elevation MI (STEMI) (1). Recent evidence strongly argues in favor of the glycoprotein (GP) IIb/IIIa inhibition in this setting (2) and reinforces the concept that platelet reactivity (PR) is a potential target of treatment beyond pure mechanical intervention. In previous studies, PR has been used to evaluate the risk of adverse events (3) and the extent of myocardial necrosis (4). Moreover, the importance of achieving a high level of platelet inhibition early after GP IIb/IIIa bolus in non-STEMI patients has been reported (5).

Whether baseline and/or drug-modulated PR influence response to treatment and myocardial injury in STEMI patients undergoing primary PCI with GP IIb/IIIa inhibition is unknown. This might further extend current paradigm linking platelet activation to outcome in STEMI population.

In order to explore this hypothesis, PR was measured before, during and after treatment as part of a pre-specified substudy of the Single High-Dose BoluS TiRofibAn and Sirolimus Eluting STEnt versus Abciximab and Bare Metal Stent in Acute MYocardial Infarction (STRATEGY) trial (6-7). To address the issue whether high baseline PR is a hallmark of clinical acuity, a matched population affected by stable angina (SA) was also similarly investigated.

METHODS

Study Population

100 patients treated with PCI in the cath-lab of the University Hospital of Ferrara were enrolled. This study population comprised 70 consecutives patients (68% male; mean age 63±12) with STEMI (STEMI group) enrolled in a previously reported trial (6) and 30 age- and sex-matched patients with SA (SA group) treated with PCI (67% male; mean age 64±6) (Table 1). This study was approved by the local Ethics Committee and all patients gave written informed consent.

Medications, Procedures and Assays

The design of the STRATEGY trial has been previously reported (7, 8). Briefly, patients with STEMI were randomly assigned to single high dose bolus tirofiban (SHDB, 25 μg/kg/3 min, followed by an infusion of 0.15 μg/Kg/min for 18-24 hours) or abciximab (bolus of 0.25 μg/Kg/3-min, followed by a 12-hour infusion 0.125 μg/Kg/min). The study drug was started in the intensive cardiac care unit. Per protocol, patients randomised to tirofiban received sirolimus eluting stent (SES), while those allocated to abciximab bare metal stent (BMS). All patients received aspirin (250 mg i.v. followed by 100 mg/die),

clopidogrel (300 mg followed by 75 mg/die), heparin (50-70 U/Kg with additional bolus if necessary) and other treatments as suggested by current guidelines. Patients with SA were treated with aspirin and received, at least 6 h before procedure, 300 mg of clopidogrel.

Angiographic Analysis

The angiographic images were acquired with a General Electrics Advantage CRS V 5.6.5 single-plane system at a cine rate of 25 frames/s before and immediately after the procedure. Angiograms were analyzed by one experienced interventional cardiologists (GP), blinded to platelet assays results. All angiograms were assessed with a respect to Thrombolysis In Myocardial Infarction (TIMI) flow scale in infarct-related artery (IRA) at baseline and after PCI (8). The corrected TIMI frame counts (CTFC) and the myocardial blush grade (MBG) were determined on final angiogram, as described previously (9-10). No reflow was defined as TIMI flow grade 0 or I despite successful ballon angioplasty or stent insertion, in spite of residual stenosis <50%, absence of significant dissection or visible thrombus or spasm in IRA. Procedural success was defined as the achievement of a final <30% residual stenosis and TIMI grade flow 3.

Blood Sample Collection

In the STEMI group, three blood samples were performed: at entry (T0) before treatment, 10 min (10±1) after the GP IIb/IIIa inhibitors bolus (T1), at discharge (T2, 7±3 days). In the SA group, blood was drawn before PCI procedure and clopidogrel intake (T0).

Platelet Function Testing

Platelet function was measured with Platelet Function Analyzer (PFA 100, Dade Behring, Miami, Fla), a US Food and Drug Administration approved device, and with light transmission aggregometry (LTA).

- *Platelet Function Analyzer 100 (PFA-100)*

In the PFA system (11) blood is forced to flow throughout a synthetic capillary (147 µm diameter), with a collagen and adenosine 5′-diphosphate (ADP) coated membrane with a central hole at its end (CADP cartridge, 50 µg of ADP and 2 µg of Type 1 equine collagen). When a haemostatic platelet plug completely obliterates the central hole, the blood flow will stop. The time necessary to stop the flow is called "closure time" (CADP-CT) and inversely reflects platelet reactivity. Its reference range in the absence of anti-platelet therapy is 69-130 seconds (11-12). This instrument confines detection of closure to a 300 secs window and, as result, "nonclosure" is obtained. This degree of platelet inhibition corresponds to >90% inhibition of platelet aggregation by means of light transmission aggregometry (20 µM ADP) (12-13). CADP cartridge was selected in the present study to monitor the effect of GP IIb/IIIa inhibitors on platelet function based on available evidence (12-13).

- *Light Transmission Aggregometry (LTA)*

Blood was centrifuged (200*g*×10 minutes) to obtain platelet-rich plasma (PRP). The platelet count in PRP was adjusted to the range of 150.000–300.000/L by dilution with autologous plasma when out of range. The remaining specimen was re-centrifuged (1500*g*×15 minutes) to obtain platelet-poor plasma (PPP). Platelets were stimulated with 20 µmol/l of ADP. Aggregation was measured at 37°C with a PACKS-4 Aggregometer (Helena Laboratoires) and expressed as the maximal percent change in light transmittance from baseline at 5 min after the addition of the agonist, with platelet-poor plasma as a reference. Percent inhibition of platelet aggregation (%IPA) was determined by the following formula: (%PA at baseline - %PA ten minutes after IIb/IIIa)/%PA at baseline.

All samples for analysis were collected into evacuated tubes containing 3.8% trisodium citrate and also in evacuated tubes containing PPACK (D-Phe-Pro-Arg-Chloromethylketone). All measurements were done 0.5 to 1 hour after blood sampling. CADP-CT measurements with citrate and PPACK were highly correlated ($r=0.96$, $p<0.001$). Coefficients of variation for duplicate analysis averaged 4%. At baseline, CADP-CT correlated with aggregability measured with LTA ($r=-0.95$, $p<0.001$). All patients who failed to achieve nonclosure at T1 show %IPA<95%. Complete platelet inhibition (CPI) was defined as CADP-CT >300 sec (nonclosure) and %IPA>95%.

Study End Points

In order to test the role of spontaneous and drug-modulated PR, platelet function was related with: a) angiographic evaluation (TIMI flow grade, incidence of no reflow, CTFC, MBG and procedural success rate), b) extent of myocardial necrosis, c) ST-segment resolution, d) clinical outcome. Extent of myocardial necrosis was assessed by CK-MB (ng/dl) and Troponin I (TnI, ng/dl) at peak. Cumulative ST-segment elevation, evaluated in all leads with any ST-segment elevation ≥1 mm, was measured to the nearest 0.5 mm at 60 min after the J point, with the aid of hand-held callipers. The clinical end points were death, reinfarction, target vessel revascularization (TVR) (major adverse cardiac events, MACE) and stent thrombosis (ST) angiographically confirmed.

Statistical Analysis

Continuous data are presented as means ± SD, with the significance of differences judged by *t* test. Since results of PFA-100 and LTA were both not normally distributed at Kolmogorov-Smirnov goodness-of-fit test, the Mann-Whitney test was used to compare PR values between groups. Kruskal-Wallis ANOVA was employed to compare more than 2 groups of patients and to generate P-value for tend-tests reported in figure 3. Categorical variables were summarized in terms of number and percentages and were compared using two-sided Fisher's exact test. Spearman's correlation coefficients were used to detect any association between variables. As exploratory analysis, linear regression analysis was used to test association between PR and variables reported in table 1. Survival curves were constructed by the Kaplan-Meier method and survival among groups was compared using the Log Rank test. Cox proportional hazards models were used to assess risk reduction of adverse events. Multivariate analysis, considering all variables in Table 3 with a p value <0.10, was performed to identify whether PR at entry was an independent predictor for adverse events at 1 year. Probability was significant at a level of <0.05. Analysis was performed using STATISTICA 6.1 (Statsoft Inc, Tulsa, Okla).

RESULTS

Baseline and procedural data of the study population are shown in Tables 1 and 2. Patients with SA, recruited in the period February-March 2004, were well matched for age, sex and all risk factors with respect to STEMI patients. Between January and April 2004, 70 STEMI patients, randomly allocated to receive tirofiban or abciximab, were prospectively enrolled in the current analysis. Their baseline and procedural characteristics did not differ from those enrolled in the cohort of the STRATEGY trial (6). Sixty-six (94%) patients were treated with stent implantation, while one patient per group received only balloon angioplasty. In one patient in the SHDB tirofiban group, coronarography was not followed by treatment due to both prompt restoration of TIMI 3 flow after intracoronary nitrates injection and absence of coronary obstruction, whereas in one patient in the abciximab group, type I aortic dissection determining occlusion of the right coronary artery was followed by emergent surgery.

Table 1. Baseline Characteristics of the Patient

Characteristics	SHDB Tirofiban group (n=35)	Abciximab group (n=35)	P Value	STEMI group (N=70)	SA group (N=30)	P Value
Age (yr)	64±13	63±12	0.6	63±12	64±6	0.3
Men no. (%)	22 (63%)	26 (74%)	0.2	48 (68%)	20 (67%)	0.5
Diabetes no.(%)	7 (20%)	6 (17%)	0.5	13 (18%)	6 (20%)	0.5
Hypertension no. (%)	23 (66%)	21 (60%)	0.4	44 (63%)	20 (66%)	0.4
Smoker no. (%)	10 (28%)	16 (46%)	0.1	26 (37%)	11 (36%)	0.6
Medical history (%)						
CABG no. (%)	0 (0%)	0 (0%)	>0.9	0 (0%)	2 (6%)	0.09
PCI no. (%)	0 (0%)	1 (3%)	0.5	1 (1.5%)	0 (0%)	0.7
Acute myocardial infarction no. (%)	2 (6%)	2 (6%)	0.7	4 (6%)	4 (13%)	0.2
Laboratory Values at entry						
Platelet Count (u/ml)	241±45	254±100	0.5	247±97	251±91	0.8
Hematocrit (%)	40±5	41±4	0.2	41±5	42±6	0.6
White blood count (u/ml)	11.9±4	12.1±3	0.8	12±4	8±3	<0.01
Fibrinogen (mg/dl)	420±162	395±116	0.4	407±139	400±129	0.7
Creatinine Clearance (ml/min)	85±38	84±28	0.9	85±33	82±28	0.8

SHDB=single high dose bolus. CABG=coronary artery bypass graft. PCI=percutaneous coronary intervention.

Platelet Reactivity Assays

PR before any treatment, evaluated both in terms of CADP-CT (76±11) and %PA (90±5) was higher in STEMI than in SA patients (96±6 and 50±6, p<0.01 for both, Figure 1). CADP-CT or %PA at entry was not related to any of the variables in Table 1. At entry, there were no differences between tirofiban and abciximab in terms of CADP-CT (77±11 vs 74±12, p=0.3) or %PA (89±4 vs. 90±4, p=0.5) (Figure 1). Overall, 4 patients were assuming aspirin as chronic treatment before entry. Their PR did not differ in terms of PFA-100 or LTA at T_0 or T_1 compared to aspirin naïve patients.

At T1, 31/35 (89%) patients treated with tirofiban vs. 30/35 (86%) receiving abciximab reached the CPI (p=0.5). In the remaining nine patients, CADP-CT was 298 [297–299] sec in the four who received tirofiban and 294 [292–296] secs in the five who received abciximab (p=0.06), whereas %PA was 11±2 vs. 14±4 (p=0.3), respectively. In these nine patients, baseline PR was significantly higher than in those reaching CPI at T1 (CADP-CT: 65±12 vs. 77±10, p=0.002; %PA: 93±4 vs. 89±4, p=0.003). Out of all variables included in Table 1, only PR at T0 was related to PR at T1. At discharge (7±3 days), PR was lower than at entry in the STEMI group (CADP-CT: 76±11 vs. 98±8, p<0.001) which was confirmed by LTA findings (Figure 1).

Platelet Reactivity and Angiographic Data

Baseline PR, measured as CADP-CT and %PA (Figure 2), was higher in patients with TIMI flow 0/1 as compared to those with TIMI flow grade 2/3 at first angiogram (p<0.001 for both). Among patients in whom angioplasty was attempted (68 patients), procedural success was reached in 61 (90%): in three patients, a final TIMI 2 flow was obtained despite repeated administration of intracoronary vasodilatators; in three, an irreversible no reflow phenomenon after stent implantation was observed, while a distal macro-embolization in a posterolateral branch occurred in the remaining patient after vessel wiring. In these seven patients, baseline CADP-CT was lower (66±7 vs. 77±11, p=0.01) and %PA higher (93±4 vs. 89±4, p=0.02) as compared to that of those with procedural success. Four (44%) out of the nine patients who failed to achieve the CPI at T1 had a not successful intervention as compared to three (5%) in whom maximum platelet inhibition was obtained (p=0.004). Patients showing no reflow had enhanced PR (CADP-CT: 62±7 vs. 77±11, p=0.03; %PA: 95±3 vs. 89±4, p=0.02). None of them reached the CPI at T1. CADP-CT and %PA at entry resulted to be related to CTFC both in all patients receiving intervention (r=-0.6, p<0.001) and in those with final TIMI 3 (r=-0.53; p<0.001). Patients with MBG 2/3 tended to have lower PR as compared to those with MBG 0/1 (CADP-CT: 77±11 vs. 71±11, p=0.06; %PA: 89±5 vs. 91±4, p=0.05).

Platelet Reactivity and ECG Resolution

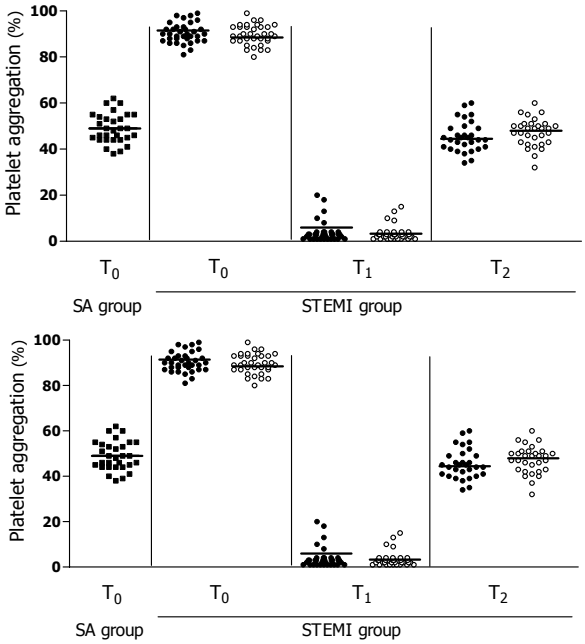
CADP-CT and %PA at baseline was directly correlated to the degree of ST-segment resolution immediately after the procedure (r=0.45 and r=-0.42, p<0.001 for both). PR at entry was higher in patients without cumulative ST resolution >50% (CADP-CT: 67±10 vs. 78±11, p=0.001; %PA: 93±4 vs. 89±4, p=0.003) or >70% (CADP-CT: 72±11 vs. 80±11, p=0.007; %PA: 91±4 vs. 88±3, p=0.006). Four (44%) and seven (78%) among the nine patients who failed to achieve CPI did not reach ST-segment the resolution >50% or >70% as compared to seven (12%) and 24 (41%) out of the 59 with CPI (p=0.03 and p=0.04, respectively).

Table 2. Procedural Data

Characteristics	SHDB Tirofiban group (n=35)	Abciximab group (n=35)	P Value	STEMI group (n=70)	SA group (n=30)	P Value
Treated artery no. (%)						
Left anterior descending (%)	10 (29%)	17 (49%)	0.07	27 (40%)	14 (47%)	0.3
Right coronary (%)	15 (44%)	13 (38%)	0.4	28 (41%)	6 (20%)	0.04
Circumflex (%)	9 (27%)	4 (13%)	0.1	13 (19%)	10 (33%)	0.4
GPIIb/IIIa-to-Balloon (min)	35±7	37±10	0.7	36±10	...	...
PCI successful no. (%)	30 (88%)	31 (92%)	0.5	61 (88%)	30 (100%)	0.07
Reference diameter, pre (mm)	2.7±0.6	2.8±0.5	0.7	2.7±0.5	2.8±0.6	0.6
Total stent length (mm)	27±17	29±15	0.6	28±16	30±15	0.2
Nominal stent diameter (mm)	3±0.5	3±0.4	0.6	3±0.4	3±0.7	0.8
Stent implantation no. (%)	33 (94%)	33 (94%)	0.7	66 (94%)	30 (100%)	0.2
TIMI flow no. (%)						
Preprocedure: Grade 0 or 1	28 (80%)	30 (86%)	0.4	58 (83%)	0 (0%)	<0.01
Grade 2	5 (14%)	4 (11%)	0.5	9 (13%)	8 (27%)	0.08
Grade 3	2 (6%)	1 (3%)	0.5	3 (4%)	22 (73%)	<0.01
Postprocedure: Grade 0 or 1	2 (6%)	1 (3%)	0.5	3 (4%)	0 (0%)	0.3
Grade 2	2 (6%)	2 (6%)	0.7	4 (6%)	0 (0%)	0.2
Grade 3	30 (88%)	31 (91%)	0.5	61 (90%)	30 (100%)	0.07
No reflow no. (%)	2 (6%)	1 (3%)	0.5	3 (4%)	0 (0%)	0.3
∑ ST resolution >50% no. (%)	31 (88%)	29 (83%)	0.3	60 (86%)	...	...
∑ ST resolution >70% no. (%)	20 (57%)	17 (48%)	0.3	37 (53%)	...	...
CK-MB at peak (ng/ml)	210±187	227±154	0.7	218±170	...	...
Troponin I at peak (ng/ml)	85±77	108±95	0.3	97±87	...	...

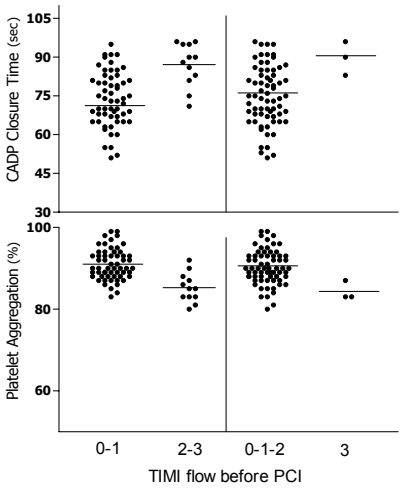
SHDB=single high dose bolus. GP IIb/IIIa: start of GP IIb/IIIa inhibitors. PCI=percutaneous coronary intervention ∑=cumulative

Figure 1. Platelet reactivity assays.



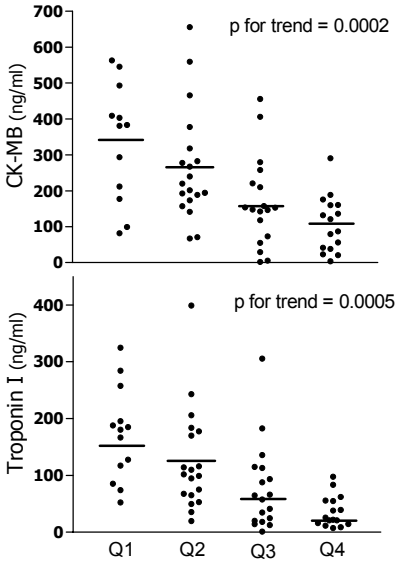
Black squares: patients with stable angina (SA). Circles: patients with STEMI. Black circles: abciximab subgroup. White Circles: single high dose bolus tirofiban subgroup. T_0: baseline. T_1: 10 min after IIb/IIIa bolus. T_2: discharge.

Figure 2. Relationship between TIMI flow grade before PCI and baseline CADP-CT.



Lower TIMI flow at first angiogram was associated to higher PR. CADP-CT was 73±11 in the TIMI 0/1 group vs. 87±8 in the TIMI 2/3 group (p<0.001) and %PA was respectively 91±4 vs. 85±3 (p<0.001). CADP-CT was 75±11 in the TIMI 0/1/2 group vs. 89±6 in the TIMI 3 group (p=0.03) and %PA was respectively 90±4 vs. 84±2 (p=0.01).

Figure 3



Peak plasma levels of CK-MB (top) and of Troponin I (bottom) are shown according to quartiles (Q) of CADP-CT at admission.

Platelet Reactivity and Infarct Size

CADP-CT at T0 resulted to be inversely correlated with CK-MB and Tn I at peak in patients with STEMI (r=-0.47, p<0.001 and r=-0.48, p<0.001). CK-MB and Tn I at peak according to CADP-CT quartiles are shown in figure 3. All data were confirmed by LTA (data not shown).

Platelet Reactivity and Clinical Outcome

Complete follow-up information up to 365 days was available for all patients. In the SA group, no adverse event was observed. In the STEMI group at 30 days, three deaths and two re-infarctions occurred due to subacute stent thrombosis (ST), which required urgent TVR. At 1 year, 13 patients (18%) experienced adverse events, including four deaths, four re-infarctions (2 due to ST) and seven TVR (2 urgent TVR).

Entry: Patients with MACE at 30 days, as compared to those without, had higher PR at T_0 (CADP-CT: 57±8 vs. 77±10, p<0.001; %PA: 97±4 vs. 89±4, p<0.001; Figure 4). Of note, the two patients who had ST failed to achieve CPI at T_1.

Patients with MACE within 1 year had lower CADP-CT at entry (65±9 vs. 78±11; p<0.001) and higher %PA (94±3 vs. 89±4, p<0.001) with respect to those with uneventful follow-up (Figure 4). The cumulative incidence of MACE was significantly lower in patients with high (above median value, low PR) compared to those with low (under median value, high PR) CADP-CT at T0 (3% vs. 34%, p=0.0006). The patients in the high reactivity group showed a 12-fold increase in the risk of composite end point (HR 12; 95%CI 2.7-125, p=0.0009) (Figure 5). As showed in Table 3, there were no statistically significant differences between groups with exception of percentages of diabetes mellitus, higher in the high PR subgroup (10% vs. 3%, p=0.03). Including diabetes, at multivariate analysis PR remained an independent predictor for MACE (HR 11; 95%CI 1.5-78, p=0.02). Based on LTA, there was an adjusted 5-fold increase in the risk of MACE (HR 5.2; 95%CI 1.1-23, p=0.03) in the high reactivity group.

Discharge: PR tended to be higher in patients with as compared to those without adverse events at follow-up (CADP-CT: 94±8 secs vs. 98±8, p=0.2, %PA: 18±6 vs. 15±5, p=0.1, respectively).

DISCUSSION

Platelet reactivity is pivotal in the pathogenesis of acute coronary syndromes (ACS) and it is a well-know predictor for adverse outcome after PCI (3). Accordingly, inhibitors of GP IIb/IIIa decrease incidence of adverse events both in the PCI setting (14) and in patients with ACS (15).

The three major findings of our study are:

1. patients with STEMI have higher PR than patients with SA
2. baseline PR affects the response to GP IIb/IIIa inhibitors soon after bolus
3. PR at baseline and, consecutively, after GP IIb/IIIa inhibitors bolus, influences the angiographic success of the procedure, as well as the degree of ST-segment resolution, the extent of myocardial necrosis and the short- and mid-term clinical outcome in patients undergoing primary intervention.

Our data demonstrated that baseline PR is a hallmark of clinical acuity. This statement is mainly based on the finding that PR was higher in the STEMI than in the control group (patients with SA).

Table 3. Clinical, biochemical and procedural data of STEMI patients stratified in accordance with the platelet reactivity at entry

Characteristics	High platelet reactivity (n=35)	Low platelet reactivity (n=35)	P Value
Age (yr)	65±12	62±12	0.4
Men no. (%)	13 (37%)	9 (26%)	0.2
Diabetes no.(%)	10 (28%)	3 (9%)	0.03
Hypertension no. (%)	23 (66%)	21 (60%)	0.4
Smoker no. (%)	12 (35%)	14 (39%)	0.4
Medical History			
CABG no. (%)	0 (0%)	0 (0%)	>0.9
PCI no. (%)	0 (0%)	1 (3%)	0.5
AMI no. (%)	1 (3%)	3 (8%)	0.3
Laboratory Values at entry			
Platelet Count (u/ml)	264±115	232±76	0.2
Hematocrit (%)	40±5	41±4	0.2
White blood count (u/ml)	12.4±4	11.6±3	0.4
Fibrinogen (mg/dl)	392±122	422±155	0.4
Creatinine clearance (ml/min)	82±29	85±35	0.3
Procedural Data			
LAD no. (%)	11 (32%)	16 (47%)	0.2
RCA no. (%)	16 (47%)	12 (35%)	0.3
Circumflex no. (%)	7 (21%)	6 (18%)	0.5
RD, pre (mm)	2.7±0.6	2.8±0.5	0.7
Total stent length (mm)	28±15	28±17	0.9
Nominal stent diameter (mm)	3±0.5	3±0.4	0.6

High platelet reactivity=CT at entry under the median value. Low platelet reactivity=CT at entry above the median value. Median value of CT at entry is 75 seconds. CABG=coronary artery bypass graft. PCI=percutaneous coronary intervention AMI=acute myocardial infarction; LAD=left anterior descending artery; RCA=right coronary artery; RD=reference diameter

It has been demonstrated that the response to clopidogrel is patient-specific, with an important inter-individual variability (16-17), and that the pretreatment platelet activity could influence final response to clopidogrel (17). Recently, two case-control studies associated the enhanced platelet aggregation and the impaired responsiveness to antiplatelet drugs with the stent thrombosis incidence (18-19). In our prospective study, with a homogenous patient population in terms of i) ethnicity (all patients were Caucasian), ii) clinical presentation (STEMI) and iii) treatment (primary PCI), we confirmed that there is an inter-individual variability in PR. This influences the response to antiplatelet therapy, also if GP IIb/IIIa inhibitors, the strongest currently available anti-platelet treatment, are used. Our study population comprised 13 diabetics: in keeping with previous evidence (20) they showed increased PR: at T0 10 out of 13 (77%) were in the high PR subgroup (p=0.03 vs. non diabetics), at T_1, both using PFA-100 and LTA, 3 out of 13 (23%) achieved incomplete platelet inhibition vs. 6 out of 57 (11%) in the non-diabetic group (p=0.26), while at T_2: CT in diabetics was lower (91±7 vs. 99±8 in non-diabetics, p=0.01) and %PA higher (19±5 vs. 14±4 in non-diabetics p=0.001). One of them experienced stent thrombosis at follow-up. Cumulatively, five diabetic patients (38%) out of 13 satisfied the composite endpoint (38% vs. 14% in non-diabetics, p=0.05). Thus, when taken together with available evidence, our data suggest that diabetics, greatly contribute to overall inter-individual variability in PR, and as such may be an ideal target population for tailored antiplatelet therapy both in the acute and chronic setting.

Failure to achieve TIMI flow grade 3, the no reflow phenomenon and higher CTFC values after reperfusion therapy have been found to be associated with more extensive myocardial necrosis and poor clinical outcome (21). In the current study, we demonstrated that TIMI flow grade <3, no reflow as well as high CTFC occur significantly more frequently in patients with enhanced baseline PR.

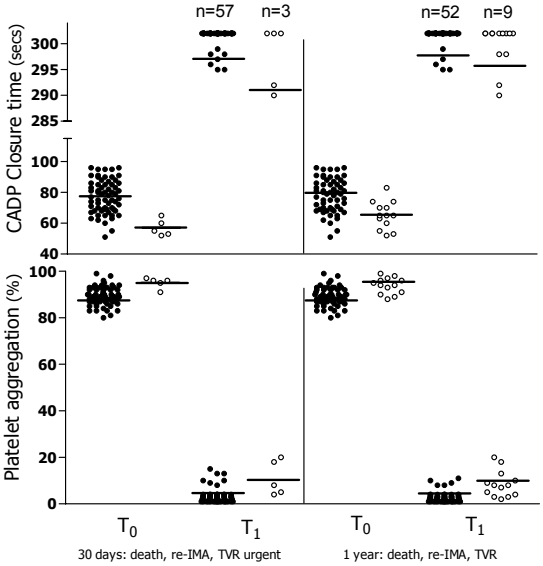
As previously reported, the enhanced platelet function correlated with the degree of myocardial damage in our study (4). Moreover, a clear association between PR and the degree of ST-segment resolution was found. This finding may be critically relevant since in STEMI patients treated with primary PCI, ST-segment reduction was independently related to 6-month mortality (2).

In the current study, we studied PR using two methodologies. LTA is still considered as the gold standard, but it has some disadvantages such as limited reproducibility and complex sample preparation. Conversely, PFA 100 is a rapid tool that can be used in the clinical practice to identify patients with higher PR, which could potentially be exploited as a mean to tailor the anti-platelet treatment to the individual need. This may be particularly relevant in the setting of primary intervention for STEMI, when a short door-to-balloon time is needed, and other biomarkers of PR may not available. Further studies are needed to establish the optimal bedside assay to evaluate the PR in this setting.

Study Limitations

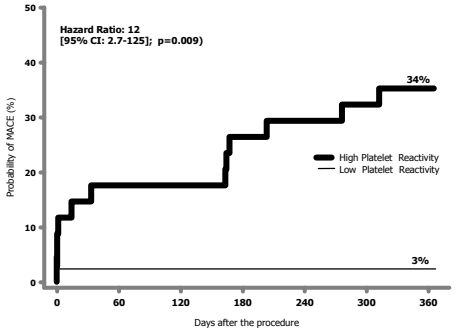
Due to limited sample size, our prospective investigation should be regarded as exploratory. In particular, in order to obtain a reliable estimate of the prognostic capability of PR at entry and to evaluate whether the response to Gp IIb/IIIa inhibitors is an independent outcome predictor beyond PR at entry, a larger prospectively collected study population is clearly in demand. Recently, it has been shown in elective patients that PR measured at least 24 hours after stenting independently predicts outcome (22). In our study, PR at discharge failed to be significantly associated to outcome: differences in patient selections, timing of platelet assays and limited statistical power may help explaining these different findings. PFA 100 confines detection of closure to a 300-second window and because in most patients nonclosure is exhibited shortly after GP IIb/IIIa inhibitor administration, this device may be suboptimal to properly identify those individuals at a higher risk for subsequent thrombotic events. Although, this was an issue in the present investigation, future studies with bigger sample size are clearly needed.

Figure 4. CADP-CT stratified in relationship with the clinical outcome at 30 days and at 1 year.



Black circles: patients that not reached the composite end point. White Circles: patients that reached the composite end point. T_0: baseline. T_1: 10 min after IIb/IIIa bolus.

Figure 5. Probability of MACE in patients stratified according to PR measured with PFA-100.



High platelet reactivity = CADP-CT at entry under the median value. Low platelet reactivity = CADP-CT at entry above the median value. Median value of CADP-CT is 75 secs.

Conclusions

In patients undergoing primary PCI for STEMI, PR at entry was related to both angiographic and elettrocardiographic response to treatment as well as to the severity of cardiac injury as measured by the release of markers of cardiac necrosis. After 1 year, PR at presentation independently predicted major cardiac adverse events. Whether modulating PR through *tailored* or *systematic* anti-platelet treatment overcomes the prognostic implications of spontaneous platelet function remains elusive and may warrant further investigations.

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Chapter 14. Impact of Stable versus Unstable Coronary Artery Disease on 1-year outcome in elective patients undergoing Multivessel revascularization with sirolimus-eluting stents. A subanalysis of Arterial Revascularization Therapies Study Part II

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Submitted for publication

Impact of Stable versus Unstable Coronary Artery Disease on One-year Outcome in Elective Patients Undergoing Multivessel Revascularization with Sirolimus-eluting Stents

A sub-analysis of Arterial Revascularization Therapies Study (ARTS) Part II

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Objective: To evaluate the impact of unstable coronary artery disease (CAD) on short- and mid-term outcome in patients with multivessel disease treated by multiple sirolimus eluting stents (SES) as part of the Arterial Revascularization Therapies Study (ARTS) Part II.
Background: The differential safety/efficacy profile of SES when implanted in patients with unstable angina (UA) in comparison with stable angina (SA) undergoing multivessel intervention is largely unknown.
Methods and Results: Between February 2003 and November 2003, 607 patients at 45 participating centres were treated, 221 of them (36%) presented with UA. At 30-days the cumulative rate of death, myocardial infarction (MI), cerebrovascular accident (CVA) and repeat revascularisation [MACCE] was 2.7% in the UA and 3.4% in the SA group (p=0.81). Angiographic subacute stent occlusion was documented in 1 (0.5%) and 4 (1%) patients in UA and SA group, respectively. At one year, the cumulative incidence of MACCE was 10.4% in both groups. Two late occlusions occurred, both in SA group. After adjustment for baseline and procedural characteristics, the presence of UA was not identified as an independent predictor of MACCE (HR 0.94 [95% CI: 0.41 to 2.12]; p=0.88). These findings remained consistent after lowering the threshold for peri-procedural MI from 3 to 1 time(s) the upper limit of normal for total creatine kinase and/or its MB fraction.
Conclusions: In ARTS II, an unstable clinical presentation did not exert a negative impact on short- and mid-term outcome after SES implantation for multivessel disease.

Submitted

INTRODUCTION

Several clinical studies, focusing on specific patient and lesion characteristics including long lesions(1), in-stent restenosis(2), small vessels(3), diabetic patients(4) and infarct related arteries(5), as well as all-comers registries(6) have established the role of the sirolimus-eluting stent (SES) in reducing the need for further re-intervention in comparison to bare metal stents. However, whether the net safety/efficacy profile of SES differs in relation to the acuity (i.e. stable vs. unstable) of clinical presentation remains an open issue.

The thrombogenic coronary milieu in patients with an acute coronary syndrome (ACS), coupled with the well-known propensity for hyper-coagulability in this patient subset and possible delayed re-endothelialization with drug-eluting stents (DES) has resulted in concerns of an increased risk of stent thrombosis after implantation of these devices in patients with ACS(7). Moreover, several prior studies have identified unstable angina as a risk factor for restenosis after bare metal stent (BMS) implantation(8,9).

The Arterial Revascularization Therapies Study part II (ARTS II) is a multicenter, European, open-label, non-randomized trial evaluating the safety and efficacy of SES as compared to the previous results of the randomized ARTS I trial(10). Thirty six percent of the 607 patients enrolled in ARTS II had unstable angina at presentation.

We sought to evaluate whether clinical outcome in this subset of patients was comparable to that observed in patients with stable angina in the attempt to evaluate whether the net efficacy/safety profile of SES is affected by acuity of clinical presentation. The one year outcome in ARTS II, stratified into stable versus unstable presentation, was also compared to that of patients undergoing percutaneous or surgical revascularization in ARTS I, in keeping with the original design of the study.

METHODS

Study design

ARTS II study design has been previously reported(11,12). Briefly, patients were consecutively enrolled via a central telephone service, after stratification by clinical site to ensure the inclusion of at least one third of patients undergoing three-vessel intervention.

Selection of patients

Patients were eligible for coronary revascularization if they had either stable angina (Canadian Cardiovascular Society class I, II, III, or IV), unstable angina (Braunwald class IB, IC, IIB, IIC, IIIB, or IIIC), or if they had silent ischemia and at least two new lesions located in different major epicardial vessels and/or their side branches (not including the left main coronary artery) that were potentially amenable to stent implantation. Patients were required to have multivessel disease with the need for treatment of the left anterior descending (LAD) artery and at least one other significant lesion (>50% diameter stenosis) in another major epicardial coronary artery. One totally occluded major epicardial vessel could also be included. The stenosis had to be amenable to stenting using a stent with a diameter of 2.5 to

3.5mm and length of 13 to 33mm, without any restriction on the total stent length implanted.
Patients with any previous coronary intervention, left main coronary disease, overt congestive heart failure or a left ventricular ejection fraction of less than 30 percent were excluded. Additional exclusion criteria included a history of a cerebrovascular accident and STEMI in the preceding week or with persistent elevation of CK. Measurement of troponin was not mandatory at screening. Patients with chest pain lasting longer than 30 minutes within the preceding 12 hours were also excluded if CK was equal or more than 2 times upper normal limit.
Written, informed consent was obtained from each patient prior to enrolment. The study was approved by the ethics committee of each participating site.

Procedures and Post-Intervention Medications

All interventions were performed according to current standard guidelines and the final interventional strategy, including the use of glycoprotein IIb/IIIa inhibitors, was left entirely to the discretion of the operator, except for the stent utilization. All patients were advised to maintain aspirin lifelong. Clopidogrel 300 mg as a loading dose, or Ticlopidine, administered at a dose of 500 mg, was to be started at least 24 hours before the procedure. Clopidogrel 75 mg per day or Ticlopidine 250 mg twice a day was prescribed for at least two months after revascularization.

Study Objectives and Endpoints

The primary objective of this ARTS II sub-analysis was to compare the safety and effectiveness of coronary stent implantation using sirolimus-eluting stents in patients with unstable angina with that of patients undergoing similar treatment for the presence of stable angina. For the purpose of the present analysis, patients with stable angina and silent ischemia (defined as 'stable angina' group) were compared to unstable angina, as previously reported in ARTS I(13). The primary outcome measure was the incidence of major adverse cardiac and cerebrovascular events (MACCE) at one year comprising all-cause death, any cerebrovascular event, non-fatal myocardial infarction, or any repeat revascularization (either percutaneous or surgical) (*contemporary comparison*).
The secondary objectives of this study are to compare 1-year MACCE in the ARTS II patients, stratified according to clinical presentation (stable versus unstable) to that of patients with stable and unstable angina who were randomized to either percutaneous bare metal stent implantation or CABG in the ARTS I trial (*historical comparison*).

End point definitions

All deaths were considered cardiac unless a non cardiac origin was established clinically or at autopsy. Death from all causes was reported.
Cerebrovascular events were divided into three main categories: stroke, transient ischemic attack (TIA), and reversible ischemic neurologic deficit (RIND). In the first seven days after the intervention, a definite diagnosis of myocardial infarction was made if there was documentation of new abnormal Q waves (according to the Minnesota code) and either a ratio of serum creatine kinase MB (CK-MB) iso-enzyme to total cardiac enzyme that was greater than 0.1 or a CK-MB value that was 5 times the upper limit of normal (ULN)[1, 11, 12] Serum creatine kinase and CK-MB iso-enzyme concentrations were measured 6, 12, and 18 hours after the intervention. Beginning eight days after the intervention (the length of the hospital stay after surgery), either abnormal Q waves or enzymatic changes were sufficient for a diagnosis of myocardial infarction. This dual method of defining myocardial infarction was developed for ARTS I to address the difficulty of diagnosing a myocardial infarction after cardiac surgery. A myocardial infarction was confirmed only after the relevant electrocardiograms had been analyzed by the electrocardiographic core laboratory and adjudicated by an

Table 1. Baseline Patient Demographics

Patient Parameters Measured	UA (N=221 patients)	SA (N=386 patients)	Difference [95% CI]	P-value
Age (years) N	221	386		
mean ± SD	62.6±10.5	62.9±9.1	-0.3 [-1.9,1.3]	0.70
(min - max)	(35 - 80)	(37 - 80)		
EF (%) N	204	334		
mean ± SD	60.0±11.5	60.3±11.6	-0.3 [-2.3,1.7]	0.76
(min - max)	(30 - 97)	(30 - 88)		
BMI (kg/m2) N	220	381		
mean ± SD	27.1±4.2	27.8±4.0	-0.7 [-1.4,0.0]	0.036
(min - max)	(15.2 - 42.9)	(18.6 -43.0)		
Number of Men	74.2% (164/221)	78.0% (301/386)	-3.8% [-10.9%,3.3%]	0.32
Diabetes Mellitus	23.1% (51/221)	28.0% (108/386)	-4.9% [-12.0%,2.2%]	0.21
Hypertension	62.0% (137/221)	70.2% (271/386)	-8.2% [-16.1%,-0.4%]	0.039
Dislypidemia	65.2% (144/221)	78.9% (303/384)	-13.7% [-21.2%,-6.3%]	<0.001
History of CVA	1.4% (3/221)	0.5% (2/385)	0.8% [-0.8%,2.5%]	0.36
Family history of MI/SD <55 yr	35.5% (78/220)	36.2% (139/384)	-0.7% [-8.7%,7.2%]	0.86
PVD	7.2% (16/221)	6.8% (26/385)	0.5% [-3.8%,4.7%]	0.87
Previous MI	48.0% (106/221)	26.7% (103/386)	21.3% [13.4%,29.2%]	<0.001
Previous CABG	0.0% (0/221)	0.0% (0/386)	0.0% [0.0%,0.0%]	
Previous PTCA	0.9% (2/221)	0.3% (1/386)	0.6% [-0.7%,2.0%]	0.30
Carotid Surgery	1.4% (3/221)	1.3% (5/385)	0.1% [-1.8%,2.0%]	1.00
COPD	2.7% (6/221)	4.2% (16/385)	-1.4% [-4.4%,1.5%]	0.50
Previous Smoker	34.8% (77/221)	44.3% (171/386)	-9.5% [-17.5%,-1.5%]	0.026
Current Smoker	24.4% (54/221)	16.3% (63/386)	8.1% [1.4%,14.9%]	0.018
Unstable Angina	100.0% (221/221)	...	...	...
Braunwald I	23.1% (51/221)	...	...	...
Ib	19.9% (44/221)	...	...	...
Ic	3.2% (7/221)	...	...	...
Braunwald II	49.3% (109/221)	...	...	...
IIb	38.0% (84/221)	...	...	...
IIc	11.3% (25/221)	...	...	...
Braunwald III	27.6% (61/221)	...	...	...
IIIb	20.8% (46/221)	...	...	...
IIIc	6.8% (15/221)	...	...	...
Stable Angina	...	83.7% (323/386)	...	...
CCS I	...	11.1% (43/386)	...	...
CCS II	...	42.2% (163/386)	...	...
CCS III	...	27.7% (107/386)	...	...
CCS IV	...	2.6% (10/386)	...	...
Silent Ischaemia	...	16.3% (63/386)	...	...
Single VD	0.0% (0/221)	0.5% (2/386)	-0.5% [-1.2%,0.2%]	0.54
Double VD	47.5% (105/221)	45.3% (175/386)	2.2% [-6.1%,10.4%]	0.61
Triple VD	52.5% (116/221)	54.1% (209/386)	-1.7% [-9.9%,6.6%]	0.74

Difference = unstable angina – stable angina; CI - Confidence Interval; CI - Diff ± 1.96 * SE; SE - sqrt(p1*q1/n1 + p2*q2/n2) ; CVA= CerebroVascular Accident; MI = Myocardial Infarction; COPD= chronic obstructive pulmonary disease; CABG =Coronary Artery Bypass Graft; PVD= periferal vascular disease; BMI= body mass index; EF= ejection fraction; VD= vessel diseased; PTCA = Percutaneous Transluminal Coronary Angioplasty; Braunwald = Braunwald Classification; CCS = Canadian Cardiovascular Society Classification; SD: sudden death

independent clinical-events committee. For the purpose of this analysis, to explore whether the current definition of MI may artificially contribute to minimize the impact of clinical acuity on outcome, the occurrence of non-Q Wave MI in the first seven days after the index procedure has also been reclassified based on any CK or CK-MB elevation or a CK or CK-MB value that was three times or more the ULN, in keeping with current ACC/AHA and ESC recommendations(14,15). All repeat revascularization procedures were recorded. Events were counted from the time of the initial procedure. Thrombotic occlusions were defined according to the protocol as either by angiographic documentation of a complete occlusion (TIMI flow 0 or 1) or angiographic documentation of a flow limiting thrombus (TIMI flow 1 or 2).

To allow cross comparisons with other contemporary investigations(16), stent thrombosis was also determined as the occurrence of any of the following events: angiographic documentation of partial or total stent occlusion detected within 30 days of the procedure (an acute clinical ischemic event in addition to angiographic documentation had to be present when the event occurred after 30 days), or sudden cardiac death or post-procedural MI after successful stent implantation not clearly attributable to another coronary lesion. All events have been reviewed and adjudicated by an independent clinical-events committee.

Statistical analysis

Continuous variables are shown as mean ± SD if not otherwise stated and were compared using Student's two-sample *t*-test. Categorical variables are presented as percentages and compared with the χ^2test. Comparison among three groups was performed using a general linear model. Survival curves were generated by the Kaplan-Meier method and survival amongst groups was compared using the log-rank test. Proportional hazards and Weibull models were used to assess risk reduction of adverse events. For the stable versus unstable comparison within the ARTS II trial, multivariable analysis, considering all variables reported in Tables 1 and 2 with a p-value of less or equal than 0.10, was performed to adjust for possible confounders and identify whether clinical presentation was an independent predictor of adverse events. Moreover, a simultaneous interaction test of the predicting variables with clinical presentation was performed. For the comparison of ARTS II versus ARTS I, multivariate analysis considering all variables reported in Table 3 with a p-value of less or equal than 0.1 were considered in order to obtain the adjusted hazard ratio. Co-linearity in the model was investigated using a correlation matrix and by inspection of the estimate parameters obtained in the model. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Probability was significant at a level of <0.05. All statistical tests were 2-tailed. Statistical analysis was performed with SAS V8.02, (SAS institute, Cary, NC, USA).

RESULTS

Patients

Between February 2003 and November 2003, 607 patients at 45 participating centers were treated. **Table 1** presents their baseline demographic characteristics based on clinical presentation. The patients were predominantly males with preserved left ventricular function; three-vessel disease was present in more than 50% of the cases. Patients with unstable angina had a slightly lower body mass index and were less frequently affected by hypertension and hypercholesterolemia. The incidence of previous myocardial infarction in the unstable group was almost double when compared to the stable patient group. Current smoking was more frequent in unstable as compared to stable patients. The two groups were otherwise comparable for all other baseline characteristics, including co-morbidities.

Table 2. Hospital Stay, Procedural Characteristics and Medications

Parameters Measured	UA (N=221 patients N=794 Lesions)	SA (N=386 patients N=1365 lesions)	Difference [95% CI]	P value
Per Patient Analysis				
Hospital Stay Ds				
mean ± SD	6.1±4.6	4.8±3.9	1.3 [0.6,2.0]	<0.001
(min - max)	(1 - 37)	(1 - 36)		
Ds to Procedure since Enrolment*				
mean ± SD	0.1±0.5	0.1±1.3	0.0 [-0.2,0.2]	0.92
(min - max)	(-1 - 4)	(-7 - 21)		
Days in Hospital since Procedure				
mean ± SD	3.7±3.1	3.2±2.4	0.5 [0.1,1.0]	0.021
(min - max)	(1 - 31)	(1 - 30)		
Duration of Procedure (min)				
mean ± SD	86.2±46.3	84.5±41.4	1.7 [-5.5,8.9]	0.64
(min - max)	(10 - 281)	(16 - 293)		
N. of lesions > 50% DS				
mean ± SD	3.6±1.3	3.5±1.3	0.1 [-0.2,0.3]	0.62
(min - max)	(2 - 8)	(1 - 8)		
N. of vessels with a lesion > 50%				
mean ± SD	2.5±0.5	2.5±0.5	0.0 [-0.1,0.1]	0.79
(min - max)	(2 - 3)	(1 - 3)		
N. of stented lesions				
mean ± SD	3.2±1.2	3.2±1.1	0.0 [-0.2,0.2]	0.70
(min - max)	(0 - 7)	(0 - 8)		
N. of stents implanted				
mean ± SD	3.6±1.5	3.7±1.5	0.0 [-0.3,0.2]	0.72
(min - max)	(0 - 9)	(0-11)		
Average stent lenght (mm)				
mean ± SD	19.4±3.5	19.6±3.5	-0.3[-0.8,0.3]	0.38
(min - max)	(13-30)	(11-31)		
Total stent lenght (mm)				
mean ± SD	71.3±32.1	73.2±32.1	-1.9 [-7.2, 3.4]	0.48
(min - max)	(18-209)	(12-253)		
IIB/IIIA inhibitors (%)	32.6 (72/221)	32.4 (125/386)	0.2% [-7.5%,7.9%]	1.00
Lipid lowering agent (%)	88.2 (195/221)	90.7 (350/386)	-2.4 % [-7.6%,2.7%]	0.33
β-blockers (%)	82.4 (182/221)	74.9 (289/386)	7.5% [0.9%,14.1%]	0.034
ACE-inhibitors (%)	57.9 128/221)	45.6 (176/386)	12.3% [4.1%, 20.5%]	0.004
Per Lesion Analysis (%)				
Ostial lesions	4.7	4.1	0.7% [-1.2%, 2.5%]	0.50
Moderate to heavy Ca++	27.4	33.4	-6.0% [-10.1%, -1.9%]	0.005
Thrombus present	1.2	0.2	1.0% [0.2%, 1.8%]	0.003
Occlusion <3 months	0.3	0.1	0.2% [-0.2%, 0.6%]	0.56
Occlusion .>3 months	2.3	2.4	-0.1% [-1.4%, 1.2%]	1.00
Classification:				
Type A/B1	33.0	28.6	4.5% [0.4%, 8.6%]	0.032
Type B2/C	67.0	71.4	-4.5% [-8.6%, -0.4%]	0.032

* In ARTS2 in total 6 patients have been enrolled post procedure. Numbers are % (counts/available field sample size) or mean ± 1 Standard Deviation. SD = Standard Deviation. Difference = unstable angina - stable angina. CI - Confidence Interval. CI - Diff ± 1.96 * SE. SE - sqrt(p1*q1/n1 + p2*q2/n2. SA= stable angina; UA= unstable angina.

Overall hospital stay was on average 1.3 days longer in unstable patients (**Table 2**). Coronary lesions in patients with unstable angina were less frequently calcified and more frequently of type A/B1 than of type B2/C, while thrombus was more commonly observed in this group. There was no other difference in procedural characteristics between the two groups, including use of glycoprotein IIb/IIIa inhibitors (**Table 2**).

Table 3.

	Unstable angina group				Stable angina group			
	ARTS II SES (221 pts , 794 les)	ARTS II BMS (226 pts, 628 les)	ARTS II CABG (224 pts, 621 les)	P value	ARTS II SES (386 pts , 1366 les)	ARTS II BMS (374 pts, 978 les)	ARTS II CABG (n= 381)	P value
Male sex (%)	74.2	80.1	75.1	0.27	78	75.1	76.6	0.65
Age, y (mean±SD)	62.6±10.5	61±9.6	60.9±9.5	0.12	62.9±9.1	60.5±9.7	61.4±9.2	0.001
BMI (Kg/m^2) (mean±SD)	27.1±4.2	26.7±3.4	27.1±3.8	0.50	27.8±4	27.5±3.8	27.5±3.6	0.49
Diabetes (%)	23.1	18.6	14.2	0.055	28	18.7	16.8	<0.001
Hypertension (%)	62	49.1	43.1	<0.001	70.2	42	46.1	<0.001
Hypercholesterolemia (%)	65.2	51.3	54	0.007	78.9	61.9	59.7	<0.001
Family history (%)	35.5	35.3	42	0.26	36.2	41.5	42	0.20
Current smoking (%)	24.4	32	47.6	0.10	16.3	25.5	21.6	0.008
Previous MI (%)	48	45.1	47.6	0.81	26.7	43.9	38.7	<0.001
Stable angina (%)	...	...	...	...	...	...	...	...
CCS 1	...	...	...	...	11.1	7.8	7.6	0.16
CCS 2	...	...	...	...	42.2	41.7	41.8	0.99
CCS 3	...	...	...	...	27.7	35	37.4	0.01
CCS 4	...	...	...	...	2.6	5.9	5.5	0.05
Silent ischemia (%)	...	...	...	...	16.3	9.6	7.6	<0.001
Unstable Angina (%)	...	...	...	...	...	...	...	...
Braunwald I	23.1	22.6	19.1	0.54	...	...	...	...
Braunwald Ib	19.9	15.9	16.0	0.47	...	...	...	...
Braunwald Ic	3.2	6.6	3.1	0.14	...	...	...	...
Braunwald II	49.3	50.4	49.8	0.97	...	...	...	...
Braunwald IIB	38	34.1	36.9	0.68	...	...	...	...
Braunwald IIC	11.3	16.4	12.9	0.29	...	...	...	...
Braunwald III	27.6	27	31.1	0.58	...	...	...	...
Braunwald IIIb	20.8	22.6	26.2	0.39	...	...	...	...
Braunwald IIIc	6.8	4.4	4.9	0.53	...	...	...	...
Ejection fraction (%)	60±11.5	62±13.1	58.7±13.6	0.03	60.3±11.6	60.3±11.7	61.3±2.9	0.44
No. vessel diseased	2.5±0.5	2.3±0.5	2.3±0.6	<0.001	2.5±0.5	2.2±0.5	2.3±0.5	<0.001
2-vessel (%)	47.5	68.3	61.8	<0.001	45.3	68.7	68.8	<0.001
3-vessel (%)	52.5	28.9	33.2	<0.001	54.1	26.6	28.2	<0.001
RCA	31	30.4	28.9	0.70	28.0	31.6	29.8	0.16
LAD	41.1	41.2	41.2	0.99	41.8	38.2	41.0	0.20
CX	28	28.2	29.7	0.74	30.2	30.2	29.1	0.82
No. Treated lesions	3.2±1.2	2.6±1.0	2.9±1.0	<0.001	3.2±1.1	2.4±0.9	2.8±1	<0.001
Type A/B1 lesions	33	32.2	38.6	0.033	28.6	32.4	37.9	<0.001
Type B2/C lesions (%)	67	67.8	61.4	0.033	71.4	67.6	62.1	<0.001
No. of stent implanted	3.6±1.5	2.8±1.2	...	<0.001	3.7±1.5	2.8±1.3	...	<0.001
Total stent lengh (mm)	71.3±32.1	47.5±19.3	...	<0.001	73.2±32.1	47.6±23	...	<0.001
L length <10mm (%)	61.8	67.9	67	0.039	60.3	64.1	68.9	<0.001
L length 10-20 mm (%)	26.4	24.4	27.2	0.52	27.7	29.3	24.1	0.029
L length >20 mm (%)	11.7	7.7	5.8	<0.001	11.9	6.6	7.0	<0.001
Occlusion < 3 mos (%)	0.3	3.0	4.3	<0.001	0.1	3.2	3.9	<0.001
Occlusion > 3 mos (%)	2.3	0.2	1.8	<0.001	2.4	0.7	0.8	<0.001
Mod. to heavy Ca++(%)	27.4	16.6	15.4	<0.001	33.4	18.1	14.4	<0.001
Thrombus present (%)	1.2	1.5	1.7	0.68	0.2	1	1.3	0.001
Maximal dilatation (atm)	16.4±2.8	14.9±2.7	...	<0.001	16.3±2.9	14.5±2.8	...	<0.001
Lipid lowering agent (%)	88.2	33.0	28.5	<0.001	90.7	42.2	33.6	<0.001
β-blockers (%)	82.4	58.9	57.9	<0.001	74.9	60.5	53.0	<0.001
ACE-inhibitors (%)	57.9	21.9	16.7	<0.001	45.6	28.1	14.6	<0.001

Table 4. Clinical outcome in ARTS II according to clinical presentation

	Unstable Angina (N=221 patients)	Stable Angina (N=386 patients)	Relative risk [95% CI]	P-value
30-day Outcome (%)				
Non Hierarchical Complications				
MACCE*	2.7 (6/221)	3.4 (13/386)	0.81 [0.31, 2.09]	0.81
MACCE†	5.4 (12/221)	5.2 (20/386)	1.05 [0.52, 2.10]	1.00
MACCE‡	19.9 (44/221)	19.9 (71/386)	1.00 [0.72, 1.39]	1.00
Death/CVA/MI*	0.9 (2/221)	1.0 (4/386)	0.87 [0.16, 4.73]	1.00
Death/CVA/MI†	4.1 (9/221)	4.1 (16/386)	0.98 [0.44, 2.19]	1.00
Death/CVA/MI‡	19 (42/221)	19.2 (74/386)	0.99 [0.71, 1.39]	1.00
Death	0.0 (0/221)	0.0 (0/386)	...	...
CVA	0.0 (0/221)	0.3 (1/386)	...	1.00
Myocardial infarction†	4.1 (9/221)	3.9 (15/386)	1.05 [0.47, 2.35]	1.00
-Q-Wave MI	0.9 (2/221)	0.8 (3/386)	1.16 [0.20, 6.92]	1.00
-Non Q-Wave MI*	0.0 (0/221)	0.0 (0/386)	...	...
-Non Q-Wave MI†	3.6 (8/221)	3.1 (12/386)	1.16 [0.48, 2.8]	0.81
-Non Q-Wave MI‡	18.6 (41/221)	18.1 (70/386)	1.05 [0.72, 1.45]	0.91
Revascularization	2.3 (5/221)	2.6 (10/386)	0.87[0.3, 2.52]	1.00
CABG	1.4 (3/221)	1.3 (5/386)	1.05 [0.25, 4.34]	1.00
RPTCA	0.9 (2/221)	1.3 (4/386)	0.87 [0.16, 4.73]	1.00
Sub-acute occlusion	0.5 (1/221)	1 (4/386)	0.70 [0.14, 3.57]	1.00
Stent thrombosis	0.9 (2/221)	1.5 (6/386)	0.58 [0.12, 2.90]	0.77
365-day Outcome				
Hierarchical Complications				
MACCE*	10.4 (23/221)	10.4 (40/386)	1.00 [0.62, 1.63]	1.00
MACCE†	12.7 (28/221)	11.9 (46/386)	0.80 [0.40, 1.60]	0.59
MACCE‡	27.1 (60/221)	24.9 (96/386)	1.09[0.83, 1.44]	0.56
Death	0.9 (2/221)	1.0 (4/386)	0.87 [0.16, 4.73]	1.00
CVA without death	0.5 (1/221)	1.0 (4/386)	0.44 [0.05, 3.88]	0.66
MI without Death or CVA‡	19 (42/221)	18.9 (73/386)	1.00 [0.72, 1.29]	1.00
-Q-Wave MI	0.9 (2/221)	0.8 (3/386)	1.16 [0.20, 6.92]	1.00
-Non Q-Wave MI*	0.0 (0/221)	0.5 (2/386)	...	0.54
-Non Q-Wave MI†	2.7 (6/221)	3.4 (13/386)	0.82 [0.16, 4.73]	0.72
-Non Q-Wave MI‡	19 (42/221)	18.7 (72/386)	1.02 [0.72, 1.44]	0.91
Revascularization without Death or CVA or MI	8.1 (18/221)	7.0 (27/386)	1.16 [0.66, 2.07]	0.63
CABG without Death or CVA or MI	2.3 (5/221)	1.8 (7/386)	1.25 [0.40, 3.88]	0.77
RPTCA without Death or CVA or MI	5.9 (13/221)	5.2 (20/386)	1.14 [0.58, 2.24]	0.71
Non Hierarchical Complications				
Death/CVA/MI*	2.3 (5/221)	3.4 (13/386)	0.67 [0.24, 1.86]	0.62
Death/CVA/MI†	5.0 (11/221)	6.2 (24/386)	0.80 [0.40, 1.60]	0.59
Death/CVA/MI‡	20.4 (45/221)	20.7 (80/386)	0.98 [0.71, 1.36]	1.00
CVA	0.5 (1/221)	1 (4/386)	0.44 [0.05, 3.88]	0.66
Myocardial Infarction*	0.9% (2/221)	1.6% (6/386)	0.58 [0.12, 2.86]	0.72
Myocardial Infarction†	4.1 (9/221)	4.7 (18/386)	0.87 [0.40, 1.91]	0.84
Myocardial Infarction‡	19.5 (43/221)	19.4 (75/386)	1.00 [0.72, 1.40]	1.00
Revascularization	9.0% (20/221)	8.0% (31/386)	1.13 [0.66, 1.93]	0.65
CABG	2.7 (6/221)	1.8 (7/386)	1.5 [0.51, 4.40]	0.56
RPTCA	6.3 (14/221)	6.5 (25/386)	0.98 [0.52, 1.84]	1.00
Late occlusion	0% (0/221)	0.5% (2/386)	0.44 [0.05, 3.88]	0.54
Stent thrombosis	0.9% (2/221)	1.8% (7/386)	0.50 [0.10, 2.38]	0.59

***:** based on protocol mandated MI definition
†: based on MI definition of CK/CK-MB 3×upper limit of normal in one or more sample(s)
‡: based on MI definition of any CK/CK-MB above upper limit of normal in one or more sample(s)
MI: Myocardial infarction; CVA: cerebrovascular accident; CABG: coronary artery bypass grafting; RPTCA: re-PTCA;

Baseline demographic, procedural characteristics and medications at discharge according to clinical presentation in ARTS II as compared to ARTS I are reported in **Table 3**.

ARTS II 30-day Outcomes

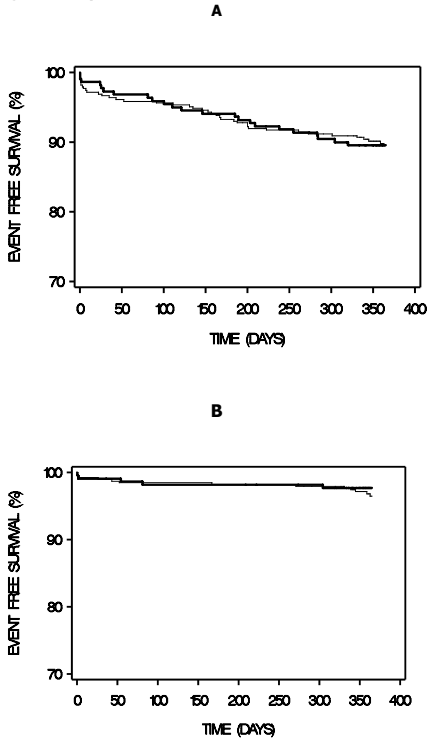
No deaths occurred in the first 30 days in either group. There were no significant differences in patients with unstable with respect to those with stable angina in the cumulative incidence of MACCE (death, infarction, cerebrovascular accident or repeat revascularisation) during the first 30 days irrespective of the applied definition for myocardial infarction (**Table 4**). The same was true when each component of the MACCE was separately analysed (**Table 4**). Up to discharge, three angiographically confirmed thrombotic occlusions occurred in the stable angina group (3/386, 0.8%) versus none in unstable angina patients (p=0.56). From

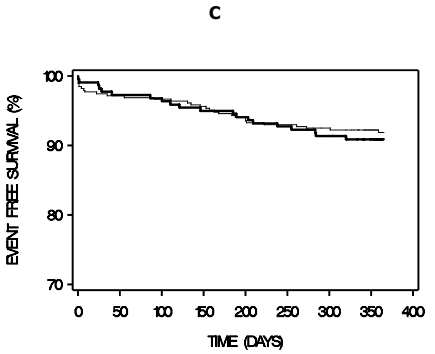
discharge to 30 days, one additional thrombotic occlusion in each group was observed resulting in a cumulative rate of 1% in SA versus 0.5% in UA group (RR 0.44 [0.05, 3.88]; p=0.66).

ARTS II 365-day outcomes

At one year the cumulative incidence of MACCE was identical in the two groups (10.4%, RR 1.00 [95% CI: 0.62-1.63]; p=1.00), reflecting a similar rate death (0.9% vs. 1.0%), cerebrovascular accident (0.5% vs. 1.0%), myocardial infarction (0.9% vs. 1.3%) and repeat revascularisation (8.1% vs. 7.0%) in unstable and stable angina groups, respectively. Unadjusted Kaplan-Meier estimates of MACCE, death, MI/CVA and TVR are shown in **Figures 1A**, **1B** and **1C**, respectively. After reclassifying peri-procedural non-Q-wave MI according to current recommendations(14,15), the overall rate of MI at one year remained similar in patients with stable angina (4.7%) as compared to the group of UA patients (4.1%; p=0.84), as was the case for the cumulative incidence of MACCE based on the revised MI definition (11.9% in SA vs. 12.7% in UA group, p=0.80). Defining non Q-wave MI as any CK/CK-MB elevation beyond the upper limit of normal resulted again in a remarkably similar, although unadjusted, outcome in stable as compared to unstable patients in terms of cumulative MI (19.4% vs. 19.5%, p=1.00) or MACCE (24.9% vs. 27.1%; p=0.56), respectively.

Figure 1. Kaplan-Meier curves





Kaplan-Meier curves reporting (A) MACCE free Survival; (B) Death/CVA/MI free survival and (C) freedom from repeat revascularization in ARTS II study stratified into unstable (bold line) and stable angina (thin line).

Sub-group and Multivariable Analysis

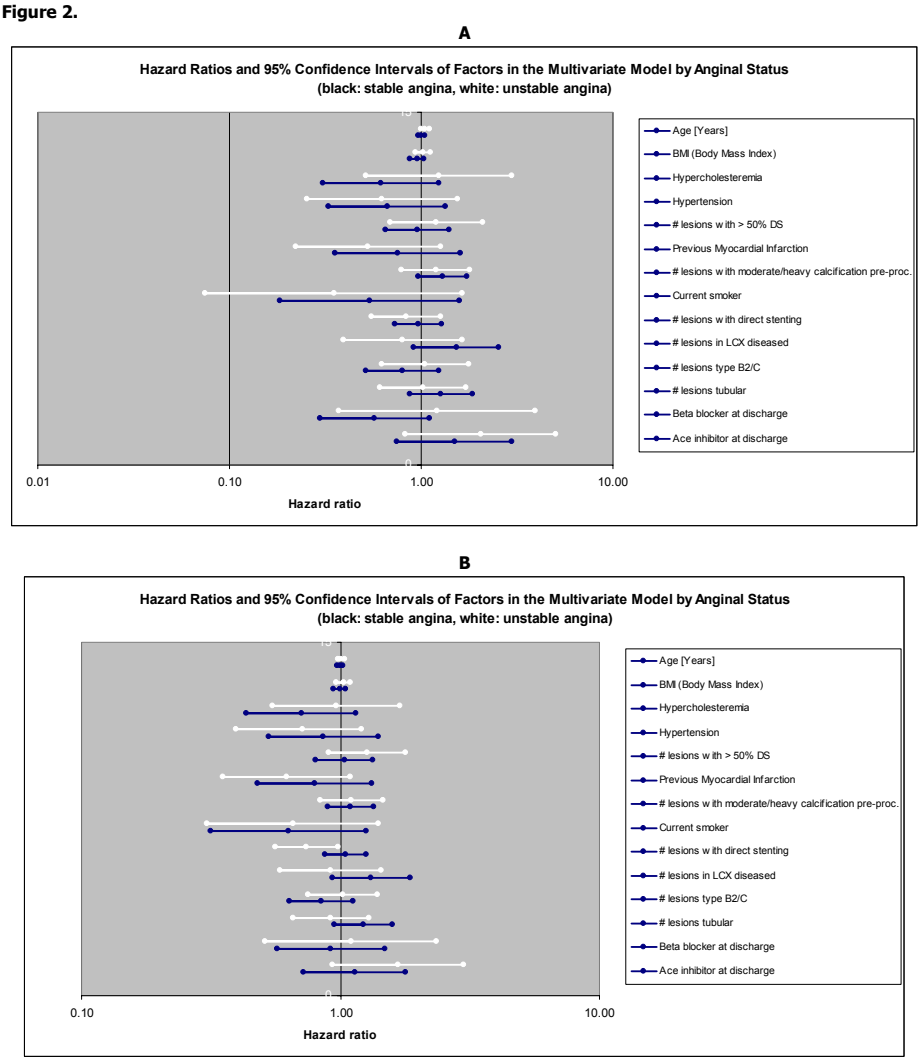
Focusing on higher risk patients presenting with Braunwald class II or III (n=170), their outcome in terms of MACCE at 30 days (2.4% vs. 3.4%; p=0.72) or one year (10% vs. 10.4%; p=0.97) did not differ compared to SA group, respectively. Based on CK/CK-MB elevation equal to or more than three times the upper limit of normal as definition of non-Q-wave MI, the MACCE rate was 4.7% and 12.4% in patients with Braunwald class II or III as compared to 5.2% (p=0.99) and 11.9% (p=0.99) in SA patients at 30 and 365 days, respectively. Finally, considering any CK/CK-MB elevation, the MACCE rate was 17.1% vs. 19.9% (p=0.84) at 30 days and 24.7% vs. 24.9% (p=0.94) at one year in UA class II or III compared to SA patients.

Using the Weibull modelling and after adjusting for covariates as reported in Tables 1 and 2, the clinical status failed to become an independent predictor of MACCE (HR 0.94 [95% CI: 0.41 to 2.12]; p=0.88, HR 0.87 [95% CI: 0.52 to 1.48]; p=0.61 and HR 0.88 [95% CI: 0.62 to 1.25]; p=0.88 based on peri-procedural non Q-Wave MI definition of CK/CK-MB elevation ≥5, ≥3 or ≥1 x the upper limit of normal, respectively). Similarly, no statistical interaction was noted between clinical status and the tested covariates in the model, irrespective of the applied peri-procedural MI definition (**Figure 2**).

ARTS part II versus ARTS part I

The cumulative incidence of MACCE, death/MI/CVA and revascularization at 1 year stratified according to clinical presentation in the SES group as compared to BMS or CABG group is shown in **Figure 3**. After adjustment for all confounders among those reported in **Table 3**, the MACCE rate observed in the ARTS II study remained consistently lower than that observed in the BMS group in stable (HR: 0.45 [95%CI: 0.16, 0.58], p=0.0004) or unstable patients (HR: 0.43 [95%CI: 0.18, 0.99], p=0.034) while it did not differ compared to the CABG group in stable (HR: 2.38 [95%CI: 0.33, 16.7], p=0.39) or unstable group (HR: 0.33 [95%CI: 0.03, 3.22], p=0.34) analyzed separately.

Figure 2.

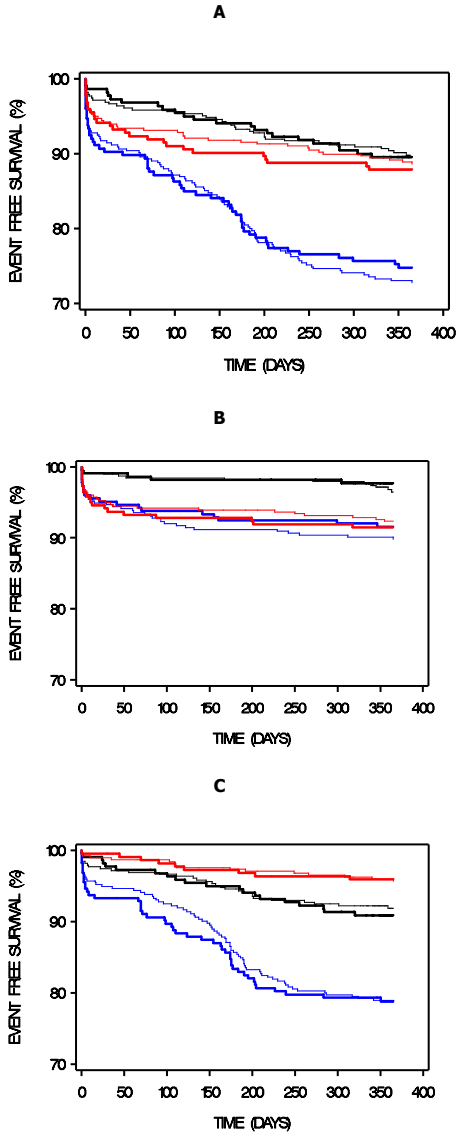


There was no observed interaction between the identified outcome predictors in the model and anginal status at presentation, irrespective of the peri-procedural applied MI definition. **A:** results based on non-Q-Wave MI defined as any CK or CK-MB elevation ≥3 x the upper limit of normal are shown, with an overall p value of 0.66 for testing interaction. **B:** results based on non-Q-Wave MI defined as any CK or CK-MB elevation beyond the upper limit of normal are shown, with an overall p value of 0.58 for testing interaction

DISCUSSION

Despite the growing body of evidence supporting the benefit of DES in different patients/lesion subsets, information regarding their differential safety/efficacy profile in patients with stable versus unstable angina is scanty and in part contradictory. Patients undergoing coronary intervention for unstable atherosclerotic coronary lesions are known to present with a smaller atherosclerotic(17) but larger thrombotic burden as compared to stable angina patients. This justifies the need to evaluate whether these devices may perform differently in these two patient subsets. In the RESEARCH registry, where 52% of the population presented with acute coronary syndromes (ACS), patients with and without ACS benefited equally from SES implantation, with a relative risk reduction in the need for target vessel revascularisation at one year in

Figure 3.



Kaplan-Meier curves out to one year in all three arms: (A) MACCE free Survival; (B) Death/CVA/MI free survival, (C) Freedom from repeat revascularization.Black: SES in ARTS II; Red: CABG in ARTS I, Blue: BMS in ARTS I. Bold line: unstable angina, thin line: stable angina

both groups when compared to BMS of 70% and 61% respectively(6).

Similar information has been provided by the STRATEGY trial, where patients undergoing primary intervention for acute myocardial infarction allocated to receive SES had a 70% relative reduction of TVR as compared to the BMS group(5). In both studies, the rate of thrombotic occlusion was low and not different in the SES with respect to control groups, suggesting that the safety profile of SES is maintained in patients with ACS.

In a sub-analysis of the TAXUS IV trial, an even lower restenosis rate was reported in patients with ACS as compared to stable patients receiving paclitaxel-eluting stents (PES)(7). However, patients with ACS treated with PES had a trend toward a higher rate of stent thrombosis at 30 days (0.8% vs. 0%, p=0.06) and of concern cardiac death at one year also trended higher in patients with ACS receiving PES (2.5% vs. 0.7%; p=0.051)(7). Thus, whether there is a specific risk in patients with ACS undergoing DES implantation remains largely debatable based on the available data.

In this sub-analysis of the ARTS II trial, the hypothesis that SES may perform differently according to clinical presentation (i.e. stable vs. unstable), which in itself reflects a difference in biology and coronary plaque composition, has been formally tested.

The main conclusion of this analysis is that elective multivessel patients with unstable angina, undergoing SES-supported coronary revascularization show a similar short and medium-term outcome with respect to those treated for stable ischemic syndromes. This conclusion is based mainly on the similar incidence of major adverse events in these two groups of patients. It is further reinforced by the observation that each individual component of MACCE i.e. death, re-infarction, CVA and repeat revascularization was very similar at 30 days as well as at one year in these two groups of patients. The rate of MI and the cumulative rate of MACCE remained remarkably similar at both univariate and multivariable-adjusted analysis between patients with SA and UA after reclassification of MI based on elevation of CK/CK-MB 3× or even 1× the upper limit of normal. Focusing on higher risk patients, identified according to class II or III of Braunwald classification, their short and long-term outcome was consistently similar compared to stable group.

Finally, the rate of thrombotic occlusion, although not statistically different in the two groups of patients, was actually numerically lower in unstable angina patients, confirming previous findings(5,6).

These results, based on a contemporary cohort of patients, were supported by the comparison of outcomes in ARTS II versus ARTS I, stratified according to clinical presentation. When adjusted for the baseline and procedural imbalance, the MACCE rate was significantly lower in both stable and unstable patients in the ARTS II with respect to those treated with BMS in ARTS I, while no difference was noted with respect to patients allocated to CABG, irrespective of stable or unstable presentation. The main analysis of ARTSII versus ARTSI based on a Bayesian statistical approach was recently reported(12). The results suggested that the use of SES in patients undergoing multivessel intervention is equivalent to the rate of major adverse events as compared to CABG treatment. In the present sub-analysis, a conventional statistical approach was employed to separately compare the two contemporary patient cohorts (i.e. UA and SA) with the same historical cohorts of ARTS I. Our current findings suggest the efficacy and safety of SES implantation irrespective of stable versus unstable presentation in the context of

elective multivessel disease patients undergoing percutaneous intervention.

Study Limitations

Against the consistent background of favourable results when the treatment with SES is compared to BMS implantation in randomized trials so far conducted, the ARTS II trial should be regarded as an intermediate step before the fulfillment of the next era of randomized trials of DES-supported percutaneous revascularization versus surgery, such as CARDIA, FREEDOM and SYNTAX and COMBAT. When ARTS II was designed, the decision was taken to use an historical control (ARTS I) in order to assess the improvement in clinical outcome when SES are implanted. This decision precluded the possibility of adjusting for unmeasured confounders between the two groups of individuals and necessitates the use of the previous definitions of primary endpoint and patient classification, such as death (cardiac and non-cardiac), cerebrovascular accident (e.g. TIA, RIND, Stroke), myocardial infarction (Q-wave and CK≥5XUNL), all revascularization (without TLR, TVR assessment), acute coronary syndrome (use of original Braunwald classification without systematic troponin triage), or thrombotic stent occlusion (angiographic definition). In this study the antiplatelet regimen was different from ARTSI due to the mandatory loading dose with thienopyridines administrated 24 hours prior to the intervention. This may have contributed in part to the more favorable outcome of ARTS II in comparison with ARTS I-BMS. Moreover, whether the neutral impact of clinical instability on outcome here observed is reproducible in the context of non-systematic thienopyridines pretreatment remains to be tested. Similarly, our results reasonably apply to medium-low risk ACS patients and cannot be extrapolated to patients with on-going or recent myocardial necrosis, haemodynamic instability or refractory ischemia since they were excluded from the study. Finally, despite the rate of confirmed or possible stent thrombosis was numerically even lower in the UA both at 30-days and one year compared to SA group, we cannot rule out the possibility that a type II error may have confounded our findings.

Conclusions

In elective patients with multivessel disease, undergoing SES-supported coronary revascularization after adequate pretreatment with thienopyridines, the rate of short and medium-term major adverse events is not affected by acuity of clinical presentation, irrespective of the applied definition of peri-procedural myocardial infarction. The performance of SES in patients with multivessel disease presenting with both stable and unstable coronary syndromes appears a promising alternative to conventional surgical revascularisation. This hypothesis, however, remains to be formally tested in the setting of a prospective randomized controlled trial.

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Chapter 15. Contemporary Use and Impact on outcomes of Glycoprotein IIb/IIIa inhibitors in patients undergoing multivessel intervention with *sirolimus*-eluting stent implantation. Insights into the Arterial Revascularization Therapies Study Part II

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Submitted for publication

Contemporary Use and Impact on Outcomes of Glycoprotein IIb/IIIa Inhibitors in Patients Pre-treated with Thienopyridines Undergoing Multivessel Intervention with *Sirolimus*-eluting Stent Implantation

INSIGHTS INTO THE ARTERIAL REVASCULARIZATION THERAPIES STUDY PART II

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Background: Current indications for glycoprotein IIb/IIIa inhibitors (GPI) after upfront administration of thienopyridines is debated and the efficacy of these drugs in patients treated with drug eluting stents (DES) remains mostly speculative.We investigated the contemporary use and impact on outcomes of GPI to support multiple *sirolimus*-eluting stent (SES) implantation in The Arterial Revascularization Therapies Study Part II (ARTS II).
Methods: In 607 elective patients with multivessel disease (MVD) consecutively treated with SES after thienopyridines pretreatment, 197 (32.4%) received GPI infusion at the discretion of the treating physician. The two groups were well matched for most clinical characteristics, including indications to revascularization, medical history and presence of diabetes mellitus, while patients treated with GPI had a greater CAD extension and underwent a more aggressive revascularization with greater number of implanted stents and total/ C-type treated lesions.
Results The 30-day event rate was similar in the two groups while at 1 year there was a non-significant excess of major adverse cardiac and cerebrovascular events (MACCE) (15.2% vs. 11%, respectively; HR 1.4 [95% CI: 0.89-2.2]; p=0.21), mainly driven by target vessel revascularization in patients treated with GPI. After adjustment with propensity analysis (C-statistic for the model 0.72, Hosmer–Lemeshow test p=0.53) the hazard ratio for MACCE was 1.08 [95% CI: 0.71-1.8]; p=0.74.
Conclusions: In MVD patients undergoing elective SES implantation after pre-treatment with thienopyridines, the use of GPI, mainly solicited by the presence of complex coronary anatomy, was not associated to an improved outcome after adjustment for a broad range of potential confounders.

Submitted

INTRODUCTION

Glycoprotein (GP) IIb/IIIa inhibitors prevent periprocedural myocardial infarction and decrease long-term cardiac mortality(1-3) in patients undergoing percutaneous coronary intervention (PCI). Developed and marketed in the pre-stent era, the GP IIb/IIIa inhibitors have been shown to be at least likewise beneficial in patients receiving bare metal stent implantation(4).
Yet, despite overwhelming evidence supporting their beneficial effects on short- and long-term outcomes, the rate of utilisation of GP IIb/IIIa inhibitors varies considerably among and within countries with a well documented discrepancy between recommendations and their actual use in clinical practice(5, 6).

Two main issues contribute to generate uncertainties regarding the use of GP IIb/IIIa inhibitors: i) current indications to the use of these drugs after upfront administration of thienopyridines is widely debated based on recent data(7) and ii) the impact of these drugs in the contemporary era with liberal use of drug-eluting stents (DES) remains unclear and somewhat speculative(8), especially based on the paradoxical results reported in a recent sub-analysis of the TAXUV IV trial(9).

The Arterial Revascularization Therapies Study Part II (ARTS II) was the first multicenter investigation to evaluate the safety and efficacy of the *sirolimus*-eluting stent (SES) in patients adequately pretreated with thienopyridines undergoing multi-vessel intervention (10). In this benchmark study, we investigated the contemporary use of GP IIb/IIIa inhibitors in the setting of multiple and often overlapping SES implantation, and their impact on short and long-term outcomes.

METHODS

Study Design and Patient Population

ARTS II was a multicenter, non-randomized, open labeled, stratified, non-inferiority trial designed to evaluate SES implantation in patients with multivessel disease using the surgical group of ARTS I as an historical control(10, 11). Patients, enrolled via a central telephone service, were stratified by clinical site in order to ensure the inclusion of at least 1/3 of patients with three-vessel disease. They were eligible for coronary revascularization if they had either stable angina, unstable angina or if they had silent ischemia and at least two new lesions located in different major epicardial vessels and / or their side branches (not including the left main coronary artery) that were potentially amenable to stent implantation using a CYPHER ® *sirolimus*-eluting stent (Cordis, a Johnon and Johnson company, Warren, NJ) with a diameter of 2.5 to 3.5mm and length of 13 to 33mm. Patients were required to have multivessel disease with need for treatment of the left anterior descending (LAD) artery and at least 1 other significant lesion (>50% diameter stenosis) in another major epicardial coronary artery. One totally occluded major epicardial vessel could also be included.
Patients with previous coronary intervention, left main coronary disease, overt congestive heart failure, left ventricular ejection fraction <30%, history of a cerebrovascular accident and STEMI in the preceding week or with persistent elevation of CK were

excluded. Measurement of troponin was not mandatory at screening. Patients with chest pain lasting longer than 30 minutes within the preceding 12 hours were also excluded if the CK level was equal to or more than 2 times the upper limit of normal.
Written, informed consent was obtained from each patient prior to enrolment. The ethics committee of each participating site approved the study.

Procedures and Post-Intervention Medications

All interventions were performed according to current standard guidelines and the final interventional strategy, including the use of GP IIb/IIIa inhibitors, was left entirely to the discretion of the operator. All patients were advised to maintain aspirin lifelong. Clopidogrel 300 mg as loading dose, or Ticlopidine, administered at a dose of 500 mg, was to be started at least 24 hours before the procedure. Clopidogrel 75 mg per day or Ticlopdine 250 mg twice a day were prescribed for at least 2 months after revascularization.

Study Objectives and Endpoints

The main objectives of this analysis are i) to analyze contemporary use of GP IIb/IIIa inhibitors in patients undergoing multiple SES implantation after upfront administration of ADP receptor blockers and ii) to analyze the impact on short- and long-term outcome in patients who received GP IIb/IIIa inhibitors infusion before or during intervention compared to those who did not. The primary outcome measures were incidence of major adverse cardiac and cerebrovascular events (MACCE) at 30-days and 1 year comprising all-cause death, any cerebrovascular event, non-fatal myocardial infarction (MI), or any repeat revascularization and the incidence of the composite of death and non-fatal MI within both 30 and 365 days. Use of GP IIb/IIIa inhibitors was referred to as i) *upstream* when drug bolus and infusion were started outside the catheterization laboratory; ii) *downstream*, if drug bolus and infusion were started in the catheterization laboratory before the start of interventional treatment and iii) bailout, when drug bolus and infusion were started after the start of the procedure.

End point definitions

Death from all causes was reported. A definite diagnosis of myocardial infarction was made if there was documentation of new abnormal Q waves (according to the Minnesota code) in association with a ratio of serum creatine kinase MB (CK-MB) isoenzyme to total cardiac enzyme that was greater than 0.1 or a CK or CK-MB value that was 3 times the upper limit of normal in one or more blood sample(s)(12). Serum CK and CK-MB isoenzyme concentrations were measured 6, 12, and 18 hours after the intervention. As a safety analysis, the end-points of major/minor bleedings were defined according to the criteria of the Thrombolysis in Myocardial Infarction Trial (13).

Statistical Analysis

Continuous variables are shown as mean±SD and were compared using Student's unpaired *t*-test. Categorical variables are presented as counts and percentages and compared with the χ^2 test. Survival curves were generated by the Kaplan-Meier method and survival among groups was compared using the log-rank test. Cox proportional hazards models were used to assess risk reduction of adverse events.
A propensity analysis was performed (14) by using a nonparsimonious logistic regression model (15) for the probability to receive GP IIb/IIIa inhibitors during index procedure based on all variables reported in table 1 and 2 with a p value of less than 0.30. The score was then incorporated into subsequent proportional-hazards models as a covariate; it was also was used to divide the population according to quartiles of propensity score.
The Hosmer–Lemeshow goodness-of-fit test and the area under the curve were used to assess the fit of the model. All statistical tests were 2-tailed. Probability was considered to be significant at a level of <0.05. Statistical analysis was performed on Statistica 6.1 (Statsoft Inc. Tulsa, Oklahoma) or SAS V8.02, SAS institute, Cary (NC).

Table 1. Baseline Characteristics of the Study Population

Variables	Use of GP IIb/IIIa Inhibitors		P value
	Yes (N=197)	No (N=410)	
Age (ys)	62±10	63±10	0.09
Males n.(%)	162 (82)	303 (74)	0.45
Body Mass Index (kg/m^2)	28±4	27±4	0.33
Diabetes n. (%)	54 (27)	105 (26)	0.63
Non-insulin dependent n. (%)	43 (80)	88 (84)	0.63
Insulin-dependent n. (%)	11 (20)	17 (16)	0.17
Hypertension n. n. (%)	132 (67)	276 (67)	0.94
Hypercholesterolemia n. (%)	161 (82)	286 (70)	0.002
Current Smokers n. (%)	36 (18)	81 (20)	0.72
Previous Smokers n. (%)	89 (45)	159 (39)	0.33
Family history n. (%)	93 (47)	124 (30)	<0.0001
Creatinine (μmol/L)	102±80	95±31	0.36
LV Ejection Fraction (%)*	59±12	61±11	0.11
MEDICAL HISTORY			
PCI n. (%)	1 (0.01)	2 (0.004)	0.97
Myocardial Infarction n. (%)	77 (39)	132 (32)	0.11
Anterior MI n. (%)	11 (6)	35 (8)	0.18
COPD n. (%)	7 (4)	15 (4)	0.94
Peripheral Arterial Disease n. (%)	15 (8)	27 (7)	0.77
Carotid Surgery n. (%)	3 (1.5)	5 (1.2)	0.76
CLINICAL PRESENTATION			
Stable Angina n. (%)	111 (56)	212 (52)	0.55
CCS n. (%)	2.23±0.7	2.27±0.7	0.64
Silent Ischemia n. (%)	14 (7)	49 (12)	0.13
Unstable Angina n. (%)	72 (37)	149 (36)	0.97
IB/IIB/IIIB n. (%)	14(19)/28(39)/ 17(24)	30(20)/56(38)/ 29(19)	0.93
IC/IIC/IIIC n. (%)	0(0)/10(14)/ 3(4)	7(5)/15(10)/ 12(8)	0.59
MEDICATIONS AT SCREENING			
β-blockers n. (%)	146 (74)	291 (71)	0.47
ACE-Inhibitors n. (%)	80 (41)	180 (44)	0.49
Statins n. (%)	153 (78)	279 (68)	0.01

ACE: angiotensin converting enzyme; PCI: percutaneous coronary intervention, LV: left ventricular, COPD: chronic obstructive pulmonary disease; MI: myocardial infarction; *: Available in 538 patients

RESULTS

Baseline and Procedural Characteristics

Baseline and procedural characteristics, stratified according to the use of GP IIb/IIIa inhibitors are shown in **TABLE 1** and **TABLE 2**. One hundred ninety seven patients (32.4%) were treated with infusion of GP

IIb/IIIa inhibitor; 20 (10%) patients underwent abciximab (n=9); tirofiban (n=9); or eptifibatide (n=2) infusion in the upstream setting, 150 (76%) received abciximab (n=95), tirofiban (n=32) or eptifibatide (n=23) as downstream infusion, while 27 (14%) patients received abciximab (n=24) or eptifibatide (n=3) as bailout strategy. The two groups of patients were well matched for most clinical characteristics, including indications to revascularization, medical history and presence of diabetes mellitus. Age and left ventricular ejection fraction tended to be lower while only hypercholesterolemia and family history of coronary disease were more frequent in the group of patients receiving GP IIb/IIIa inhibitors. Conversely, the two study groups differed with respect to most procedural data including a greater number of treated lesions and implanted stents, longer total stent length, higher number of C and bifurcation treated lesions and more frequent bifurcation stenting in the group of patients receiving GP IIb/IIIa inhibitors (**TABLE 2**). In both groups, there was an average of 2 thrombus-containing lesions per 100 patients treated. Use of β-blockers, ACE-inhibitors and Statins at screening is reported in table 1. In the group of patients receving GP IIb/IIIa inhibitors, 99% of the patients received clopidogrel (90%) or ticlopidine (9%) pretreatment according to the protocol compared to 98% (91% clopidogrel; 7% ticlopidine) of patients who did not receive treatment with GP IIb/IIIa inhibitors (p=0.98).

There was a considerable variability in the use of GP IIb/IIIa inhibitors in the 45 enrolling centers with 18 (40.9%) and 4 (9%) sites showing minimal (0-20% of the cases) and systematic (80-100% of the cases) use of GP IIb/IIIa inhibitors, respectively (**FIGURE 1**).

30-day and 1 year Outcome

30-day outcome both in terms of clinical events and bleeding rates are reported in table 3. There was no difference in any of the measured end-points between the two groups, including major and minor bleeding rates. Among the 27 patients receiving GP IIb/IIIa infusion as bailout strategy, one underwent reintervention within 30 days.

The cumulative incidence of MACCE (death, cerebrovascular accident, myocardial infarction or target vessel revascularization) at one year did not differ in the group of patients who underwent GP IIb/IIIa inhibitor infusion compared to patients who did not (15.2% vs. 11%, respectively; HR 1.4 [95% CI: 0.89-2.2]; p=0.21) (**FIGURE 2A**). The composite of death, CVA or non-fatal MI (7.1% vs. 4.9% in those not receiving GP IIb/IIIa inhibitors; HR 1.44 [95% CI: 0.73-2.87]; p=0.44) (**FIGURE 2B**) and the rate of TVR (10.6% vs. 7%; HR 1.54 [95% CI: 0.88-2.71]; p=0.12) (**FIGURE 2C**) were both numerically higher in the GP IIb/IIIa inhibitor group, but none of the clinical endpoints considered, either combined or individually, achieved statistical significance (**TABLE 3**).

Table 2. Angiographic and Procedural Characteristics of the Study population

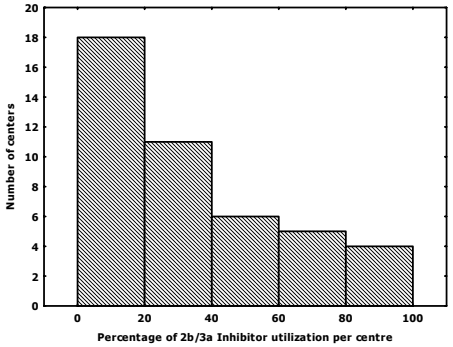
Variables	Use of GP IIb/IIIa Inhibitors: Yes (197 Patients 653 Lesion)	Use of GP IIb/IIIa Inhibitors: No (410 Patients 1486 Lesions)	P value
Diseased Segments	3.6±1.3	3.5±1.25	0.34
Diseased vessels	2.5±0.5	2.5±0.5	0.84
Vessel territory with stenosis			
LAD	197 (100)	408 (99)	0.82
CFX	146 (74)	317 (77)	0.44
RCA	157 (80)	312 (76)	0.32
Treated Vessel			
LAD	196 (99)	404 (99)	0.74
CFX	142 (72)	303 (74)	0.53
RCA	152 (77)	289 (70)	0.11
Patients receiving 2-vi.	100 (51)	224 (55)	0.67
Patients receiving 3-vi.	97 (49)	186 (45)	0.64
Patients with complete revascularization	129 (65)	235 (57)	0.054
Treated lesions	3.33±1.2	3.09±1.1	0.017
≤ 2	57 (29)	125 (30)	0.83
3-4	102 (52)	240 (58.5)	0.44
≥5-6	36 (18)	41 (10)	0.018
>6	2 (1)	4 (1)	0.69
Treated vessels	2.49±0.51	2.49±0.55	0.22
Number of implanted stents	4.1±1.7	3.5±1.4	<0.0001
Maximal pressure of stent deployment	16.5±3	16.3±2.8	0.34
Total stent length per patient (mm)	81.4±36	68.17±29	<0.0001
Treated lesions, n. (%)			
Type A	0.22±0.50	0.27±0.50	0.25
Type B1	0.83±0.90	0.89±0.90	0.46
Type B2	1.97±1.20	0.93±1.17	0.69
Type C	0.65±0.76	0.40±0.64	<0.0001
Total occlusion < 3 months	0.015±0.16	0.0048±0.07	0.26
Total occlusion > 3 months	0.065±0.25	0.088±0.29	0.37
Moderate to severly calficied lesions	1.05±1.16	1.06±1.13	0.89
Thrombus containing lesions	0.02±0.14	0.017±0.13	0.78
Bifurcated lesions	1.26±0.99	1.09±0.99	0.03
Stented side branch	1.10±0.89	0.89±0.85	0.007
Balloonned side branch	0.046±0.2	0.07±0.28	0.31

LAD: left anterior descending; CFX: circumflex; RCA: right coronary artery. Vi: vessel intervention.

Four patients in the bailout group underwent repeat percutaneous intervention within one year. In patients receiving planned (either up- or down-stream) GP IIb/IIIa inhibitor infusion, the unadjusted MACCE rate at 1 year was 16.5% vs. 10.8% in those who did not, HR 1.56 [95% CI: 0.95-2.5]; p=0.07).

When the overall patient population was stratified according to the median rate of GP IIb/IIIa inhibitors utilization in the enrolling sites (median use 27%), the MACCE rate in patients treated with vs. without GP IIb/IIIa inhibitors was respectively 17.4% (8/46) vs. 9%(22/244) (HR 1.95 [95% CI: 0.87-4.36]; p=0.11) in centers with low drug use, while it was respectively 14.5% (22/151) vs. 13.9% (23/166) (HR 1.01 [95% CI: 0.58-1.76]; p=0.94 in centers with high use of GP IIb/IIIa inhibitors. The 1-year MACCE rate was 14.8% in

Fig. 1 Histogram for the proportion of patients treated with GP IIb/IIIa inhibitors per enrolling site.



patients treated with abciximab and 15.9% in patients receiving small molecules (HR 0.93[95% CI: 0.41-2.2]; p=0.84).

Propensity Analyses

The median propensity value for the use of GP IIb/IIIa inhibitors during the index procedure (n=522) was 0.50 (IQR: 0.3-0.73) in the group receiving GP IIb/IIIa inhibitors and 0.19 (IQR: 0.09-0.32) in the group who did not. The C-statistic for the propensity score model was 0.72 indicating good but not excellent discrimination. (Hosmer–Lemeshow test p=0. 53). The adjusted hazard ratio for MACCE was 1.08 [95% CI: 0.71-1.8]; p=0.74.

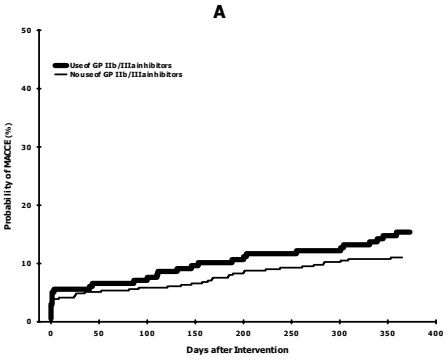
Matched event rates at both 30 days and one year in terms of the composite of death and non-fatal MI in the group of patient receiving treatment with GP IIb/IIIa inhibitor, as compared to those who did not, are shown in **figure 3**. None of the comparisons reached statistical significance.

Notably, in the fourth quartiles, where the overall incidence of death and non-fatal MI and the discrimination capacity of the propensity model were numerically higher, the event rate was reduced by more than 50% in the group of patients treated with GP IIb/IIIa inhibitors compared with those who did not.

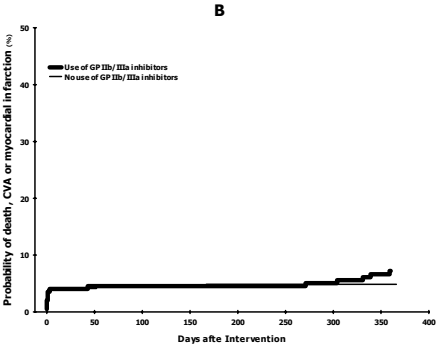
DISCUSSION

Despite the remarkable body of evidence supporting the benefit of GP IIb/IIIa inhibitors in different patients/lesions subsets (2-4, 16), information regarding their efficacy profile in patients undergoing drug eluting stent intervention is scant. There are several theoretical reasons why the impact of GP IIb/IIIa inhibitors may differ in patients undergoing BMS as compared to DES placement, including the different thrombogenic potential of the two stent types (17, 18) and the fact that complete revascularization strategy is usually more aggressively sought in the DES era with a higher number of stents deployed and more complex lesions approached (19). At the same time however, elective patients are increasingly more likely to undergo intervention once a steady state of ADP receptor blocker has been achieved, either through a longer period of pretreatment or administration of higher loading doses (20-22). This may

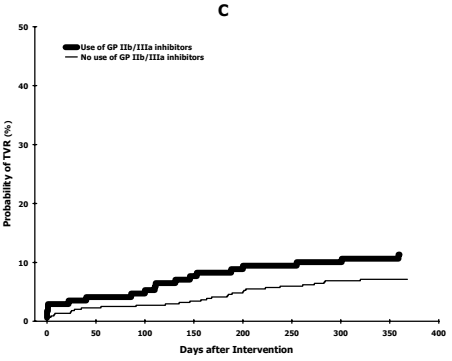
Fig. 2 One-year adverse events in patients treated with or without GP IIb/IIIa inhibitors.



Cumulative risk of major cardio- and cerebro-vascular adverse events (MACCE



Death, cerebrovascular accident (CVA) or myocardial infarction



Myocardial infarction (B); and target vessel revascularization (TVR)

in turn reduce the need for more potent antiplatelet agents, such as GP IIb/IIIa inhibitors, in patients with low-risk clinical profiles (7).

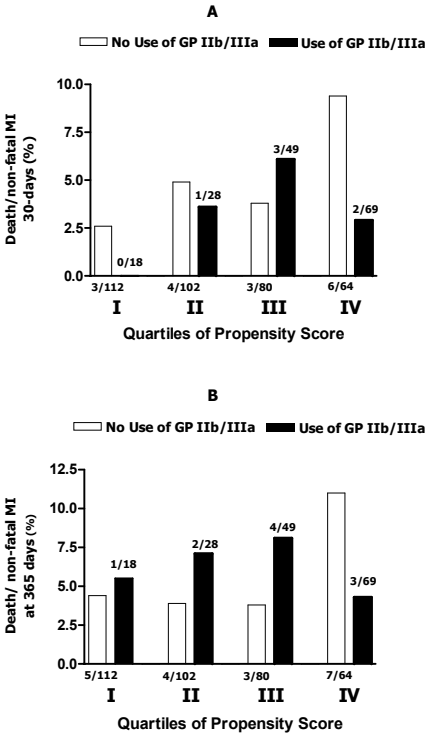
Thus, there is renewed interest in evaluating the short and long-term benefit of GP IIb/IIIa inhibition when employed as part of the contemporary interventions with DES (8).

Table 3. 30-Day and 1-year Outcome

Variables	Use of GP IIb/IIIa Inhibitors: Yes (N=197)	No (N=410)	P-value
30-DAY OUTCOME			
MACCE	12 (6.1) §	21 (5.1)	0.76*
Death/CVA/non-fatal MI	8 (4.1)	17 (4.2)	0.87*
Death/non-fatal MI	7 (3.6)	17 (4.2)	0.90*
Death	0 (0)	0 (0)	…
CVA	1 (0.5) ‡	0 (0)	0.71*
Non-fatal MI	7 (3.6)	17 (4.2)	0.72*
Q-wave MI	3 (1.5)	2 (0.5)	0.20*
Non-Q Wave MI	4 (2.0)	15 (3.7)	0.26*
Target Vessel Revascularization	7 (3.5)§	9 (2.2)	0.50*
Re-PCI	3 (1.5)§	5 (1.2)	0.93*
CABG	4 (2)	4 (1)	0.49*
Sub-acute Occlusion†	2 (1)	3 (0.7)	0.91*
Bleedings n. (%)			
Major	2 (1)	2 (0.5)	0.83*
Minor	9 (4.5)	13 (3.2)	0.53*
1-YEAR OUTCOME			
MACCE	30(15.2)**	45(11)	0.15
Death/CVA/non-fatal MI	14(7.1)	20 (4.9)	0.29
Death/non-fatal MI	12 (6.1)	20 (4.9)	0.55
Death	4 (2)	2 (0.5)	0.10
CVA	2 (1)	2 (0.5)	0.83
Non-fatal MI	9 (4.6)	18 (4.4)	0.93
Q-wave MI	3 (1.5)	2 (0.5)	0.40
Non-Q Wave MI	6 (3.0)	16 (3.9)	0.60
Target Vessel Revascularization	21 (10.6)**	29 (7)	0.19
Re-PCI	14 (7.1)**	24 (5.1)	0.61
CABG	6 (3)	7 (1.7)	0.37
Late Occlusion†	1(0.5)	1 (0.2)	0.82

*: By Fischer's exact test; 1-year outcome p-values were obtained by Log Rank test †: Angiographically documented, ‡: ischemic stroke occurred 3 days after intervention. §: in one patient receiving bailout treatment with GP IIb/IIIa inhibitor, a repeat percutaneous intervention (PCI) occurred within 30 days. **: in 4 patients receiving bailout GP IIb/IIIa inhibitors infusion a repeat PCI occurred within 365 days.

Fig. 3 Rate of death or non-fatal myocardial infarction at 30-days (A) and one year (B) stratified into quartiles of propensity score (n=522 patients).



In a recent analysis of TAXUS IV, use of Gp IIb/IIIa inhibitors in association with the TAXUS ™ paclitaxel-eluting stent was independently and paradoxically associated with the occurrence of periprocedural myocardial necrosis(9). Although this may have been due to preferential use of GP IIb/IIIa inhibitors in more complex patients or lesions, no such risk factors were identified among the variables examined (9). Moreover, these unexpected findings could not be explained by an increased use of GP IIb/IIIa inhibitors for bailout or by differences in GP IIb/IIIa inhibitors use among patients.

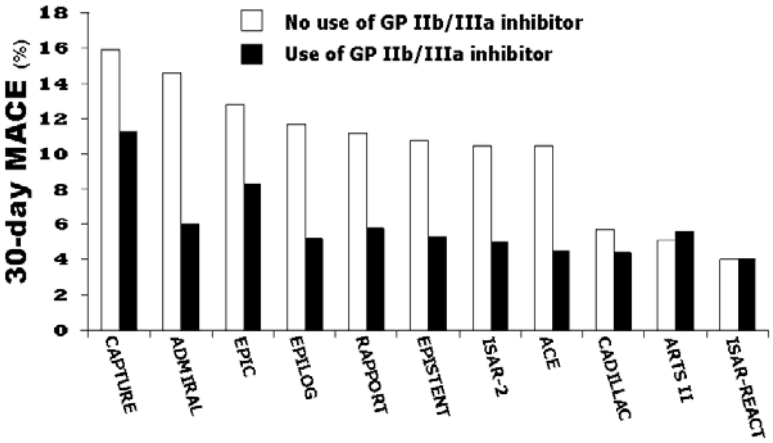
In the present ARTS II sub analysis, focusing on patients undergoing multiple vessel stenting with the *sirolimus*-eluting stent, no detrimental interaction was observed between the stent and use of GP IIb/IIIa inhibitors by both univariate and propensity-adjusted analysis. Nevetheless, patients treated with GP IIb/IIIa inhibitors had a numerically higher MACCE rate than those not undergoing GP IIb/IIIa inhibition.

The excess of events in the GP IIb/IIIa inhibitor arm in ARTS II was largely driven by TVR, while the unadjusted composite of death and non-fatal MI were similar at both 30 days and 1-year in the treated and untreated arms. Moreover, patients treated with GP IIb/IIIa inhibitors in the present trial had a more severe angiographic profile than patients who did not receive such treatment. This suggests a selection bias among patients undergoing treatment with GP IIb/IIIa inhibitors. This hypothesis has been confirmed by i) the stratified analysis according to enrolling sites, where the excess of events at one year was almost totally confined to centers with low use of Gp IIb/IIIa inhibitors and ii) the propensity-adjusted analysis.

Our results may question the value of GP IIb/IIIa inhibition in the DES era in elective patients adequately pretreated with thienopyridines. It is tempting to speculate that the paradoxical (9), or neutral results in the present study, of the effect of GP IIb/IIIa inhibition so far reported in the DES era, may reflect the complex interplay of multiple variables.

1) Most of the studies supporting the benefit of GP IIb/IIIa inhibitors in patients undergoing intervention date back to the pre-clopidogrel era, when ticlopidine was seldom administered much before PCI procedure (23-26) or the duration of pretreatment was not always accurately tracked (27). Thus, despite some preliminary evidence supporting the additional benefit of GP IIb/IIIa inhibition when given on top of pretreatment with ADP receptor blockers(28, 29), this may not necessarily be

Fig. 4 30 days MACE in patients allocated to receive GP IIb/IIIa inhibitors (white column) or placebo (black column) in all major randomized controlled trials evaluating abciximab in patients undergoing coronary intervention and in ARTS II study



In studies where the overall event rate in the placebo-untreated group was around 6% or less, no or negligible risk reduction of MACE was observed by the use of GP IIb/IIIa inhibit

the case in stable (7) or cooled-off patients like those enrolled in the ARTS II study.

2) There is not a single large-scale, randomized trial evaluating the benefits of GP IIb/IIIa inhibitors when administered based upon coronary anatomy *per se*. Although, complex anatomy has sometimes been considered as an inclusion criterion in trials (23, 25), patients presenting with clinical instability (i.e. troponin elevation, ongoing chest pain, acute or recent ECG changes) have always been the predominant (26, 30) or even the only patient population in whom the benefit of GP IIb/IIIa inhibitors has been clearly established (16, 26, 31-33). Moreover, even at post-hoc analyses of the EPIC and EPILOG trials, it was shown that the reduction in complications of angioplasty with abciximab is largely independently of baseline lesion morphology (34). This further supports the concept that the clinical status of the patients rather than the coronary anatomy may explain most of the observed benefit of GP IIb/IIIa inhibitors administration in patients undergoing PCI. This paradigm has been recently supported by a sub-analysis of the ESPRIT trial (35) and by the ISAR-REACT-2 study(33).
In ARTS II, investigators selected patients to receive GP IIb/IIIa inhibitors based on coronary anatomy rather based on clinical presentation. Indeed, even among the 98 patients in whom this information was collected, 16% (6/37) of the group receiving GP IIb/IIIa inhibitors compared to 31% (19/61) (p=0.15) of those who did not had troponin elevation at screening. Thus, in the DES era, the propensity to administer GP IIb/IIIa inhibitors based purely on coronary anatomy may increase as a consequence of treating more complex lesion subsets. Whether such an approach is justified will need to be addressed by future randomized trials.

3) In ARTS II, the overall MACCE rate at 30 days was low while at one year it was predominantly driven by TVR, especially in the GP IIb/IIIa inhibitor group. This is consistent with the fact that elective patients with complex and multiple coronary lesions have been selected to test the performance of the sirolimus-eluting stent. Intimal hyperplasia is not affected by the use of GP IIb/IIIa inhibitors (36) and when the present 30-days MACE rate is viewed in the context of all major trials evaluating the benefit of abciximab in the setting of PCI (**FIGURE 4**), the lack of benefit from GP IIb/IIIa inhibitors in the ARTS II trial is not surprising. This may explain why a trend favoring the use of GP IIb/IIIa inhibitors in the ARTS II trial was only seen in the highest quartile of the propensity score.

Study Limitations
This study has several limitations. First of all, ARTS II was not designed or powered to evaluate the effect of GP IIb/IIIa inhibitors on outcomes. This analysis should be viewed as exploratory and hypothesis generating. In an attempt at correcting for all recorded confounders between patients receiving or not receiving GP IIb/IIIa inhibitors, a non-parsimonious propensity analysis was employed in the study. However, we cannot rule out the possibility that unmeasured residual confounders might still have affected our overall adjusted results.

Measurement of troponin was not mandatory in the trial, so that this information was not available for the majority of the enrolled patients. This has prevented us from adjusting for troponin status at entry in the present analysis. Considering the well-known interaction between troponin elevation and favorable response to GP IIb/IIIa inhibitors (31, 33), this information, if available for all patients, might have shed important light on the effect of

the study drugs between the treated and untreated patients.

Conclusions

In the ARTS II, in the context of multivessel disease patients undergoing elective sirolimus eluting stent implantation after pre-treatment with thienopyridines, the use of GP 2b/3a inhibitors was mainly solicited by the presence of complex coronary anatomy more than by patient clinical profile. The use of this class of antiplatelet agents to "bail out" situations (where efficacy has not been established) was not infrequent. This did not translate into an improved outcome in those receiving the treatment compared with patients who did not after adjustment for a broad range of potential confounders. Our results suggest, even if cannot prove, that even in the DES era, where complex and extensive CAD is more aggressively treated percutaneously, the use of GP IIb/IIIa inhibitors should be triggered by the clinical more than angiographic characteristics of the patients undergoing coronary revascularization.

Future studies investigating the role of GP IIb/IIIa blockers are warranted to establish the benefit of this drug class when administered in patients with high risk clinical profile during contemporary DES-supported coronary intervention.

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Chapter 16. One-year outcome in patients with multivessel disease involving the proximal left anterior descending artery after implantation of sirolimus-eluting stents compared with either bare-metal stents or coronary artery bypass grafting. A Combined Analysis of the Arterial Revascularization Therapies Study (ARTS) I and II

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One-year outcome in patients with multivessel disease involving the proximal left anterior descending artery after implantation of sirolimus-eluting stents compared with either bare-metal stents or coronary artery bypass grafting

A Combined Analysis of the Arterial Revascularization Therapies Study (ARTS) I and II

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Aims: Coronary revascularization with bare metal stents (BMS) in patients with multivessel disease (MVD) and involvement of the proximal left anterior descending artery (pLAD) is associated with an increased risk of in-stent restenosis and frequently necessitates re-intervention. In this setting, the use of sirolimus eluting stents (SES) may prove superior to BMS and equalize outcomes compared with coronary artery bypass grafting (CABG). We evaluated the incidence of major adverse cardiac and cerebrovascular events (MACCE) at 1 year after SES in MVD patients with pLAD disease compared with BMS or CABG.
Methods and Results: A total of 289 MVD patients with pLAD disease recruited at 45 centres undergoing SES implantation in the Arterial Revascularization Therapies Study (ARTS) part II were compared with 187 and 206 patients with pLAD obstruction enrolled in ARTS I receiving BMS and CABG, respectively. At one year the cumulative incidence of MACCE in the SES was lower (10.4%) than in the BMS group (20.3%, RR 0.51 [95% CI: 0.33-0.79]; p=0.003), while it was almost identical to CABG patients (10.2% RR 1.02 [95% CI: 0.60-1.73]; p>0.99). After adjustment, patients undergoing SES implantation had a better outcome compared with those receiving BMS (adjusted HR 0.29 [95% CI: 0.14-0.59]; p=0.0006), while they did not differ in terms of MACCE when compared with the CABG group (adjusted HR 0.94 [95% CI: 0.43-2.08]; p=0.89).
Conclusions: Intervention assisted by SES in MVD with pLAD involvement, by reducing the need for re-intervention associated with BMS, may equalize one year outcomes compared with CABG.

Submitted

INTRODUCTION

Coronary revascularisation in patients with multivessel disease (MVD) eligible for catheter-based intervention can be achieved either by a surgical or a percutaneous approach yielding similar results with respect to long-term mortality and rates of infarction [1,2]. While the use of bare metal stent (BMS) has led to a significant improvement in the early and late patency rate of treated arteries [3,4], the need for repeated revascularisation has remained substantially higher after percutaneous compared to surgical intervention due to high rate of in-stent restenosis [1,2,5]. Hence, the decision as to which revascularisation strategy to perform in the BMS era was mainly influenced by feasibility of the percutaneous treatment integrated by the predicted risk of restenosis based on clinical and angiographic findings.

This process of clinical decision-making is critical particularly for MVD patients with involvement of the proximal left anterior descending artery (pLAD), who are at relatively high risk for developing in-stent restenosis when treated percutaneously [6-8] while they are known to derive the most benefit from surgical revascularisation with mammary artery conduits[9-12].

The superior performance of drug-eluting stents (DES) in terms of restenosis prevention compared to BMS [13] renovates the interest to evaluate the clinical benefit of contemporary percutaneous intervention in a selected subset of patients traditionally referred for surgical intervention.

The short and mid-term outcomes of patients with MVD and involvement of pLAD who underwent sirolimus eluting stents (SES) implantation in the Arterial Revascularization Therapies Study (ARTS) part II was investigated and compared with patients with pLAD disease randomly allocated to receive either BMS or CABG as part of ARTS I.

METHODS

Study design

The ARTS II study design has been previously reported[2,14]. Briefly, patients were consecutively enrolled via a central telephone service, after stratification by clinical site to ensure the inclusion of at least one third of patients undergoing three-vessel intervention.

Selection of patients

Patients were eligible for coronary revascularization if they had either stable angina (Canadian Cardiovascular Society class I, II, III, or IV), unstable angina (Braunwald class IB, IC, IIB, IIC, IIIB, or IIIC), or if they had silent ischemia and at least two new lesions located in different major epicardial vessels and/or their side branches (not including the left main coronary artery) that were potentially amenable to stent implantation. Patients were required to have multivessel disease with the need for treatment of the left anterior descending (LAD) artery and at least one

other significant lesion (>50% diameter stenosis) in another major epicardial coronary artery. One totally occluded major epicardial vessel could also be included. The stenosis had to be amenable to stenting using a stent with a diameter of 2.5 to 3.5mm and length of 13 to 33mm, without any restriction on the total stent length implanted.
Patients with any previous coronary intervention, left main coronary disease, overt congestive heart failure or a left ventricular ejection fraction of less than 30 percent were excluded. Additional exclusion criteria included a history of a cerebrovascular accident and STEMI in the preceding week or with persistent elevation of CK. Measurement of troponin was not mandatory at screening. Patients with chest pain lasting longer than 30 minutes within the preceding 12 hours were also excluded if CK was equal or more than 2 times upper normal limit.
Written, informed consent was obtained from each patient prior to enrolment. The study was approved by the ethics committee of each participating site.

Procedures and Post-Intervention Medications

All interventions were performed according to current standard guidelines and the final interventional strategy, including the use of glycoprotein IIb/IIIa inhibitors, was left entirely to the discretion of the operator, except for the stent utilization. All patients were advised to maintain aspirin lifelong. Clopidogrel 300 mg as a loading dose, or Ticlopidine, administered at a dose of 500 mg, was to be started at least 24 hours before the procedure. Clopidogrel 75 mg per day or Ticlopdine 250 mg twice a day was prescribed for at least two months after revascularization.

Study Objectives and Endpoints

The primary objective of this ARTS II sub-analysis was to compare the safety and effectiveness of coronary stent implantation using sirolimus-eluting stents with the use of metallic stent implantation or CABG in patients with multivessel disease involving the pLAD. The primary outcome measure was the incidence of major adverse cardiac and cerebrovascular events (MACCE) at one year comprising all-cause death, any cerebrovascular event, non-fatal myocardial infarction, or any repeat revascularization.

End point definitions

All deaths were considered cardiac unless a non cardiac origin was established clinically or at autopsy. Death from all causes was reported.
Cerebrovascular events were divided into three main categories: stroke, transient ischemic attack (TIA), and reversible ischemic neurologic deficit (RIND). In the first seven days after the intervention, a definite diagnosis of myocardial infarction was made if there was documentation of new abnormal Q waves (according to the Minnesota code) and either a ratio of serum creatine kinase MB (CK-MB) iso-enzyme to total cardiac enzyme that was greater than 0.1 or a CK-MB value that was 5 times the upper limit of normal (ULN)[1, 11, 12] Serum creatine kinase and CK-MB iso-enzyme concentrations were measured 6, 12, and 18 hours after the intervention. Beginning eight days after the intervention (the length of the hospital stay after surgery), either abnormal Q waves or enzymatic changes were sufficient for a diagnosis of myocardial infarction. This dual method of defining myocardial infarction was developed for ARTS I to address the difficulty of diagnosing a myocardial infarction after surgery. A myocardial infarction was confirmed only after the relevant electrocardiograms had been analyzed by the electrocardiographic core laboratory and adjudicated by a clinical-events committee. All repeat revascularization procedures were recorded. Events were counted from the time of the initial procedure. Thrombotic occlusions were defined either by angiographic documentation of a complete occlusion (TIMI flow 0 or 1) or angiographic documentation of a flow limiting thrombus (TIMI flow 1 or 2). All events were reviewed and adjudicated by an independent clinical-events committee.
Angiographic data, including the characteristics of each lesion and target coronary segment, were adjudicated by an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands). The proximal LAD was defined as the segment between the branching point of the left main stem and the first major septal branch (segment 6 in the American Heart Association classification)[15]. To avoid any bias related to investigator-driven adjudication, involvement of the pLAD was centrally defined as a lumen obstruction equal or more than 50% at visual estimation according to the analysis performed by the independent angiographic core-lab.

Statistical analysis

Continuous variables are shown as mean $\pm$ SD if not otherwise stated and were compared using Student's two-sample *t*-test. Categorical variables are presented as percentages and compared with the χ^2test. Survival curves were generated by the Kaplan-Meier method and survival amongst groups was compared using the log-rank test. Cox's regression proportional hazards models were used to assess risk reduction of adverse events. Multivariable analysis, considering all potential confounders of primary outcome measures, defined as those with a univariate p-value of 0.1 or less at Cox's regression, was performed for both SES vs. BMS and SES vs. CABG comparisons. Factors causing co-linearity in the model (investigated using a correlation matrix and by inspection of the estimate parameters) were removed. Moreover a simultaneous interaction test of the predicting variables with revascularisation strategy was performed. The interaction was calculated by comparing the cumulative model fit statistics of the above analysis with the fit statistics of an analysis stratified by treatment. The fit statistic used is the -2 log(Likelihood), which has a χ^2 distribution with v degrees of freedom. Probability was significant at a level of <0.05. All statistical tests were 2-tailed. Statistical analysis was performed with SAS V8.02, (SAS institute, Cary, NC, USA).

RESULTS

Patients

From April 1997 to June 1998, 1,205 patients were randomly assigned to undergo CABG (605 patients) or angioplasty with stent implantation (600 patients) at 67 participating centers in the ARTS I. A total of 393 patients presented with pLAD disease, of whom 187 were randomly assigned to stenting and 206 to CABG. Between February 2003 and November 2003, 607 patients at 45 participating centers, of whom 289 were affected by pLAD disease, were treated with SES as part of the ARTS II. **Table 1** presents their baseline demographic characteristics.
Patients treated with SES were older than those allocated to BMS and had a higher prevalence of diabetes mellitus, hypertension and hypercholesterolemia compared with both BMS and CABG groups; in ARTS II there were fewer smokers compared with ARTS I and patients suffered less frequently from a previous MI than those in the BMS group but had three vessel disease in more than 50% of cases compared with approximately 30% in those recruited in the ARTS I. The cumulative r number of diseased and treated lesions was also higher in ARTS II. Overall, A and B1 type lesions were more frequently observed in ARTS I patients, while B2 or C type lesions were more common in ARTS II patients (**Table 2**). Glycoprotein 2b/3a inhibitors were used in 33.6% in the SES group but in only a few patients during ARTS I. The left internal mammary artery (LIMA) was employed in 93% of the cases in the CABG group while 16.5% of patients had bilateral left and right internal mammary artery (BIMA) grafting.

Table 1 Baseline Patient Demographics

Patient Parameters Measured	SES Group (N=289 patients)	BMS Group (N=187 patients)	CABG Group (N=206 patients)	P-value [1]	P-value [2]
Age (years)					
mean ± SD	63.1±10.1	60.1±9.5	62.0±9.0	0.001	0.21
(min - max)	(35 - 80)	(30 - 77)	(31 - 80)		
Ejection Fraction (%)					
N	247	175	190		
mean ± SD	59.2±11.5	60.8±12.2	60.5±13.3	0.18	0.28
(min - max)	(30 - 97)	(30 - 92)	(30 - 91)		
Body Mass Index (kg/m2)					
mean ± SD	27.5±4.1	26.9±3.6	27.4±3.4	0.10	0.68
(min - max)	(19.9 - 42.0)	(19.1 - 39.7)	(18.5 - 37.0)		
Number of Men	80.6% (233/289)	78.1% (146/187)	81.1% (167/206)	0.56	1.00
Diabetes Mellitus	24.9% (72/289)	11.2% (21/187)	14.6% (30/206)	<0.001	0.005
Hypertension	65.7% (190/289)	41.2% (77/187)	44.2% (91/206)	<0.001	<0.001
Hypercholesterolemia	73.6% (212/288)	63.1% (118/187)	58.5% (120/205)	0.019	<0.001
History of CVA	0.7% (2/289)	1.1% (2/187)	0.5% (1/206)	0.65	1.00
Family history of MI/sudden death <55 yr	36.5% (105/288)	39.7% (73/184)	43.9% (90/205)	0.50	0.11
Peripheral Vascular Disease	8.0% (23/289)	5.3% (10/187)	5.3% (11/206)	0.36	0.28
Previous MI	32.5% (94/289)	44.4% (83/187)	37.9% (78/206)	0.011	0.25
Previous CABG	0.0% (0/289)	0.0% (0/187)	0.0% (0/206)		
Previous PTCA	0.7% (2/289)	1.1% (2/187)	2.4% (5/206)	0.65	0.13
Carotid Surgery	1.7% (5/289)	1.1% (2/187)	1.5% (3/206)	0.71	1.00
Chronic Obstructive Pulmonary Disease	4.8% (14/289)	6.4% (12/187)	4.4% (9/206)	0.54	1.00
Smoking History					
Previous	39.1% (113/289)	43.5% (81/186)	51.9% (107/206)	0.34	0.006
Current	17.6% (51/289)	27.4% (51/186)	20.4% (42/206)	0.016	0.48
Unstable Angina	32.9% (95/289)	41.7% (78/187)	34.5% (71/206)	0.052	0.77
Braunwald I	9.3% (27/289)	7.5% (14/187)	5.3% (11/206)	0.51	0.12
Braunwald Ib	8.3% (24/289)	4.8% (9/187)	5.3% (11/206)	0.20	0.22
Braunwald Ic	1.0% (3/289)	2.7% (5/187)	0.0% (0/206)	0.27	0.27
Braunwald II	15.6% (45/289)	20.9% (39/187)	15.5% (32/206)	0.14	1.00
Braunwald IIb	12.8% (37/289)	13.4% (25/187)	13.1% (27/206)	0.89	1.00
Braunwald IIc	2.8% (8/289)	7.5% (14/187)	2.4% (5/206)	0.024	1.00
Braunwald III	8.0% (23/289)	13.4% (25/187)	13.6% (28/206)	0.06	0.051
Braunwald IIIb	6.9% (20/289)	11.8% (22/187)	12.1% (25/206)	0.10	0.057
Braunwald IIIc	1.0% (3/289)	1.6% (3/187)	1.5% (3/206)	0.68	0.70
Stable Angina	57.4% (166/289)	53.5% (100/187)	59.7% (123/206)	0.40	0.64
CCS I	9.0% (26/289)	4.8% (9/187)	3.9% (8/206)	0.11	0.030
CCS II	28.0% (81/289)	26.7% (50/187)	26.2% (54/206)	0.83	0.68
CCS III	19.4% (56/289)	17.6% (33/187)	28.2% (58/206)	0.72	0.023
CCS IV	1.0% (3/289)	4.3% (8/187)	1.5% (3/206)	0.029	0.70
Silent Ischaemia	9.7% (28/289)	4.8% (9/187)	5.8% (12/206)	0.055	0.13

SES: Sirolimus eluting stent, BMS: bare metal stent, CABG: coronary artery bypas grafting; CVA= CerebroVascular Accident; MI = Myocardial Infarction; CABG =Coronary Artery Bypass Graft; PTCA = Percutaneous Transluminal Coronary Angioplasty; Braunwald = Braunwald Classification; CCS = Canadian Cardiovascular Society Classification; p-value 1: SES vs. BMS, p-value 2: SES vs. CABG

30-day Outcomes

The MACCE rate was 2.8% in patients receiving SES compared with 8.6% in the BMS group (RR 0.32 [95% CI: 0.14-0.74]; p=0.009) and 5.8% (RR 0.48 [95% CI: 0.20-1.14]; p=0.11) in the CABG group (**Table 3**). A reduced incidence of death and MI was noted in the SES (0% and 0.7%) compared with the CABG group (2.4%, p=0.012 and 4.4%, RR 0.16 [95% CI: 0.03-0.73]; p=0.010, respectively). This was counterbalanced by the higher need for re-intervention observed in the group of patients undergoing sirolimus-eluting stenting (2.1% vs. 0%, p=0.044), which was almost entirely due to surgical revascularization in patients in whom percutaneous intervention was not successful. In a single patient in the SES group, sub-acute occlusion occurred, which required percutaneous re-intervention.

One-year Outcomes

At one year the cumulative incidence of MACCE in the SES group was lower (10.4%) than in the BMS group

Table 2: Procedural Characteristics and Medications

Parameters Measured	SES Group (N=289 patients N=1048 lesions)	BMS Group (N=187 patients N=560 lesions)	CABG Group (N=206 patients N=611 lesions)	p-value [1]	p-value [2]
Per Patient Analysis					
Number of Diseased Arteries					
Single	0.7% (2/289)	3.2% (6/187)	2.9% (6/206)	0.06	0.07
Double	45.3% (131/289)	67.4% (126/187)	60.2% (124/206)	<0.001	0.001
Triple	54.0% (156/289)	29.4% (55/187)	36.9% (76/206)	<0.001	<0.001
Number of lesions > 50% DS	3.7±1.3	3.0±1.0	3.0±1.1	<0.001	<0.001
Number of vessels with a lesion > 50% DS	2.5±0.5	2.3±0.5	2.3±0.5	<0.001	<0.001
Number treated lesions: anastomoses/stented lesions	3.3±1.2	2.7±1.0	3.0±1.0	<0.001	<0.001
Number of Stents Implanted	3.8±1.6	2.9±1.2	**...**	<0.001	**...**
Average stent length (mm)	19.4±3.5	16.7±3.3	**...**	<0.001	**...**
Total stent length (mm)	73.9±33.4	48.3±21.5	**...**	<0.001	**...**
Maximum Dilatation pressure (Atm)	16.5±28	15.0±2.7	**...**	<0.001	**...**
Pharmacological Treatment					
Lipid-lowering agents	88.9% (257/289)	41.8% (77/184)	35.6% (72/202)	<0.001	<0.001
Thienopyridines	97.9% (283/289)	94.6% (174/184)	**...**	0.07	**...**
Aspirin	95.8% (277/289)	96.7% (178/184)	84.2 (170/202)	0.81	<0.001
ACE-inhibitors	49.1% (142/289)	21.2% (39/184)	15.8% (32/202)	<0.001	<0.001
β-blockers	76.5% (221/289)	62.0% (114/184)	59.9% (121/202)	<0.001	<0.001
Per Lesion Analysis (%)					
Length					
- Discrete (< 10 mm.)	60.7% (617/1016)	65.4% (351/537)	68.9% (398/578)	0.08	0.001
- Tubular (10-20 mm.)	26.3% (267/1016)	26.6% (143/537)	25.8% (149/578)	0.90	0.86
- Diffuse (> 20 mm.)	13.0% (132/1016)	8.0% (43/537)	5.4% (31/578)	0.003	<0.001
Concentric Lesion	13.8% (140/1016)	13.4% (72/536)	16.1% (93/578)	0.88	0.21
Readily Accessible Segment	95.7% (969/1013)	96.3% (515/535)	96.4% (557/578)	0.69	0.51
Lesion Angulation					
- None	87.8% (891/1015)	83.4% (446/535)	86.3% (499/578)	0.020	0.43
- Moderate	12.1% (123/1015)	16.3% (87/535)	13.3% (77/578)	0.029	0.48
- Severe Bend Point	0.1% (1/1015)	0.4% (2/535)	0.3% (2/578)	0.28	0.30
Irregular Contour	9.3% (94/1011)	11.8% (63/534)	9.0% (52/578)	0.13	0.93
Ostial Lesion	7.0% (71/1015)	12.2% (65/534)	9.5% (55/578)	<0.001	0.08
Calcification: Moderate to Heavy	34.9% (354/1014)	21.3% (115/539)	16.3% (94/578)	<0.001	<0.001
Thrombus Present	0.5% (5/1036)	1.5% (8/534)	1.0% (6/578)	0.043	0.22
Occlusion					
- Less than Total	98.2% (1029/1048)	96.2% (533/554)	94.6% (578/611)	0.019	<0.001
- Total < 3 Months Old	0.1% (1/1048)	3.6% (20/554)	4.4% (27/611)	<0.001	<0.001
- Total >=3 Months Old	1.7% (18/1048)	0.2% (1/554)	1.0% (6/611)	0.006	0.29
Bifurcation or Side Branch Lesion					
- No Major Branch Involvement	64.8% (658/1016)	65.5% (349/533)	67.5% (390/578)	0.82	0.30
- Bifurcation Requiring Double Guide Wire	35.2% (358/1016)	34.1% (182/533)	32.5% (188/578)	0.69	0.30
- Inability to Protect Major Side Branches	0.0% (0/1016)	0.4% (2/533)	0.0% (0/578)	0.12	
Lesion classification *					
- Type A	7.1% (74/1048)	5.2% (29/560)	6.1% (37/611)	0.16	0.48
- Type B1	21.9% (230/1048)	28.0% (157/560)	30.6% (187/611)	0.007	<0.001
- Type B2	56.6% (593/1048)	58.2% (326/560)	57.0% (348/611)	0.56	0.92
- Type C	14.4% (151/1048)	8.6% (48/560)	6.4% (39/611)	<0.001	<0.001
- Type A/B1	29.0% (304/1048)	33.2% (186/560)	36.7% (224/611)	0.09	0.002
- Type B2/C	71.0% (744/1048)	66.8% (374/560)	63.3% (387/611)	0.09	0.002

p-value1: SES vs. BMS, p-value2: SES vs. CABG

(20.3%, RR 0.51 [95% CI: 0.33-0.79]; p=0.003), while it was almost identical compared with patients who underwent CABG (10.2% RR 1.02 [95% CI: 0.60-1.73]; p>0.99), reflecting a lower rate of the composite of death/CVA/MI in the SES group (RR 0.31 [95% CI: 0.13-0.74]; p=0.008) and a higher need for cumulative re-intervention (RR 2.85 [95% CI: 1.19-6.85]; p=0.013).

Table 3: Non hierarchical clinical outcome in ARTS II compared to ARTS I

	SES Group (N=289 patients)	BMS Group (N=187 patients)	CABG Group (N=206 patients)	P-value[1]	P-value[2]
30-day Outcome (%)					
MACCE	2.8 (8/289)	8.6 (16/187)	5.8 (12/206)	0.009	0.11
Death/CVA/ MI	1.0 (3/289)	5.9 (11/187)	5.8 (12/206)	0.004	0.003
Death	0.0 (0/289)	3.2 (6/187)	2.4 (5/206)	0.003	0.012
CVA	0.3 (1/289)	0.5 (1/187)	0.5 (1/206)	>0.99	>0.99
MI	0.7 (2/289)	3.2 (6/187)	4.4 (9/206)	0.06	0.01
Q-Wave MI	0.7 (2/289)	2.7 (5/187)	3.9 (8/206)	0.12	0.02
Non Q-Wave MI	0.0 (0/221)	0.5 (1/187)	0.5 (1/206)	0.39	0.42
Revasc.	2.1 (6/289)	4.8 (9/187)	0.0 (0/206)	0.11	0.044
CABG	1.7 (5/289)	0.5 (1/187)	0.0 (0/206)	0.41	0.08
Re-PTCA	0.3 (1/289)	4.3 (8/187)	0.0 (0/206)	0.003	>0.99
Sub-acute occlusion	0.3% (1/289)	2.7% (5/187)	0.0 (0/206)	0.037	>0.99
365-day Outcome					
MACCE	10.4 (30/289)	20.3 (38/187)	10.2 (21/206)	0.003	>0.99
Death/CVA/ MI	2.4 (7/289)	9.1 (17/187)	7.8 (16/206)	0.002	0.008
Death	1.0 (3/289)	3.7 (7/187)	3.4 (7/206)	0.054	0.1
CVA	0.7 (2/289)	1.1 (2/187)	1.0 (30/289)	0.65	>0.99
MI	0.7 (2/289)	5.3 (10/187)	4.9 (10/206)	0.002	0.005
Q-Wave MI	0.7 (2/289)	4.8 (9/187)	4.4 (9/206)	0.009	0.01
Non Q-Wave MI	0.0 (0/221)	0.5 (1/187)	0.5 (1/206)	0.39	0.42
Revasc.	8.3 (24/289)	15.5 (29/187)	2.9 (6/206)	0.017	0.013
CABG	2.8 (8/289)	4.3 (8/187)	0.5 (1/206)	0.44	0.09
Re-PTCA	5.9 (17/289)	12.3 (23/187)	2.4 (5/206)	0.017	0.08
Occlusion	0.7 (2/289)	2.7 (5/187)	0.0 (0/206)	0.12	>0.99
Late occlusion	0.3% (1/289)	0.0% (0/187)	0.0 (0/206)	>0.99	>0.99

p-value1: SES vs. BMS, p-value2: SES vs. CABG
MI: myocardial infarction

Kaplan-Meier estimates of MACCE, death/CVA/MI and repeat revascularization are shown in **Figures 1A**, **1B** and **1C**, respectively.

Multivariable Analysis

After adjustment for a range of potential confounders, patients undergoing SES implantation had a better outcome compared with patients receiving BMS (adjusted HR 0.29 [95% CI: 0.14-0.59]; p=0.0006), while they did not differ in terms of MACCE in comparison with the CABG group (adjusted HR 0.94 [95% CI: 0.43-2.08]; p=0.89).

As shown in **Figure 2**, no statistical interaction was noted among all identified risk factors and type of treatment when the SES was compared with the BMS group (p=0.34 for overall interaction) or when SES was compared to the CABG group (p=0.14 for overall interaction). Of interest, the presence of hypertension tended to favour outcome in the SES as compared to the CABG group while the presence of diabetes tended to favourably affect outcome in the CABG when contrasted to the SES group (**Figure 2B**).

DISCUSSION

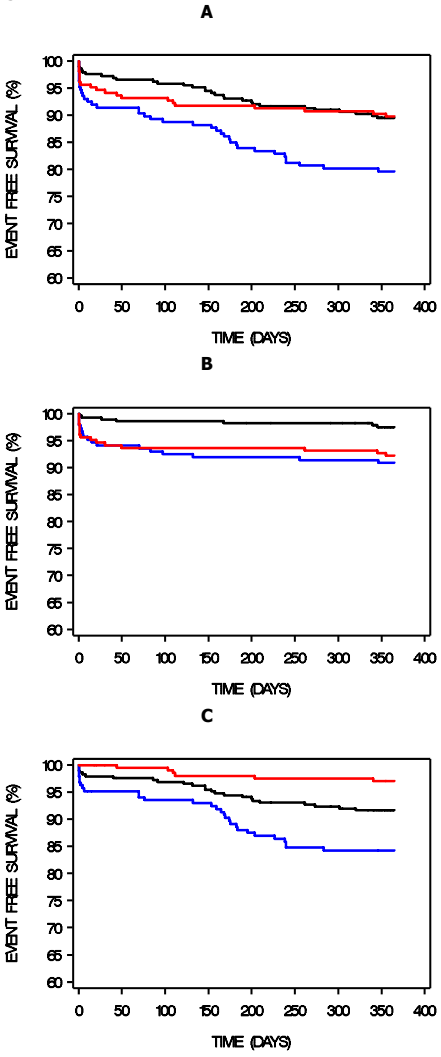
The 1-year outcomes in the total cohort of ARTSII in comparison to ARTSI was recently reported [14]. The results suggested that the use of SES in patients undergoing multivessel intervention is superior to BMS while it emerged as an equivalent strategy to CABG in terms of major adverse events. Whether these overall findings apply to patients with involvement of the pLAD, who are at increased risk for in-stent restenosis and benefit particularly from surgical revascularisation, remains uncertain. This information is important and may have a relevant impact on the clinical decision making before the results of the ongoing randomized trials comparing multi-vessel DES implantation versus surgery become available.

Our current findings suggest that if SES are used today in patients with multivessel disease and pLAD involvement, the need for re-intervention can be safely and markedly reduced compared with the use of BMS and that the overall outcome at one year can be similar to that obtained with surgical revascularisation. Of interest, this overall equivalence between SES implantation and CABG reflects a different impact of these two treatment strategies on the single components of the composite MACCE endpoint: the cumulative rate of death, myocardial infarction and cerebrovascular accidents was lower in the SES group, while the need for further revascularisation was lower in the CABG group. If confirmed by the on-going randomized controlled trials, these results may have a tremendous clinical and economical impact on the way multivessel disease patients are treated.

Our findings however, also raise an additional key question. Are these historical cohorts of patients who underwent BMS implantation or CABG in ARTS I fully representative of the contemporary results obtainable today when BMS implantation or CABG are undertaken in MVD patients?

The discussion as to whether the difference in outcome between the SES and the BMS groups is entirely driven by the superior performance of SES may have limited interest at a time when DES are progressively replacing BMS in all western countries. Thus, the major issue which remains to be addressed is whether we can accept the results that in MVD patients with pLAD involvement SES implantation can lead to comparable 1-year outcome with respect to CABG. To ensure the highest comparability with ARTS I, special care has been paid in designing ARTS II, including stratification by clinical site for patients undergoing three-vessel intervention, adoption of identical inclusion and exclusion criteria, end-points definitions, primary end-point and even sites selection. This has finally resulted in enrolling in ARTS II a patient population with a higher risk profile and more extensive and diffuse CAD compared with ARTS I, reflecting the increased confidence of the interventional cardiologists to treat more complex

Figure 1



Kaplan-Meier curves reporting (A) MACCE free Survival; (B) Death/CVA/MI free survival and (C) freedom from repeat revascularization in patients receiving sirolimus-eluting stent (black line), bare metal stent (blue line) and surgical revascularisation (red lines)

disease. Conversely, the pharmacological environment in which the patients were revascularized remained clearly and inevitably different in ARTS I vs. ARTS II with a higher use of lipid lowering agents, ACE-inhibitors and β-blockers in the contemporary treated patients. This may contribute to explain the observed higher prevalence of hypertension and hypercholesterolemia –since treatment for these conditions is inevitably part of the definition for the presence of these risk factors- in the contemporary cohort of patients. The impact of the different pharmacological approaches on the observed outcome remains elusive and despite our multivariable model adjusted for these potential confounders, we cannot rule out the possibility that they might have contributed to improved outcomes in the contemporary compared with the historical cohorts of patients.

Large observational studies have established the internal mammary artery as the "gold standard" graft in CABG[9-11]. These studies have shown that the use of an internal mammary artery graft to the LAD coronary artery improves survival and reduces the incidence of late myocardial infarction, recurrent angina, and the need for further cardiac interventions. In keeping with this notion, in the CABG group enrolled in ARTS I, 93% of the patients received an internal mammary artery graft. It has been more recently shown that the BIMA grafting is able to further improve mid and long-term outcomes compared with the use of a single mammary artery[16-20]. In ARTS I, 16.5% of the patients undergoing CABG received both arterial conduits. Although still not widely practised, BIMA is known to be feasible and safe in the great majority of patients who require multivessel bypass, including those with insulin-dependent diabetes[21-23]. Thus, the relative low use of BIMA in ARTS I is likely to reflect the fact that this approach was not scientifically established at the time the study was conducted. As a consequence, our findings should not be extrapolated to the scenario where BIMA is the strategy of choice for MVD patients undergoing surgical revascularisation. Other technical refinements of surgical coronary revascularization have been recently proposed and clinically tested such as off-pump surgery, minimally invasive approaches, and robot facilitation. None of them, however, was conclusively shown to provide a similar benefit over the above-mentioned surgical standard approach in terms of the endpoints of ARTS I and ARTS II.

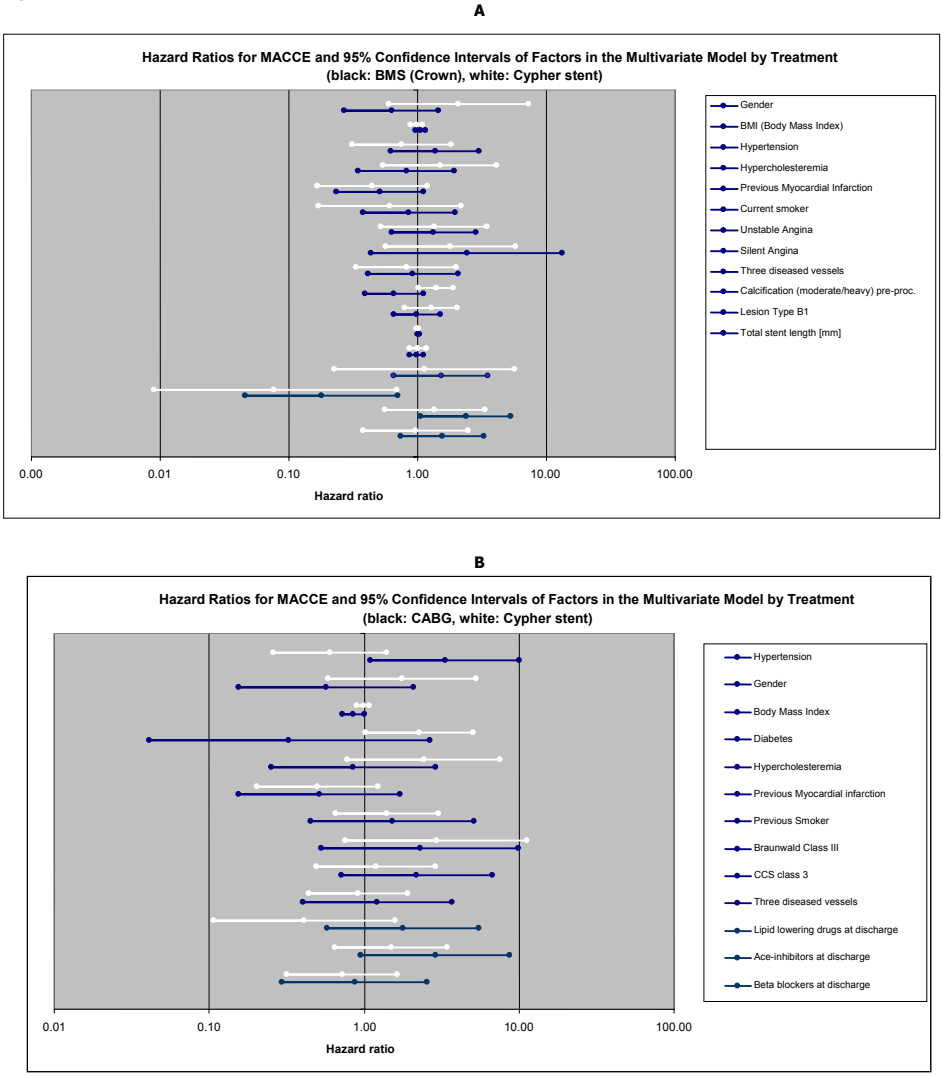
Longer clinical follow-up are necessary in order to establish whether the mid-term benefit of SES in patients with complex and diffuse coronary disease is maintained beyond one year, especially in light of the controversial results recently reported[24,25]. Finally, the adjusted impact of clinical or angiographic variables on outcome based on the actual revascularisation strategy received should be regarded as exploratory and hypothesis-generating.

Conclusions

Our results suggest that if PCI using SES is performed on patients with MVD involving the pLAD, together with appropriate secondary preventive medication 1) the rate of major adverse events can be safely and markedly reduced compared with historical results based on the use of BMS; and 2) a similar overall outcome at one year may be obtained compared with an historical cohort of patients in whom a single arterial conduit and multiple vein grafts was the strategy of choice for revascularisation.

In spite of all the above mentioned limitations, in particular the lack of randomization of the ARTS II cohort, our results represent the best

Figure 2



Hazard ratios for 1-year MACCE and 95% confidence intervals (corrected for multivariate model) by treatment (sirolimus eluting stent (Cypher) vs. bare metal stent (BMS) (A) and SES versus coronary artery bypass grafting (CABG) (B).

available evidence supporting the safety and efficacy of SES in MVD patients with involvement of the pLAD and suggest for the first time that the unrestricted use of SES in this context may lead to a comparable outcome with respect to the surgical approach. Prospective randomized studies, such as CARDIA, FREEDOM, SYNTAX and COMBAT trials are ongoing to confirm and extend these preliminary findings. Their results are expected to be available in the two year period 2009-2011.

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Chapter 17. *Cyphering* the Complexity of Coronary Artery Disease to Predict Clinical Outcome in Patients with 3-Vessel Lumen Obstruction undergoing Contemporary Coronary Intervention. Application of the Syntax Score

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Submitted for publication

Cyphering the Complexity of Coronary Artery Disease to Predict Clinical Outcome in Patients with 3-Vessel Lumen Obstruction undergoing Contemporary Coronary Intervention

APPLICATION OF THE SYNTAX SCORE

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Objective: We sought to assess the predictive value of the recently described Syntax score (SYSCO) in patients undergoing percutaneous intervention (PCI) for three-vessel disease and compare it with the modified AHA/ACC lesion classification system.
Background: The SYSCO was recently developed as a comprehensive angiographic scoring system aiming to assist in patient selection and risk-stratification for individuals with extensive coronary artery disease (CAD) undergoing contemporary revascularisation. A validation of this angiographic classification scheme is lacking.
Methods and Results: SYSCO, applied to 1292 lesions in 306 patients undergoing PCI for three-vessel disease in the Arterial Revascularization Therapies Study part II, ranged from 4 to 54.5 and after a median of 370 days (range: 274-400) predicted the rate of major adverse cardiac and cerebrovascular events (MACCE) (HR 1.08/unit increase [95% CI: 1.05, 1.11]; p<0.0001), with patients in the highest SYSCO tertile having a significantly higher event rate (27.9%) than patients in the lowest (8.7%) (HR 3.5 [95% CI: 1.7, 7.4]; p=0.001). By multivariable analyses, SYSCO independently predicted outcome with an almost 4 fold adjusted increase in the risk of MACCE in patients with high as compared to low values, based on the discrimination level provided by classification and regression tree analysis. When compared to the modified AHA/ACC lesion classification scheme, SYSCO showed a higher discrimination ability (*c*-index 0.58±0.08 vs. 0.67±0.08, p<0.001, respectively) and a better goodness of fit at the Hosmer-Lemeshow statistic.
Conclusions: SYSCO is a promising tool to risk stratify outcome in patients with extensive CAD undergoing contemporary PCI.

Submitted

Since the earliest reports of coronary angiography, the extent of coronary artery narrowing has been considered a primary determinant of survival in patients with coronary artery disease(1-4). The simple division into one, two and three vessel disease has provided a convenient scheme for classifying patients and it has been extensively employed across literature(5-7). This straightforward scoring system, however, is known to underestimate the prognostic importance of anatomy, especially in patients with complex and diffuse coronary artery disease (CAD)(8,9). To overcome this limitation, two approaches have been successfully applied: the cumulative appraisal of each lesion's morphology(9,10) and the overall quantification of the myocardium in "jeopardy", i.e. distal to every individual lesion in the coronary tree(8,11).
Dramatic changes have occurred in the approach to percutaneous intervention since that time, which include liberal use of drug eluting stents(12) and upfront administration of ADP receptor blockers(13,14), allowing treatment of more complex and extensive lesions(15) and lower overall risk(16).
The syntax score (SYSCO) was recently developed as a comprehensive angiographic tool, which, merging and tailoring several previously validated CAD scoring systems to current era of intervention, aims to assist in patient selection and risk-stratification for individuals with extensive CAD undergoing contemporary revascularisation(17). A validation of this angiographic classification scheme is lacking.
We applied SYSCO to 1292 lesions in 306 patients undergoing treatment for three vessel disease in the Arterial Revascularization Therapies Study part II (ARTS II) to examine its role in predicting short- and long-term incidence of major adverse events. The predictive value of SYSCO and the modified AHA lesion classification system were compared and the additive role of combining SYSCO to other independent outcome predictors in our dataset was explored.

METHODS

Study Design and Patient Population

ARTS II was a multicenter, non-randomized, open label, stratified, non-inferiority trial designed to evaluate sirolimus eluting stent (SES, Cypher®, Cordis, Warren, NJ) implantation in patients with multivessel disease using the surgical group of ARTS I as an historical control(18,19). The inclusion and exclusion criteria for ARTS II have been previously reported (18,19). Clopidogrel 300 mg as loading dose, or Ticlopidine, administered at a dose of 500 mg, was to be started at least 24 hours before the procedure. Clopidogrel 75 mg per day or Ticlopidine 250 mg twice a day was prescribed for at least 2 months after revascularization. Written, informed consent was obtained from each patient prior to enrolment. The ethics committee of each participating site approved the study.

Patients underwent stratification by clinical site in order to ensure the inclusion of at least 1/3 of patients with three-vessel disease. Out of a total number of 607 patients included in the ARTS II, 325 patients suffered from 3-vessel disease according to site investigators. For 19 (5.8%) of them, the diagnostic angiogram was not available or of poor imaging quality. Thus, a total of 306 patients were finally included in the current analysis.

Syntax Score and Angiographic Analysis

Each coronary lesion producing 50% or more obstruction of the lumen in vessels ≥1.5 mm was separately scored and added to provide overall SYSCO the. The SYSCO was calculated using a dedicated software which integrates i) the number of lesions with their specific weighting factors based on the amount of myocardium distal to the lesion according to the Leaman score(11) and ii) the morphologic features of each single lesion, as previously reported(17) (available at http://www.europcronline.com/eurointervention/2nd_issue/36/). An example of SYSCO calculation in one of the included patients is shown in **Figure 1A**. All angiographic variables pertinent to the SYSCO calculation were computed by two of three experienced cardiologists (MV, KT, SV), blinded to procedural data and clinical outcome at the angiograms obtained before the procedure. In case of disagreement, the opinion of the third observer was obtained and the final decision was taken by consensus. All other angiographic characteristics, including the modified ACC/AHA lesions classification computed before the procedure and the completeness of revascularization by intent, defined as successful dilatation (i.e. residual diameter stenosis less than 20%) of all intended lesions, were derived from the angiographic core laboratory database (Cardialysis BV, Rotterdam, The Netherlands). For the purpose of statistical analysis, type A stenoses were coded 1 point, type B1 stenoses 2 points, type B2 stenoses 3 points, and type C stenoses 4 points as previously described(9).

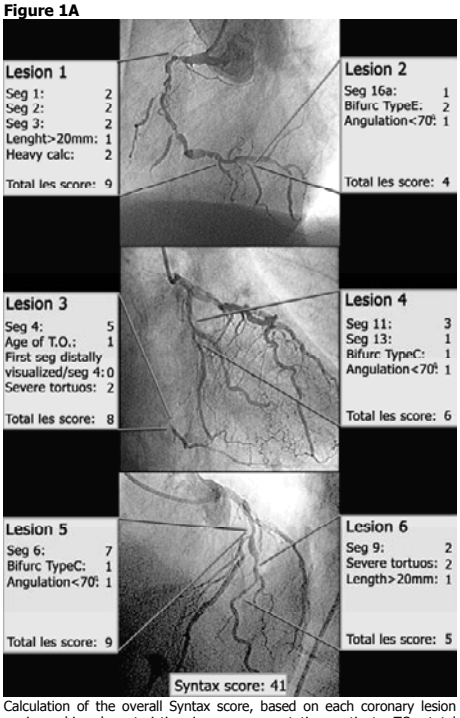
Study Objectives and Endpoints

The primary objective of this study was to analyze the value of the SYSCO in predicting short- and long-term outcome in patients with 3-vessel disease undergoing percutaneous revascularization with unrestricted use of SES. The primary endpoint was the incidence of major adverse cardiac and cerebrovascular events (MACCE), which is a composite of all-cause death, cerebrovascular event, myocardial infarction and repeat revascularization. We report the incidence of the primary endpoint at 30 and 400 days.

End point definitions

Death from all causes was reported. Cerebrovascular events, including stroke, transient ischemic attacks, and reversible ischemic neurologic deficits were considered. In the first 7 days after the intervention, a diagnosis of myocardial infarction was made if there was documentation of new abnormal Q waves (according to the Minnesota code) with an increase in creatine kinase (CK) or CK-MB fraction or in the absence of pathologic Q waves, an increase in CK or CK-MB levels to ≥ 3 times the upper limit of normal (ULN) in keeping with current ACC/AHA and ESC guidelines for percutaneous coronary intervention (PCI) (*PCI definition*)(20,21). For an analysis of sensitivity, peri-procedural MI was also defined according to ARTS I and ARTS II protocol-mandated definition if there was documentation of new abnormal Q waves and either a ratio of serum creatine kinase MB (CK-MB) iso-enzyme to total cardiac enzyme that was greater than 0.1 or a CK /CK-MB value that was 5 times the (ULN) (*surgical definition*)(18,19,22).
Serum CK and CK-MB iso-enzyme concentrations were measured 6, 12, and 18 hours after the intervention. Beginning 8 days after the intervention, either abnormal Q waves or enzymatic changes were sufficient for a diagnosis of myocardial infarction. All repeat revascularization procedures were recorded. Events were counted from the time of the initial procedure. Thrombotic occlusions were defined based either on angiographic documentation of a complete occlusion (TIMI flow 0 or 1) or angiographic documentation of a flow limiting thrombus (TIMI flow 1 or 2).

Figure 1A



Calculation of the overall Syntax score, based on each coronary lesion angiographic characteristics in a representative patient. TO: total occlusion; Les: lesion; Calc: calcification; Bifurc: bifurcation; Seg: segment

Statistical Analysis

Continuous variables are shown as a mean value ± one standard deviation (SD) or as a median value and corresponding inter-quartile range [IQR]. Differences in continuous variables between subgroups of patients were evaluated using Student's unpaired *t*-tests or Mann-Whitney non-parametric tests, as appropriate. The distribution of the SYSCO in relation to the number of score lesions was analyzed through the analysis of variance. The normality assumption for continuous variables was evaluated by the Kolmogorov-Smirnov test. Categorical variables are presented as counts and percentages, and differences in categorical variables between patient subgroups were evaluated with the χ^2 test. Survival curves were generated by the Kaplan-Meier method, and differences in survival between subgroups of patients was evaluated using the log-rank test.
We applied univariable and multivariable Cox' proportional hazard regression models to evaluate the relation between the SYSCO and the incidence of the primary endpoint, based on either the PCI or the surgical peri-procedural MI definition. In our multivariable model, we adjusted for a broad range of potential confounders, including the clinical and angiographical characteristics that are presented in tables 1 and 2. In order to avoid data-overfitting, we followed a stepwise modeling approach applying 1) a variable selection by means of the Akaike information criterion (AIC) (that is, a backward elimination with a threshold of significance depending on the degrees of freedom (DF) associated with the variable at hand; if DF = 1, then P≈0.157)(23) and 2) a bootstrapped variance

estimation of the final model(24). We report crude and adjusted hazard ratios (HR) and corresponding 95% confidence intervals (CI).
The performance of the SYSCO and the AHA/ACC-classification scheme were studied with respect to discrimination and calibration. Discrimination refers to the ability to distinguish patients with MACCE from those without; it was quantified at 30-days by the receiver operating characteristics (ROC) with their area under the curve (AUCs) and by the *c*-index for contrasting the long-term outcomes. The *c*-indices for AHA and SYSCO were compared by means of U-statistics(25). Calibration refers to whether the predicted probability of MACCE is in agreement with the observed probability; it was measured with the Hosmer-Lemeshow goodness-of-fit test.
All variables associated to outcome at a p-value of 0.10 at Cox proportional regression analysis, including the AHA and SYSCO were subjected to classification and regression tree (CART) analysis to identify the best outcome predictors, in terms of MACCE at follow-up, and develop the risk stratification model(26). This method is based on recursive partitioning analysis and involves the segregation of different values of classification variables through a decision tree composed of progressive binary splits. This approach has the advantage to uncover possible interaction among predictors. All statistical tests were 2-tailed and probability was significant at a level of <0.05. Statistical analysis was performed on Statistica 6.1 (Statsoft Inc. Tulsa, Oklahoma) and R-language (R Foundation).

RESULTS

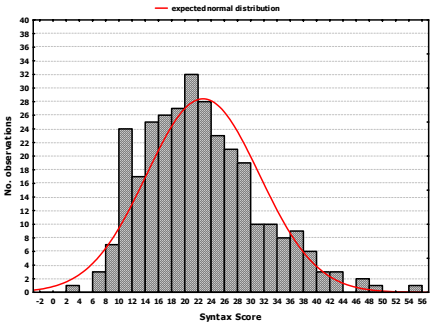
Syntax score and baseline or procedural characteristics

Three hundred and six patients and 1292 lesions in total, with an average of 4.22±1.2 lesions per patient, were analyzed. The overall SYSCO in the studied population had an approximately normal distribution (p=0.37) with a slight left-skewness (**Figure 1B**); it ranged from 4 to 54.5 with a mean (95% CI) ±SD of 22.7 (21.8-23.7) ±8.6 and a median [IQR] of 22 [16-28]. As shown in **Figure 1C**, there was a clear progression in the central values of the SYSCO according to the number of scored lesions (p<0.001); however a substantial overlap in the interquartile ranges of the SYSCO from 2/3 up to 6 scored lesions and in the overall ranges from 2/3 up to 7 scored lesions was observed. In 4 patients, 2 lesions only were scored since the third treated lesion in each of these cases was judged to result in less than 50% lumen obstruction at visual estimation. Baseline characteristics of the study population stratified across SYSCO tertiles are shown in **table 1**. Age progressively increased while history of coronary artery disease progressively decreased from the first to the third SYSCO tertile. Left ventricular ejection fraction, history of previous anterior MI and unstable angina at presentation and diagnosis of stable angina were also not uniformly distributed among the three groups. As might be expected, there was generally a progressive increase in complexity in most angiographic and procedural characteristics from first to third tertile (**Table 2**).

30-day Outcome

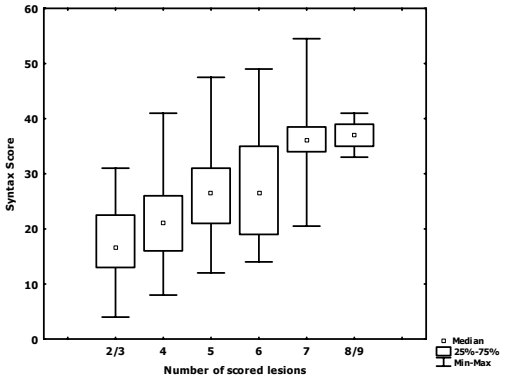
Short-term outcome after intervention according to SYSCO tertiles is reported in table 3. No death occurred within the first 30 days. Patients in the first SYSCO tertile showed the lowest and those in the third tertile the highest rate of major adverse cardiac and cerebrovascular events. This difference was driven by both re-intervention and occurrence of myocardial infarction, particularly when the PCI definition of peri-

Figure 1B



Histogram showing the distribution of the Syntax score in the considered population

Figure 1C



Distribution of the Syntax score according the number of scored coronary lesions

procedural MI was applied. One cerebrovascular accident and two angiographically confirmed subacute vessel occlusions occurred in the third SYSCO tertile, while none of these events were observed in the first or second SYSCO tertiles.

Long-term Outcome

After a median follow-up of 370 days (range: 274-400), SYSCO significantly predicted the rate of MACCE [death, CVA, MI or TVR] (HR 1.08/unit increase [95% CI: 1.05, 1.11]; p<0.0001). The distribution of MACCE rate according to SYSCO tertiles is shown **Figure 2A**. Patients in the highest SYSCO tertile had a significantly higher event rate (27.9%) compared both with patients in the lowest (8.7%, HR 3.5 [95% CI: 1.7, 7.4]; p=0.001) or the 2 lowest SYSCO tertiles combined (9.9%, respectively, HR 3.09 [95% CI: 1.7, 5.5]; p=0.0001). Mortality was low in all the three groups (0% in the first, 1% in the second and third SYSCO tertile (p=0.44), while the rate of death or MI (2.9% in the first, 3.6% in the second, 12.9% in the third SYSCO tertile; p=0.006), the composite death/CVA/MI (2.9% in the first, 3.6% in the second, 15% in the third SYSCO tertile; p=0.001) (**Figure 2B**) and the need for TVR (5.8% in the first, 6.4% in the second, 15% in the third SYSCO tertile;

Table 1. Baseline Characteristics of the Study Population

Variables	Syntax Score			
	I Tertile (≤18)	II Tertile (>18-26)	III Tertile (>26)	P value
	(N=103)	(N=110)	(N=93)	
Age (ys)	61±10	64±8	66±10	0.00025
Males n.(%)	81 (79)	82 (75)	71 (76)	0.78
BMI (kg/m^2)	28±4	27±4	27±4	0.42
Diabetes n.(%)	19 (18)	28 (38)	26 (36)	0.26
Insulin-dep. (%)	5 (5)	5 (5)	6 (6)	0.81
Hypertension n.(%)	67 (65)	78 (71)	68 (73)	0.44
Hyperchol.terolemia n.(%)	83 (80)	80 (72)	68(73)	0.34
Current Smokers n.(%)	21 (20)	23 (21)	14 (15)	0.51
Family history n.(%)	49 (48)	39 (35)	25 (27)	0.01
Creatinine elevation n.(%)	0 (0)	1 (1)	2 (2)	0.30
LV E F (%)	63±11	59±12	60±11	0.044
Medical History n.(%)				
PCI	0 (0)	0 (0)	0 (0)	...
Myocardial Infarction	29 (28)	47 (43)	33 (35)	0.08
Anterior MI	6 (6)	16 (15)	5 (5)	0.03
COPD	1 (1)	5 (5)	5 (5)	0.20
Peripheral Arterial Disease	10 (10)	4 (4)	10 (10)	0.11
Carotid Surgery	2 (2)	1 (1)	2 (2)	0.73
Clinical Presentation n.(%)				
Stable Angina	64 (62)	44 (40)	57 (61)	0.001
CCS	2.3±0.64	2.20±0.70	2.24±0.73	0.90
Silent Ischemia	6 (6)	15 (14)	7 (8)	0.11
Unstable Angina	33 (32)	51 (46)	29 (31)	0.03
IIIB/IIIC	7 (21)/ 1 (3)	8 (16)/ 5 (10)	5 (17)/ 2 (7)	0.71
Medications at screening n.(%)				
Aspirin	93 (90)	99 (90)	79 (85)	0.42
β-blockers	72 (70)	89 (81)	65 (70)	0.10
ACE-Inhibitors	45 (44)	50 (45)	42 (45)	0.96
Statins	79 (77)	75 (68)	64 (69)	0.32
Medications at discharge n.(%)				
Aspirin	102 (99)	107 (97)	89 (96)	0.34
β-blockers	77 (75)	91 (83)	71 (76)	0.33
ACE-Inhibitors	49 (48)	59 (54)	46 (49)	0.66
Statins	90 (87)	96 (87)	79 (85)	0.85

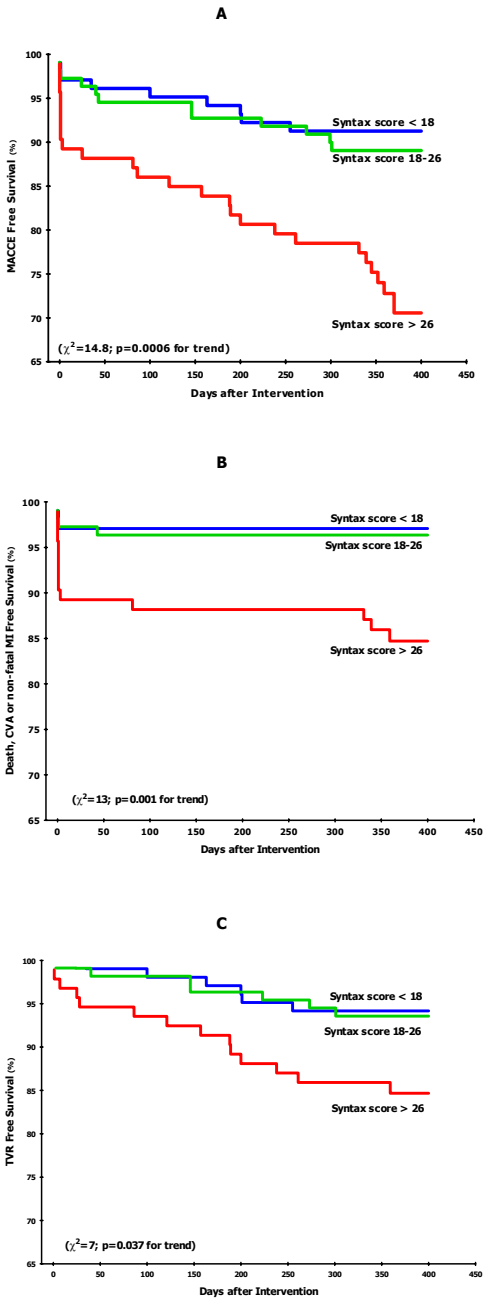
ACE: angiotensin converting enzyme; PCI: percutaneous coronary intervention, LV: left ventricular, COPD: chronic obstructive pulmonary disease; MI: myocardial infarction;

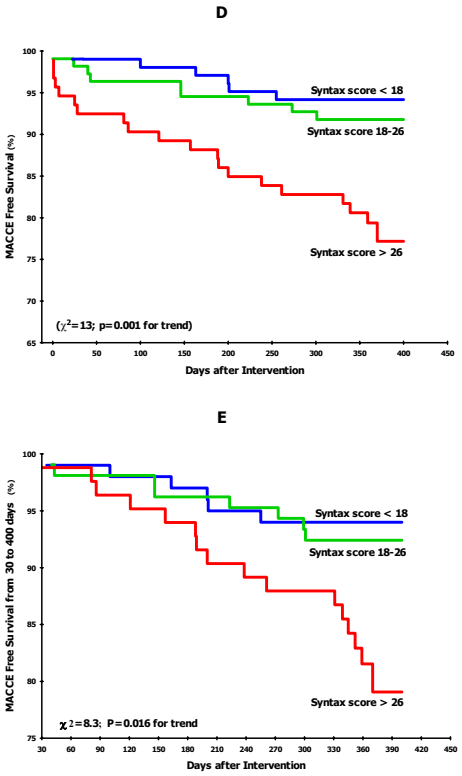
(p=0.01) (**Figure 2C**) varied significantly different across SYSCO tertiles. When the surgical definition of peri-procedural MI was employed, the cumulative incidence of MACCE, remained significantly different in relation to SYSCO tertiles (p=0.001), with a higher overall event rate in the highest (21.5%) compared to the lowest (5.8%; HR 4.0 [95% CI: 1.6, 9.9]; p=0.003) or the 2 lowest (7.0%; HR 3.3 [95% CI: 1.7, 6.3]; p=0.0005) SYSCO tertiles (**Figure 2D**). The impact of SYSCO on mid and long term outcome remained consistent after censoring those events occurring early – within 30 days– after the index procedure (**Figure 2E**).

Multivariable Analysis

After adjustment for a range of potential confounders (**Table 4**), a higher SYSCO remained significantly associated with MACCE (adjusted HR 1.07 [95% CI: 1.03, 1.11]; p=0.0003), with an adjusted HR of 3.1 [95% CI: 1.38, 6.9, p=0.006] or 2.8 [95% CI: 1.39, 5.5, p=0.003] going from the lowest or the middle to the highest SYSCO tertile, respectively, or of 2.94 [95% CI: 1.6, 5.3, p=0.0004] from the two lowest to the highest SYSCO tertile. Others predictors of outcome at multivariable analysis, independent of the applied definition of peri-procedural MI, were diabetes and complete revascularization (**Table 4**).

Figure 2





One-year adverse events stratified according to the Syntax score tertiles, based on the PCI (A, B, E) or the surgical (D) definition of peri-procedural myocardial infarction. Cumulative risk of major cardio- and cerebro-vascular adverse events (MACCE) (A, D, E); death, cerebrovascular accident (CVA) or myocardial infarction (B) and target vessel revascularization (TVR) (C). In E, those events occurring within 30 days after the index procedure have been censored.

Kaplan-Meier curves were constructed according to the four combinations generated by having high or low (according to the third tertile) SYSCO while undergoing complete or incomplete revascularization or presenting with or without diabetes. As shown in **Figure 3A**, incomplete revascularization tended to worsen prognosis independently from baseline SYSCO, while the presence of diabetes negatively influenced outcome only in patients with low SYSCO at baseline (**Figure 3B**).

Comparing AHA lesion classification scheme to the Syntax score

When coded as previously described(9), the modified AHA/ACC lesion classification scheme ranged from 3 to 26 with a mean±SD of 11.6 ±8.6, showing with SYSCO a significant but not tight correlation (r=0.48, p<0.0001).
By univariable Cox proportional hazard analysis, the AHA/ACC score significantly predicted outcome in terms of MACCE at 400 days (1.09/unit increase [95% CI: 1.01, 1.17, p=0.02], with patients in the highest AHA/ACC lesion classification tertile having a significantly higher event rate (30.6%) compared with both patients in the lowest (12.9%, HR 2.2 [95% CI: 1.06, 4.9]; p=0.03) or the 2 lowest AHA/ACC score tertiles combined (13.7%, respectively, HR 2.01 [95% CI: 1.11, 3.6]; p=0.019).
When forced into the multivariable model reported in **Table 4**, however, the AHA/ACC score failed to emerge as an independent predictor of outcome (1.001 [95% CI: 0.83, 1.06, p=0.24]) while the estimate and 95%CI for SYSCO remained unchanged. Similarly, including the AHA/ACC score among the univariable MACCE predictors reported in table 4 while excluding B2 or C type lesions in order to avoid co-linearity in the model, the AHA/ACC score failed to emerge as an independent predictor of MACCE (irrespective from the definition of MI applied) based on AIC selection process.
By ROC analysis, the AUC for MACCE rate at 30-days was higher for SYSCO than for the AHA/ACC score (0.73, 95%CI: 0.61-0.86 vs. 0.56, 95%CI: 0.42-0.69, p=0.02).
At 400 days, the *c*-index for SYSCO resulted to be higher than that for the AHA/ACC score based on both the PCI (0.58±0.08 and 0.67±0.08, p<0.001) or the surgical definition (0.58±0.1 and 0.66±0.09, p=0.001) of peri-procedural MI. The *c*-index for the full model, including both SYSCO and the AHA/ACC score was 0.73, which became 0.67 and 0.73 after removal of SYSCO and AHA/ACC score, respectively. The Hosmer-Lemeshow statistic was χ2= 4.5, p=0.81for SYSCO and χ2= 12.1, p=0.15 for the AHA/ACC scoring system.

Classification tree analysis

By evaluating all variables related to 400-day MACCE at a p value of 0.10 or less at univariable Cox regression analysis (**Table 4**), including the AHA score, the CART method confirmed SYSCO as the best single discriminator between patients with and without MACCE, with a discrimination level of 31 or 35 according to the PCI or surgical definition of peri-procedural MI (**Figure 4**). When stratified into the discrimination level suggested by CART analysis, the adjusted hazard ratio for MACCE was 3.9 [95%CI: 2, 7.3; p<0.0001] or 4.5 [95%CI: 2.1, 9.6; p=0.0001] for patients with high compared to those with low SYSCO based on PCI or surgical MI definition, respectively.
Based on the threshold provided by CART analysis, completeness of revascularization successfully stratified outcome in patients with high SYSCO (**Figure 3C**), while the presence of diabetes failed to impact on outcome in patients with both high and low SYSCO levels (**Figure 3D**).

DISCUSSION

The identification of a variety of distinct features associated with poor prognosis in patients with CAD has been a major breakthrough in the modern medicine, both as an aid to allocate resources and as a tool to tailor intervention based on individual risk. Despite the continuous effort to detect new and progressively more sophisticated markers of prognosis in patients with CAD, the implementation of unconventional and expensive risk-stratification algorithms in the clinical setting remains problematic. Since the earliest reports of coronary angiography, the extent of coronary artery narrowing has been considered a primary and readily available determinant of survival in patients with coronary artery disease(1-4). Moreover, despite continuous refinement in peri-procedural anti-thrombotic therapy and intra-coronary devices, the extent and the complexity of CAD

Table 2. Angiographic and Procedural Characteristics of the Study population

Variables	Syntax Score			P-value
	I Tertile (≤18) (N=103)	II Tertile (>18-26) (N=110)	III Tertile (>26) (N=93)	
Diseased Lesions	3.6±0.9	4.2±1	4.9±1.3	<0.0001
Treated lesions	3.33±0.84	3.80±1.08	3.9±1.40	0.00041
Treated Vessel				
LAD	101 (99)	109 (100)	90 (98)	0.30
CFX	99 (97)	103 (95)	86 (94)	0.49
RCA	97 (95)	102 (94)	80 (87)	0.09
Patients receiving 2-vessel intervention	11 (10)	14 (13)	19 (19)	0.88
Patients receiving 3-vessel intervention	93 (90)	96 (87)	73 (79)	0.98
Number of implanted stents	3.80±1.08	4.30±1.4	4.71±1.9	<0.0001
Total stent length per patient (mm)	73.8±22	82.8±28	95±40	<0.0001
Maximal pressure of stent deployment	16.8±2.8	16.4±2.8	16.6±3.1	0.55
Treated lesions, no. (%)				
Type A	0.33±0.61	0.30±0.54	0.20±0.43	0.23
Type B1	0.9±0.9	1.05±0.97	1.08±1	0.35
Type B2	2.20±1.1	2.22±1.1	2.58±1.4	0.02
Type C	0.25±0.48	0.60±0.6	0.87±0.99	<0.0001
Total occlusion < 3 months	0±0	0.02±0.2	0.01±0.1	0.03
Total occlusion > 3 months	0.02±0.1	0.15±0.36	0.22±0.4	0.0002
Moderate to severely calcified lesions	0.96±1.1	1.18±1.2	1.67±1.4	0.0003
Thrombus containing lesions	0.05±0.2	0.03±0.2	0.0±0	0.10
Eccentric lesions	91 (90)	93 (87)	81 (90)	0.71
Bifurcated lesions	1.06±0.95	1.17±0.93	1.62±1.2	0.0003
Stented side branches	0.91±0.8	1.0±0.8	1.3±1.1	0.02
Balloonned side branches	0.03±0.2	0.11±0.3	0.06±0.3	0.11
Use of GP IIb/IIIa inhibitors	36 (35)	37 (34)	24 (26)	0.32
Patients with complete revascularization	75 (73)	60 (55)	28 (30)	<0.0001

LAD: left anterior descending; CFX: circumflex; RCA: right coronary artery

remains a well-recognized major determinant of short and long-term prognosis in patients undergoing percutaneous coronary revascularisation(27). The AHA/ACC lesion classification scheme was proposed in 1986(28) and modified in 1990(9). It remains by far the most commonly employed lesion classification system worldwide.

The SYSCO was recently developed in an attempt at assisting in patient selection and risk-stratification of individuals with extensive CAD undergoing revascularisation(17) of the left main coronary artery and/or of the three main coronary arteries; i.e. a subset of patients which were not or only poorly represented when the AHA scoring system was created and validated.

Table 3. 30-Day Outcome

Variables	Syntax Score I Tertile (≤18) (N=103)	II Tertile (>18-26) (N=110)	III Tertile (>26) (N=93)	P-value*
***PCI* MI DEFINITION**				
MACCE	0 (0)	2 (2)	7 (8)	0.005
Death/CVA/non-fatal MI	0 (0)	1 (1)	4 (4)	0.05
Death/non-fatal MI	0 (0)	1 (1)	3 (3)	0.12
Non-fatal MI	0 (0)	1 (1)	3 (3)	0.12
Non-Q Wave MI	0 (0)	0 (0)	0 (0)	...
***SURGICAL* MI DEFINITION**				
MACCE	3 (3)	5 (5)	11 (12)	0.03
Death/CVA/non-fatal MI	3 (3)	3 (3)	10 (11)	0.02
Death/non-fatal MI	3 (3)	3 (3)	9 (10)	0.04
Non-fatal MI	3 (3)	3 (3)	9 (10)	0.04
Non-Q Wave MI	3 (3)	2 (2)	6 (6)	0.23
Death	0 (0)	0 (0)	0 (0)	...
CVA	0 (0)	0 (0)	1 (1)	0.32
Q-wave MI	0 (0)	1 (0)	3 (3)	0.12
Target Vessel Revascularization	0 (0)	1 (1)	5 (5)	0.02
Re-PCI	0 (0)	0 (0)	2 (2)	0.10
CABG	0 (0)	1 (1)	3 (3)	0.12
Sub-acute Occlusion†	0 (0)	0 (0)	2 (2)	0.10

*: By Fischer's exact test; †: Angiographically documented.
CK: creatine kinase; PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, MI: myocardial infarction, CVA: cerebrovascular accidents; ULN: upper limit of normal

To obtain some insights into the performance of the SYSCO in this context, patients undergoing intervention for three vessel disease as part of the ARTS II were studied, including a total of 306 patients and 1292 lesions. Our findings suggest that SYSCO may be a suitable tool to risk-stratify early and late outcome in this subset of patients. Moreover, in the context of 3-vessel disease patients who have been selected according to the inclusion and exclusion criteria imposed by the ARTS II investigation(19), the SYSCO performed significantly better than the modified AHA/ACC lesion classification system in terms of prognostic accuracy. These statements are mainly based on the following observations:

1) SYSCO predicted the rate of MACCE, with patients in the highest SYSCO tertile showing a significant higher event rate at both 30 days and 1-year compared to patients in the lowest or the 2 lowest SYSCO tertiles combined. This was true for both applied peri-procedural MI definitions. The impact of SYSCO on outcome remained consistent even after censoring those events occurring within the first 30 days after the index procedure. They might be more frequently related to the procedural success or the interplay between procedural success and coronary lesion complexity than on coronary lesion extension/complexity alone.

2) After adjustment for all potential confounders, including clinical presentation and lesion characteristics, SYSCO remained an independent predictor of MACCE at one year follow-up, with an almost three fold increase in the risk of events in patients in the highest compared to two lowest SYSCO tertiles.

3) Using a time-*independent* analysis, a better goodness of fit was obtained when modelling the risk provided by SYCO than that by the modified AHA lesion classification. This implies a closer relationship between observed and predicted event rates when SYSCO is employed.
In keeping with previous analysis, the AUC for SYSCO was greater than the AHA/ACC score for MACCE at 30-days. Similarly, using a time-*dependent* analysis, based on the *c*-index computation, the prognostic accuracy provided by SYSCO was confirmed to be significantly higher. This was further corroborated after calculating the *c*-index for the whole model, which decreased from 0.73 to 0.67, after forcing SYSCO out, while it remained unaffected after exclusion of the AHA lesion classification.

Table 4.

Variables	P-Values	Hazard Ratios (95%) CI	χ^2
UNIVARIABLE ANALYSIS			
Syntax score	>0.0001	1.08 (1.05, 1.11)	26
Complete revascularisation	0.004	0.42 (0.23, 0.76)	8.7
No. C type lesions	0.002	1.46 (1.06, 2.6)	7.9
No. diseased lesions	0.01	1.33 (1.08, 1.66)	6.0
Diabetes	0.01	2.17 (1.17, 3.8)	5.8
No. calcified lesions	0.02	1.32 (1.02, 1.60)	4.8
No. treated lesions	0.04	0.75 (0.57, 0.98)	4.4
Stable angina	0.08	0.78 (0.58, 1.04)	3.1
No. bifurcated lesions	0.08	1.25 (0.96, 1.61)	2.9
Age	0.10	1.02 (1.00, 1.04)	2.7
Use of β-blockers at screening	0.09	0.60 (0.33, 1.08)	2.7
Use of GP IIb/IIIa inhibitors	0.10	1.61 (0.92, 2.8)	2.6
Total stent length	0.11	1.00 (0.99, 1.01)	2.3
Total occlusion > 3 months	0.12	1.75 (0.85, 3.6)	2.1
Unstable angina	0.20	1.45 (0.82, 2.5)	1.6
History of COPD	0.30	1.84 (0.57, 6.0)	0.9
Previous MI	0.38	0.75 (0.40, 2.4)	0.8
Previous anterior MI	0.54	0.70 (0.22, 2.21)	0.4
No. implanted stents	0.54	0.94 (0.77, 1.14)	0.4
No. of ballooned side branches	0.62	1.27 (0.48, 3.3)	0.2
Number of B2 type lesions	0.69	1.05 (0.83, 1.33)	0.2
RCA treated	0.76	0.86 (0.31, 2.3)	0.08
LVEF (%)	0.83	1.0 (0.98, 1.02)	0.05
Family history	0.87	1.05 (0.58, 1.89)	0.03
No. stented side branches	0.85	1.00 (0.73, 1.4)	0.03
History of PAD	0.90	1.06 (0.38, 2.9)	0.01
No. eccentric lesions	0.97	0.99 (0.39, 2.49)	0.00
MULTIVARIABLE MODEL			47
Syntax score	0.0003	1.07 (1.03-1.11) *(95%CI at BS: 1.02-1.12)**	
Diabetes	0.002	2.07 (1.12-3.08) *(95%CI at BS: 1.13-4.1)**	
Use of β-blockers	0.09	0.57(0.30, 1.09) *(95%CI at BS: 0.30-1.08)**	
Stable angina	0.029	0.72 (0.54-0.97) *(95%CI at BS: 0.48-0.98)**	
Complete revascularisation	0.006	0.51 (0.25-0.89) *(95%CI at BS: 0.26-0.93)**	

*: variance matrix estimated by bootstrap (BS) analysis. GP: glycoprotein, PAD: peripheral arterial disease, LVEF: left ventricular ejection fraction, COPD: chronic obstructive pulmonary disease. RCA: right coronary artery. To test for co-linearity among C-type and number of calcified or bifurcated lesions, separate models were constructed including the number of C-type lesions only or the number of bifurcated or calcified lesions while excluding the number of C-type lesions, which confirmed the validity of the multivariable model reported above. Based on the surgical definition of peri-procedural myocardial infarction, the Syntax score remained an independent outcome predictor (HR: 1.08 [95% CI: 1.03-1.1]), together with diabetes and complete revascularisation.

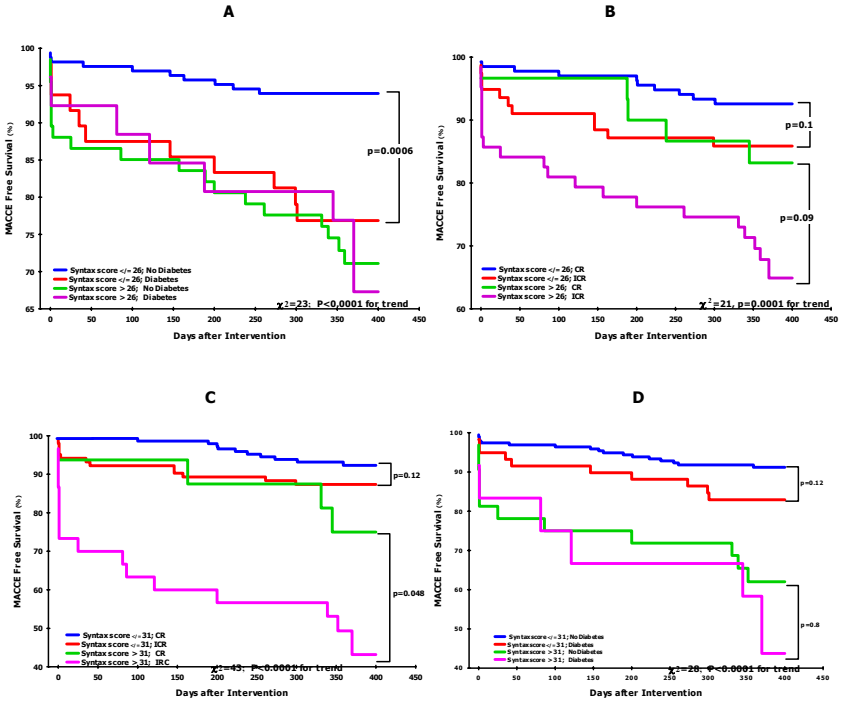
4) CART is a recently developed nonparametric technique that can select from among a large number of variables and their interactions those that are most important in determining the outcome variable to be explained. Based on this statistical tool, SYSCO was identified as the best single predictor between patients with and without MACCE at follow-up, with a discrimination level of 31 and 35 according to the threshold set to define the occurrence of significant peri-procedural necrosis. This was in keeping with the *c*-index analysis, which showed a value of 0.68 for SYSCO, individually considered, while the full model, in the absence of SYSCO computed 0.67. Based on these discrimination levels, the adjusted hazard ratio for MACCE at follow-up increased to 3.9 or 4.5 for patients with high compared to those with low SYSCO according the PCI or surgical MI definition. Of note, this CART-based stratification analysis minimized the prognostic impact of diabetes while intensified the role of completeness of revascularization in the group of patients with high SYSCO. However, all attempts to combine SYSCO with other independent outcome predictors in our dataset, i.e. completeness of revascularization and diabetes, should be regarded as exploratory due to limited statistical power.

Our current findings, while supporting the potential value of the recently described SYSCO, should be critically considered in the light of the following considerations:

1) The majority of the prognostic models so far proposed has been derived from an original dataset, either from large scale registry or a randomized controlled trial(29). In this context, a vital aspect of prediction is to consider whether such a model is transportable to similar patients in another location(30). The concept is sometimes referred to as generalizability or validity, and a model which is found to pass such a test is said to be have been validated(30).

2) SYSCO has not been derived from an analysis of an original dataset. Rather, it was created by an international group of expert interventional cardiologists and cardiac surgeons by merging together and tailoring, based on personal expertise, several previously proposed CAD scoring systems(17).

Figure 3. Cumulative risk of major cardio- and cerebro-vascular adverse events (MACCE)



MACCE, based on the PCI definition of peri-procedural MI) according to the four combinations generated by having low (first or second tertile) or high (third tertile) Syntax score and undergoing complete (CR) or incomplete revascularization (ICR) (A) or presenting with or without diabetes (B). In C and D, the threshold defining high or low Syntax score was based on results of CART analysis

The present report is the first attempt to evaluate the predictive value of this recently developed angiographic scoring system. Thus, we currently face the uncommon situation where a new scoring system is tested on a dataset which is different from the original one, yet the new score cannot be considered fully validated because this the only dataset in which the model has been tested. As such, it remains unclear whether and to what extent our current findings can be reproduced in a different group of patients with extensive CAD.

The prognostic implications of SYSCO for patients with three-vessel and/or left main disease undergoing either percutaneous or surgical coronary revascularization will be further evaluated in the ongoing SYNergy between Percutaneous Coronary Intervention with TAXus™ and Cardiac Surgery (SYNTAX) study(31). As soon as this dataset will be available, each single item of SYSCO will be "weighed" according to discrepancy between observed and predicted event rate in order to further optimize calibration and the interaction between global score and its single components with type of revascularisation (i.e. percutaneous versus surgical) investigated.

Conclusions

Our current findings are encouraging and support the concept that SYSCO, a recently developed angiographic scoring system, is potentially able to reliably and easily risk-stratify patients with three-vessel disease undergoing contemporary percutaneous intervention. Further confirmation from different and larger datasets is required before SYSCO can be considered to be reasonably validated and implemented into routine clinical practice.

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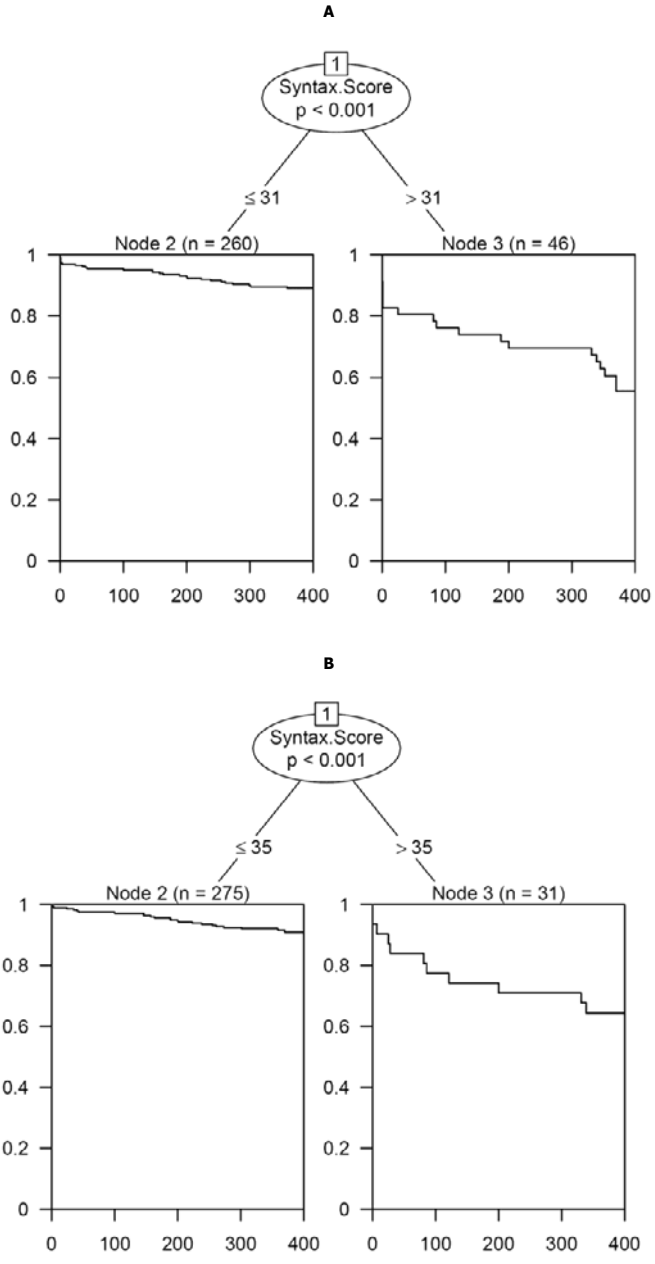
A complete list of investigators and committees of the ARTS II study has been previously reported(19). We acknowledge helpful suggestions and editorial comments by Dr Brian Firth.

Figure 4.



Binary splits based on classification and regression tree (CART) analysis. Among all tested univariable predictors of outcome, the Syntax score emerged as the best single discriminator between patients with and without MACCE during the period of observation, with a discrimination level of 31 (A) or 35 (B) depending on the applied PCI or surgical peri-procedural myocardial infarction definition, respectively.

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Part. 5. Intervention assisted by percutaneous impella LP 2.5 assist device

Chapter 18. Left ventricular unloading and concomitant total cardiac output increase by the use of percutaneous Impella RECOVER LP 2.5 assist device during high-risk coronary intervention

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Case Reports

Left Ventricular Unloading and Concomitant Total Cardiac Output Increase by the Use of Percutaneous Impella Recover LP 2.5 Assist Device During High-Risk Coronary Intervention

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A number of techniques have been proposed for circulatory support during high-risk percutaneous coronary interventions (PCI), but no single approach has achieved wide acceptance so far. We report on a patient with severe left ventricular (LV) impairment who underwent a PCI with the use of a new left ventricular assist device, the Impella Recover LP 2.5 system. The effects on global cardiac output were determined by thermodilution (TD) and LV pressure-volume loops obtained by conductance catheter. The activation of the pump resulted in a rapid and sustained unloading effect of the LV. At the same time, the continuous expulsion of blood into ascending aorta throughout the cardiac cycle produced by the pump resulted in an increase of systemic overall CO, measured by the TD technique, of 1.43 L/min. The procedure was uncomplicated and the patient remained uneventful at follow-up. Our single experience gives new input for future trials to assess the effect of the Impella Recover LP 2.5 assist device on outcome in this subset of patients. © 2005 Wiley-Liss, Inc.

Key words: left ventricular assist device; high-risk percutaneous coronary intervention; pressure-volume loop

INTRODUCTION

The growing heart failure population, combined with technical advances in interventional procedures and imaging, has led to an increased number of percutaneous coronary interventions (PCIs) that are performed in patients with severely depressed left ventricular (LV) function. The low rate of restenosis with drug-eluting stents is likely to stimulate this trend further [1]. However, the benefit of revascularization in patients with LV dysfunction is offset by an absolute increase of short- and long-term mortality after contemporary PCI [2,3].

Therefore, a number of techniques have been proposed for circulatory support during these high-risk PCI, but no single approach has achieved wide acceptance so far [4–9]. Limited effectiveness of actual support and device-related complications have hampered the widespread use of these devices [10].

The recently published ACC/AHA PCI guidelines report that cardiopulmonary support for high-risk PCI should be reserved only for patients at the extreme end of the spectrum of hemodynamic compromise, such as those patients with extremely depressed left ventricular function and patients in cardiogenic shock. However, it should be noted that support for high-risk catheterization and angioplasty was nearly as frequent as support for cardiogenic shock (27.2% vs. 27.3%, respectively) in the recently published benchmark registry [11], further reinforcing the notion that circulatory assistance in high-risk patients is often felt to be required even during contemporary PCI.

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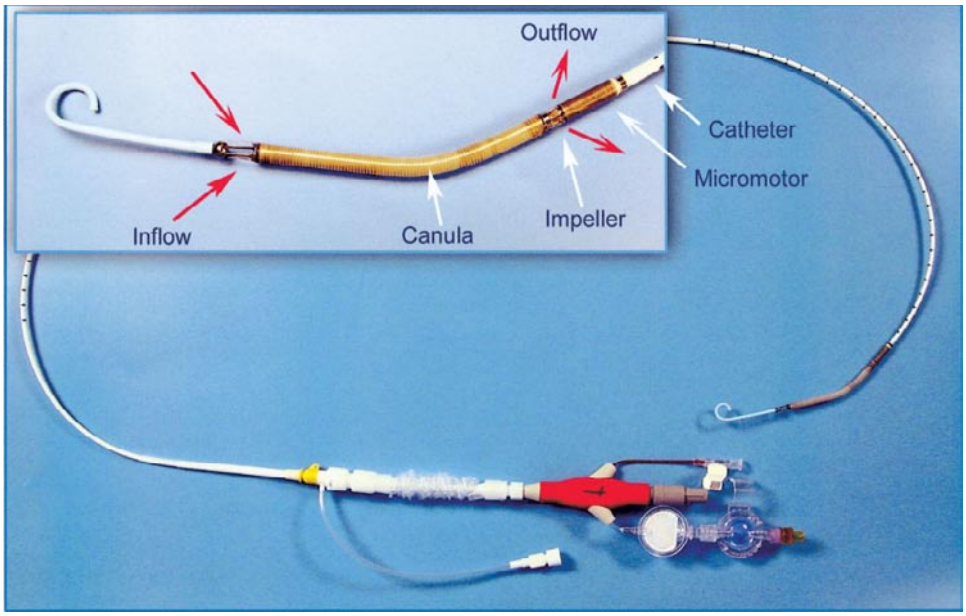


Fig. 1. Impella recover LP 2.5 catheter. In the insert, the pigtail tip is shown at bigger magnification, revealing the site where blood is aspirated from the left ventricle (Inflow), together with the rotor (Impeller) whose rotation generates the force needed for the continuous expulsion of blood into ascending aorta (Outflow). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com]

We report on a patient with severe LV impairment who underwent a PCI with the use of a new LV assist device (LVAD), the Impella Recover LP 2.5 system. The effects on global cardiac output were determined by thermodilution (TD) Swan-Ganz catheter, whereas changes in LV function and LV (un)loading were monitored by LV pressure-volume loops obtained by conductance catheter [12]. The procedure was also monitored with intracardiac echocardiography (ICE; AcuNav, Siemens).

Device Description

The Impella LVAD Recover LP 2.5 (Impella Cardiotechnik, Aachen, Germany) is a miniaturized rotary blood pump (4 mm, 12 Fr, in outer diameter), which is placed through the aortic valve, aspirates blood from LV cavity, and expels it in the ascending aorta (Fig. 1). In clinical conditions, the pump provides up to 2.5 L/min at its maximal rotation speed of 50,000 rpm. The device, which has the great advantage to be inserted percutaneously through a 13 Fr femoral sheath, is mounted on 9 Fr pigtail catheter, so that it can be easily and quickly delivered in the LV and safely left in place up to 5 days. The Impella Recover LP 2.5 catheter is distally connected to a portable mobile console, in which invasive pressure, recorded from the catheter, is displayed with the actual rpm of the pump, thus guiding the correct positioning and functioning of the device.

CASE REPORT

A 56-year-old man with a history of four myocardial infarctions and symptomatic severe LV dysfunction (LVEF = 27%; NYHA class III) was admitted to hospital for Braunwald class IB unstable angina. The patient had been submitted to balloon angioplasty of the circumflex artery (CFx) in 1992. However, the procedure, supported by intra-aortic balloon counterpulsation (IABP), was then complicated by periprocedural myocardial infarction.

His coronary angiogram revealed total occlusions of a small nondominant right coronary artery and of an intermediate branch at mid and ostial segments, respectively. The left anterior descending artery was free

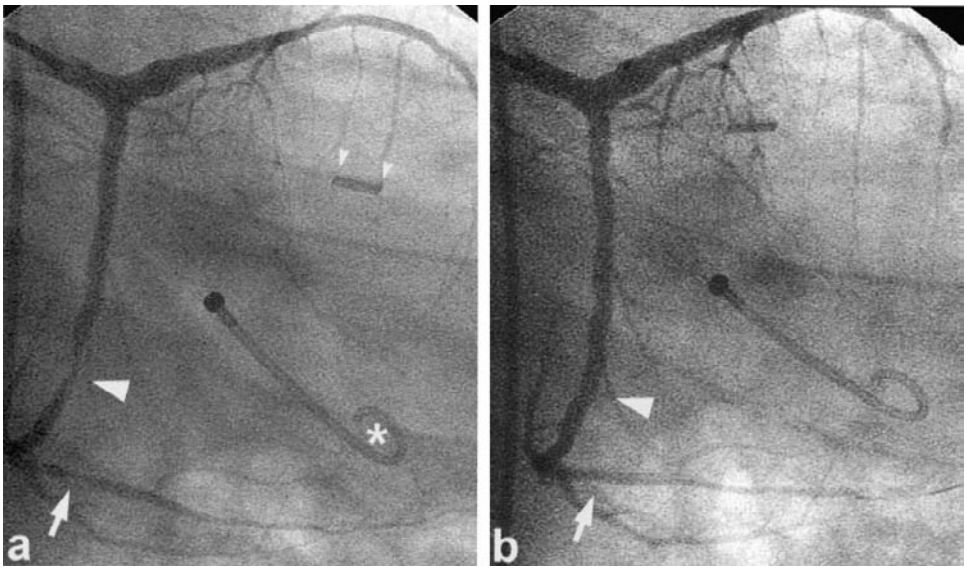


Fig. 2. Angiographic image in right anterior oblique and caudal projection of the left coronary artery before (a) and after (b) coronary intervention. Arrow indicates lesion in the left posterolateral branch. Arrowhead indicates lesion in the mid circumflex artery. Double arrowhead indicates tip of the AcuNav catheter positioned in the right ventricle. Asterisk indicates Impella Recover LP 2.5 catheter positioned in the left ventricle.

from significant stenoses. The dominant CFx, with significant narrowings in the mid segment and in the first posterolateral branch (Fig. 2a), was considered the culprit vessel based on the finding of a reversible perfusion defect in the LV inferior and posterlateral walls at a stress-single photon emission computed tomography.

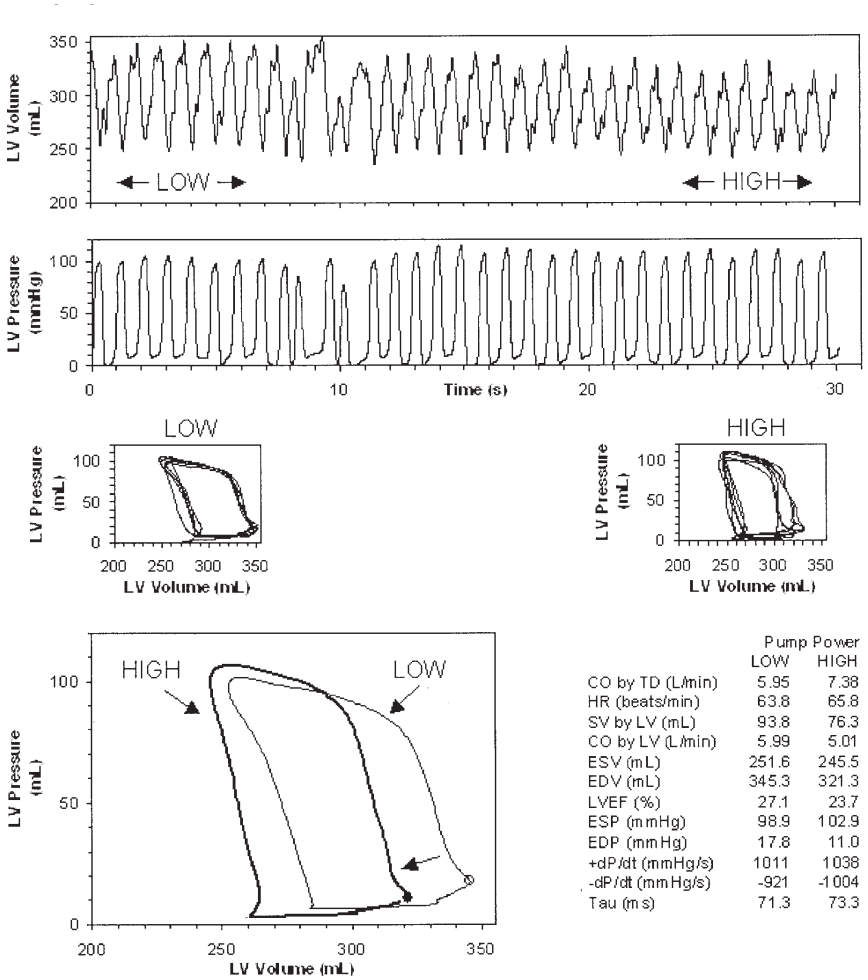
After inserting a 13 Fr sheath in the right femoral artery, an angiographic Judkins right catheter was used to deliver a dedicated exchange 0.14″ guidewire in the LV; the diagnostic catheter was then removed and the Impella pump was positioned over the wire across the aortic valve under angiographic guidance. The intracardiac AcuNav echocardiographic catheter was also inserted in the right ventricle in order to confirm a stable position of the pump during intervention and to investigate any change in aortic regurgitation after pump insertion. The actual rpm of the pump and aortic pressure were monitored on the Impella console.

After positioning of the Impella, a 7 Fr combined pressure-conductance catheter was introduced 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 [13].

The hemodynamic effects of the Impella are illustrated in Figure 3, which shows the acute changes in LV volume and pressure while changing the pump from its minimal (20,000 rpm) to its maximal speed (50,000 rpm). A continuous minimal speed is required to prevent backward leakage from the aorta to the LV through the pump cannula.

The average pressure-volume loops from the pump low (20,000 rpm) period and the pump high (50,000 rpm) period indicate an acute unloading of the LV documented by a reduced end-diastolic pressure (18 to 11 mm Hg), end-diastolic volume (345 to 321 mL), and stroke volume (94 to 76 mL). Consequently, the output generated by the LV dropped from 5.99 to 5.01 L/min. End-systolic pressure increased slightly, whereas ejection fraction was reduced. Remaining indexes did not show important changes.

Despite the unloading of the LV, thermodilution measurements obtained during low- and high-speed pumping showed that cardiac output increased from 5.95 to 7.38 L/min. This 1.43 L/min increase in global flow, despite the 0.98 L/min drop in output provided by the



	Pump Power	
	LOW	HIGH
CO by TD (L/min)	5.95	7.38
HR (beats/min)	63.8	65.8
SV by LV (mL)	93.8	76.3
CO by LV (L/min)	5.99	5.01
ESV (mL)	251.6	245.5
EDV (mL)	345.3	321.3
LVEF (%)	27.1	23.7
ESP (mmHg)	98.9	102.9
EDP (mmHg)	17.8	11.0
+dP/dt (mmHg/s)	1011	1038
-dP/dt (mmHg/s)	-921	-1004
Tau (ms)	71.3	73.3

Fig. 3. Top: Continuous left ventricular volumes and pressures recording from the conductance catheter with Impella pump at its minimum (left) and maximum (right) degree of activation. Middle: By combining instantaneous pressures and volumes during cardiac cycle, the beat-to-beat pressure-volume (PV) loop is created before (left) and after (right) pump maximum activation. Bottom: Average PV loops at pump low and high (left), together with mean hemodynamic measurement at thermodilution (TD) and at conductance catheter (right).

LV, indicates that the Impella output was 2.41 L/min. This is close to the 2.5 L/min predicted by in vitro tests at maximal speed.

At this stage, the conductance catheter was removed and replaced with guiding catheter to position a balance middle-weight 0.14″ wire (Guidant) in the CFx. The lesion of the posterolateral branch was predilated with a 1.5 × 15 mm Maverick balloon (Boston Scientific) and the distal and proximal lesions subsequently stented with Taxus (Boston Scientific) 2.25 × 24 mm at 14 atm and 3.0 × 24 mm at 20 atm, respectively, with good final angiographic result (Fig. 2b). The intervention was uneventful and the hemodynamic status of the patient remained stable during procedure

as well. The Impella LVAD system and the 13 Fr arterial femoral sheath were removed immediately after the procedure and the patient follow-up remained uneventful thereafter.

DISCUSSION

We reported the use of a percutaneous Impella Recover LP 2.5 as a support strategy during high-risk coronary intervention. Our single experience shows a rapid and sustained unloading effect of the LV. At the same time, the continuous expulsion of blood into ascending aorta throughout the cardiac cycle produced by the pump resulted in an increase of systemic overall CO, measured by the TD technique, of 1.43 L/min.

In our case, the cardiac and systemic hemodynamic status recorded during Impella working at minimum speed (20,000 rpm) was taken as baseline because at this degree of activation, the pump just compensates the amount of blood that would flow back into LV through the lumen of the pump during diastole as a consequence of pressure gradient between aorta and LV. In addition, the simultaneous positioning of a 12 (Impella LVAD) and a 7 Fr (pressure-conductance) catheter through the aortic valve might theoretically also induce aortic regurgitation by disturbing valve closure. However, no significant increase of aortic regurgitation was recorded at ICE Doppler investigation after both catheters were in place.

Finally, it should be noted that the unloading effect of Impella on LV function was immediate, consistent with a Frank-Starling law-related response. This would possibly translate into a reduced cardiac metabolic need due to the extracardiac work accomplished by the Impella pump activation.

To evaluate this hypothesis in the future, the Impella device could be tested both as a means to reduce LV oxygen consumption (i.e., in patients with stable hemodynamic status but severely decreased oxygen supply; in other words, patients with acute myocardial infarction) and as a real LV supportive technique (i.e., in patients with low-output syndrome). Since patients undergoing high-risk PCI can fall into both categories, future trials assessing the hemodynamic and outcome effect of the Impella Recover LP 2.5 assist device in this subset of patients seem highly warranted.

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Chapter 19 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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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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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 (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 1 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: The Impella RECOVER LP 2.5 remains an investigational device. Additional studies are required to elucidate the mechanisms responsible for the acute LV volume loading and also to quantify the degree of haemolysis induced by the pump in a broader set of patients.

Submitted

INTRODUCTION

The need for hemodynamic 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 ischemia 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 judgment made by the physician based on the high-risk characteristics of coronary anatomy and the overall status of the patient(3,4). 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) (Impella CardioSystems GmbH, Aachen, Germany) is a catheter-based miniaturized rotary blood pump (4 mm -12Fr- in outer diameter), that is placed retrogradely through the aortic valve and aspirates blood from 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(5). 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 thermodiluition 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 (Impella Cardiotechnik, 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 1650×g. 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 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.

The duration of LVAD support was 144±88 min (median (range) [IQR]: 108 (60-352) [85-198]); in one patient the

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)
Hypercholesterolemia 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 severly calficied lesions	16 (73)
Bifurcated lesions	6 (27)
Bifurcation stenting	4 (18)

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.

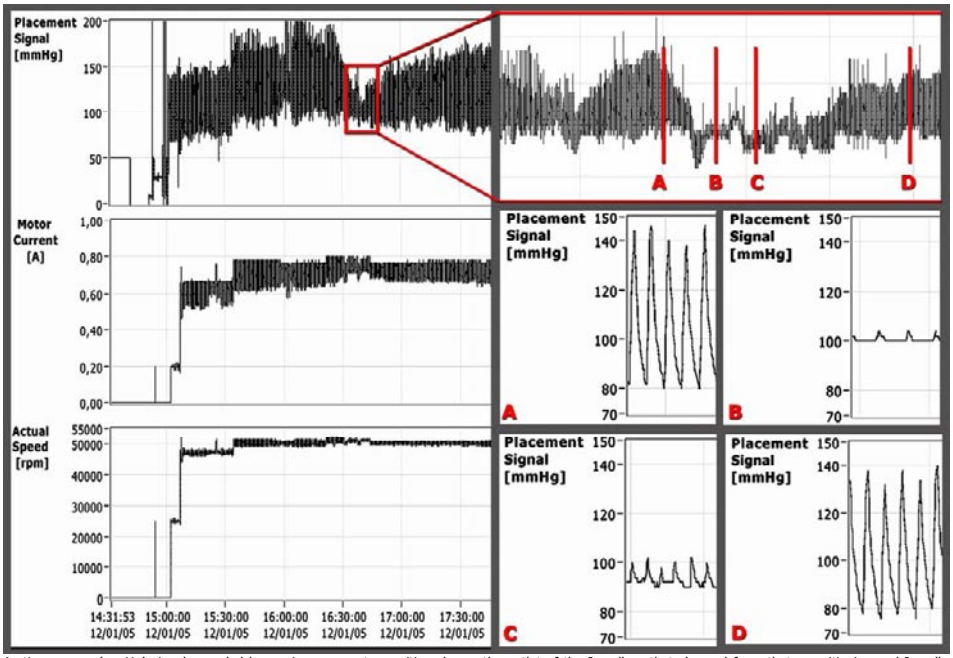
Impact of Impella on haemolysis

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 t removal of the Impella. In all of the other patients (n=7) fHb level peaked at the time of Impella removal.

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 hemodynamic 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 T_0) followed by a decrease soon after the Impella was maximally activated (13±8 mmHg at

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

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.

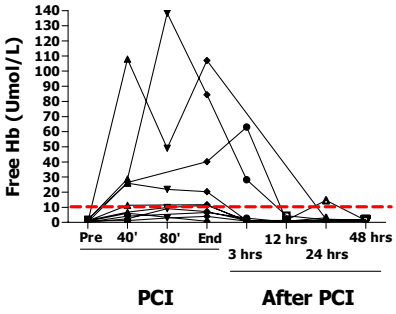
The maximal activation of the pump (T2) produced an opposite effect, with variable degrees of LV volume unloading as compared to T1. In all these individual cases, however, a volume increase compared to baseline was still noted at T2. In patient #2 a progressive volume unloading going from baseline to 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

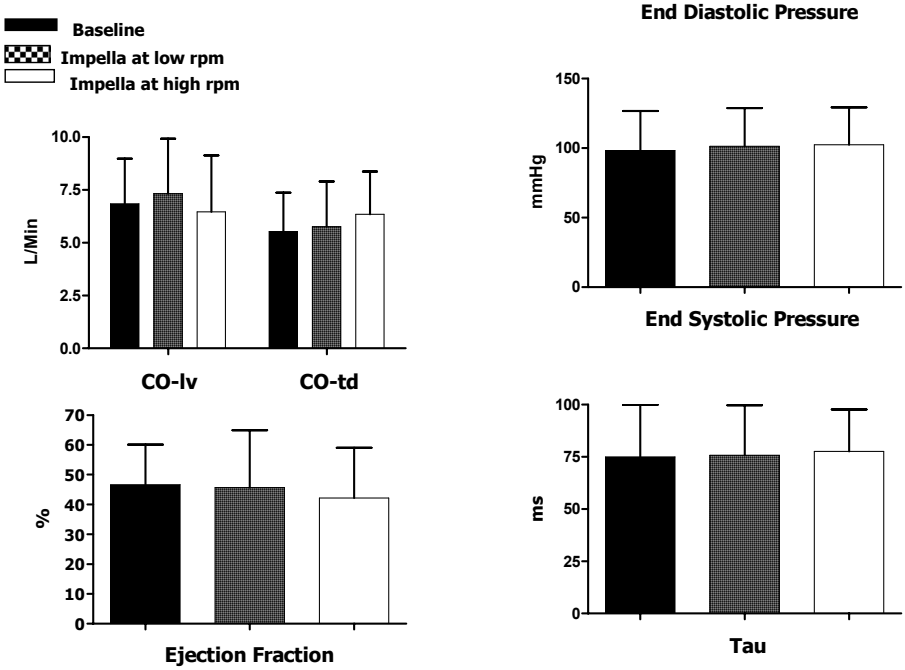
Figure 2.

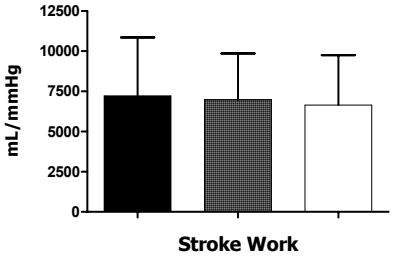


Free haemoglobin (Hb) levels in relation to timing of intervention (PCI). The red line represents the upper limit of normality of the tested parameter according to the employed photometer test

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.

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; COlv, cardiac output according to left ventricle stroke volume as measured by the conductance catheter

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 43000 rpm during diastolic and systolic phases, respectively (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.

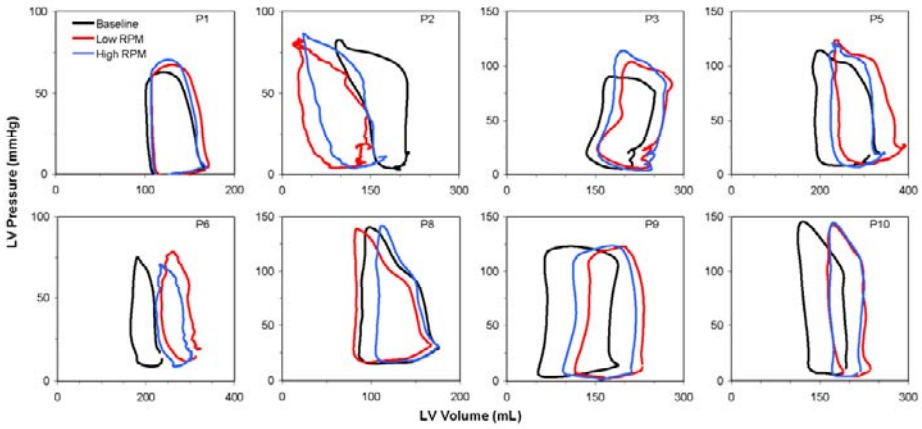
However our findings indicate that after Impella positioning and with minimal activation at T1, a substantial volume overload occurred with respect to baseline in 7 out of 8 patients studied, with only one individual able to (over)compensate for the initial volume increase during maximal activation of 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 2out 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, trans-septal 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 ischemia (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

Figure 4.



Individual pressure-volume loops at baseline (black line), immediately after positioning the Impella catheter at miniminal level of activation (blue line), and with Impella at maximal speed (red line).

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.

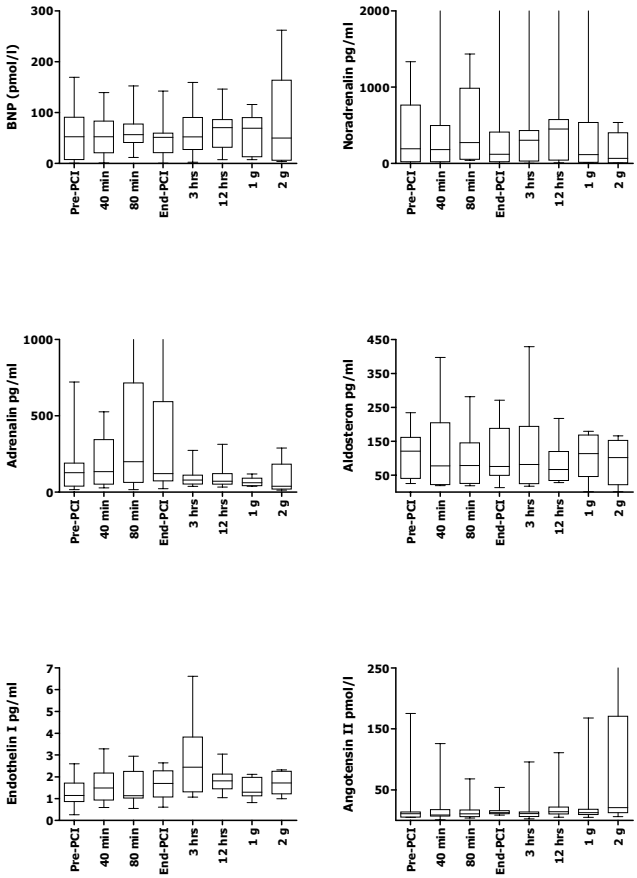
If our speculations are correct the haemodynamic effects provided by the Impella catheter dependent a great deal on the haemodynamic status of the patient but may also be affected by the actual position of the Impella catheter. Future studies, potentially including trans-septal placement of the conductance catheter and slow pull-back of the Impella device after initial positioning, may be needed to substantiate our speculations. Concomitant, trans-esophageal 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 substantial 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

Figure 5.

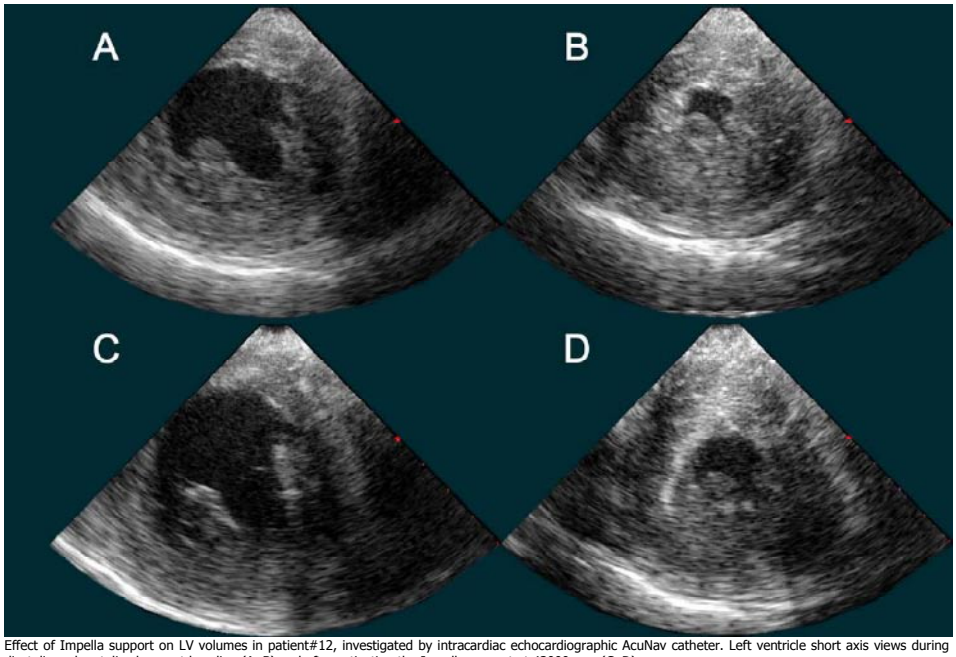


Levels of tested biomarkers in relation to the timing of intervention. None of the studied parameters were significantly affected by the Impella-supported intervention at the analysis of variance. BNP: B-type natriuretic peptide

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
3,500 rpm	6.5	2.5	4.1	34.5	5.8	8.8
4,300 rpm	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 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)

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.

Conclusions

Our findings, although based on a limited sample size, support the idea that Impella RECOVER LP 2.5 may potentially become an effective and easy to use percutaneous LVAD. However in our view important technical refinements have to be considered before its use may be recommended outside investigational protocols. Additional studies are required to investigate the mechanisms behind the acute LV volume overload observed in the majority of the cases enrolled in the present study. Our study suggests that this may well occur despite positioning the Impella catheter according to manufacture's instructions. 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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Summary and Conclusions

High-risk Intervention in the Drug-eluting stent era

The use of drug-eluting stents in high-risk interventions, including those undertaken to treat the left main coronary artery (Chapter 2), multivessel disease (Chapter 14) or on-going ST-segment elevation myocardial infarction (Chapters 11 and 12) appeared overall beneficial in comparison with traditional metallic stents. In particular, the use of drug eluting stents was associated to a remarkable decrease in late loss (Chapter 3) which ultimately resulted in lower need for re-intervention (Chapter 2), while no clear effect on death and myocardial infarction was observed.

The safety profile of these new coronary devices appeared overall consistent with what has been reported in the pivotal trials focusing on selected patient/lesion subsets (Chapters 2, 3, 7, 8, 12, 14, 15, 16). The incidence of possible or confirmed acute, sub-acute or late thrombosis was low in this high-risk subset of patients patients undergoing treatment for left main coronary artery disease (Chapters 2, 3, 7, 8, 12, 14, 15, 16) and importantly we could not confirm previous concerns regarding the potential association between intimal hyperplasia and sudden death in patients undergoing treatment for left main coronary artery disease (Chapters 7 and 8).

Our findings may question the class III indication for the percutaneous treatment of left main coronary artery in patients without contra-indication to surgery. This may be particularly true in patients where the lesion at the left main coronary artery does not require the treatment of its bifurcation in whom the percutaneous treatment with drug eluting stent was associated to a remarkably low incidence of major adverse events at long-term follow-up (Chapter8). At the same time however, our data may suggest that drug eluting stents may expose to a time-dependent increase in late loss and as such to the occurrence delayed in-stent restenosis in a probably small but still undefined proportion of patients (Chapter 6). Similarly, it remains unclear whether this finding may be more frequent in selected high-risk lesion/patient subsets or may potentially apply to all drug eluting stent treated lesions.

In the setting of acute ST-segment elevation myocardial infarction, sirolimus eluting stent implantation did not result in an increased risk of acute, subacute or late thrombotic complications compared to bare metal stent (Chapter 12). However, larger studies with longer follow-up are needed to further elucidate this issue. Drug eluting stents are almost three times more costly than traditional metallic stents and their costs are limiting their up-take in those countries where no specific reimbursement is provided. Tirofiban-supported sirolimus eluting stent infarct artery implantation is a promising strategy to improve outcome while limiting healthcare expenditure in patients with myocardial infarction undergoing primary intervention. Our study provides proof of concept for a new treatment strategy, which incorporates unrestricted use of sirolimus eluting stent, but results in no increase in medical expenditure (Chapter 12).

In the setting of acute myocardial infarction, platelet reactivity at entry was related to both angiographic and elettrocardiographic response to treatment as well as to the severity of cardiac injury. At 1 year, platelet reactivity predicted the occurrence of major cardiac adverse events (Chapter 13). Whether modulating platelet aggregation through *tailored* or *systematic* anti-platelet treatment overcomes the prognostic implications of spontaneous platelet function remains elusive and warrants further investigations.

The availability of drug eluting stents with their single digit restenosis rate even in complex coronary lesions is giving renewed interest to the concept of locally applied preventive treatment in order to prevent plaque rupture and its consequences. Despite the recognition that all major well recognized effectors involved in the pathogenesis of plaque vulnerability are widespread throughout the circulatory bed, the distribution of ruptured or prone to rupture plaques is known to be non-uniform throughout the coronary tree, with the existence of high-risk coronary spots. We found that plaques located in these "hot spots" are characterized by increased necrotic-lipid core content (Chapters 9 and 10). The knowledge of relative plaque composition may be pivotal in the future for the process of clinical decision-making both in the primary and secondary prevention setting.

In the context of multivessel disease patients, undergoing elective intervention the use of sirolimus eluting stent was safe with low rate of thrombotic complications (Chapters 14, 15, 16). Unstable coronary artery disease failed to emerge a predictor of worse outcome in this setting (Chapter 14), whereas the propensity to administer GP IIb/IIIa inhibitors, based purely on coronary anatomy, may increase as a consequence of treating more complex lesion subsets. Our analysis of the ARTS II trial, where the use of GP IIb/IIIa inhibitors was entirely left to the discretion of the operator, suggested than when these potent anti-platelet agents are mainly solicited by the presence of complex coronary anatomy more than by patient clinical profile they may fail to impact on short and long-term outcome (Chapter 15). Focusing on multivessel disease patients with involvement of proximal left anterior descending artery, use of multiple sirolimus eluting stent was associated to a reduced rate of major adverse events compared to historical results based on the use of bare metal stents and to a similar overall outcome at one year compared to an historical cohort of patients in whom a single arterial conduit and multiple vein grafts was the strategy of choice for revascularisation (Chapter 16).

Of interest, even in the context of unrestricted use of sirolimus eluting stent, coronary disease extension/complexity remained a strong and independent predictor of outcome in elective patients undergoing

intervention for three vessel coronary disease. The Syntax score is a promising tool to quantify coronary artery disease extension and complexity (Chapter 17).
By drastically reducing the rate of in-stent restenosis, drug eluting stents opens the way to the treatment of patients with extensive coronary disease. In this population, the presence of concomitant left ventricular dysfunction may constitute a limitation factor for obtaining safe catheter-based coronary revascularisation. The availability of a safe and effective percutaneous circulatory supportive system would greatly impact on contemporary intervention. The Impella RECOVER LP 2.5 is a percutaneous catheter-based miniaturized rotary blood pump that is placed retrogradely through the aortic valve and aspirates blood from left ventricular cavity and expels it in the ascending aorta. Despite preliminary findings supporting its value in terms of haemodynamic support (Chapter 18), we concluded that this device should remain in the investigational phase due to concerns both related to its efficacy and safety profile (Chapter 19)

In conclusion, the introduction of coronary devices, such as drug-eluting stents, able to drastically reduce intimal hyperplasia after arterial injury, is extensively affecting the field of interventional cardiology. Some of the traditional subsets of coronary lesions, for which the results of percutaneous intervention remained sub-optimal compared to traditional surgery in the bare metal stent era, such as left main coronary artery or diffuse multivessel disease, may be effectively treated percutaneously in the near future. The possibility to combine *in-vivo* tools for plaque composition evaluation and coronary devices leading to low rate of recurrences after intervention will unravel new venues for the prevention of plaque rupture through locally applied treatment.
In the drug-eluting stent era, the need to risk-stratify patients before intervention will increase as the natural consequence of undertaking revascularisation in progressively more complex patients. The complexity of coronary artery disease remains a promising and ready available tool to risk stratify outcome in patients with extensive coronary disease undergoing contemporary elective percutaneous intervention, while in the setting of acute ST-segment elevation myocardial infarction markers of platelet activation are promising to tailor aggressiveness of pharmacological intervention to individual needs. There is great need for a miniaturized percutaneous device able to support circulation and unload left and right cardiac chambers. Ideally, this should be tweaked in high-risk elective interventions with the aim to extend its use in emergent cases where safety, efficacy and easiness of use should be granted. This step has still to come, perhaps being the fourth revolution in the field of percutaneous coronary intervention.

Samenvatting en conclusies

Hoog-risico percutane coronaire interventies (PCI) in het tijdperk van drug-eluting stents

Het gebruik van drug-eluting stents (DES) voor hoog-risico procedures, inclusief hoofdstamlesies (hoofdstuk 2), meervats coronair lijden (hoofdstuk 14), of ST-segment elevatie myocardinfarct (hoofdstukken 11 en 12), is geassocieerd met een betere outcome in vergelijking met bare metal stents. Meer specifiek reduceren DES in belangrijke mate de "late loss" (hoofdstuk 3), hetgeen gepaard gaat met een reductie in het aantal herinterventies (hoofdstuk 2). Wat betreft de eindpunten mortaliteit en myocardinfarct is er geen duidelijk effect van DES.

Deze nieuwe generatie van stents heeft een goed veiligheidsprofiel zoals reeds werd aangetoond in eerdere studies in een geselecteerde populatie van patienten en coronaire lesies (hoofdstukken 2, 3, 7, 8, 12, 14, 15, 16). De incidentie van acute, subacute of laattijdige vormen van stent thrombose, al dan niet angiografisch bevestigd, was gering binnen de hoog-risico groep patienten die een PCI ondergingen wegens hoofdstamlesies (hoofdstukken 2, 3, 7, 8, 12, 14, 15, 16). De hypothese dat er een associatie bestaat tussen neointimahyperplasie en plotse dood bij patienten die percutaan werden behandeld voor een vernauwing van de hoofdstam, kon door ons niet worden bevestigd (hoofdstukken 7 en 8).

Het uitvoeren van een PCI voor hoofdstamlesies bij patienten die geen contraindicatie hebben voor cardiale chirurgie vormt tot op heden een klasse III indicatie, en wordt met andere woorden niet onderbouwd door wetenschappelijke evidentie. Deze richtlijn kan door onze bevindingen in vraag worden gesteld, meer in het bijzonder bij patienten waarbij de stentimplantatie zich niet uitbreidt tot de hoofdstambifurcatie. In deze patientengroep is de incidentie van majeure cardiale events zeer laag op langere termijn (hoofdstuk 8). Langs de andere kant is het zo dat DES aanleiding kunnen geven tot een verdere toename van "late loss" over een langere termijn en bijgevolg tot het optreden van laattijdige in-stent restenose (ISR), weliswaar bij een vermoedelijk klein percentage van de patienten (hoofdstuk 6). Het is onduidelijk of dit fenomeen zich frekwenter voordoet in een geselecteerde hoog-risico groep van coronaire lesies/ patienten dan wel of het zich voordoet bij het gebruik van DES in het algemeen.

Bij de behandeling van het ST-segment elevatie myocardinfarct, gaat het gebruik van sirolimus-eluting stents (SES) niet gepaard met een hoger risico op acute, subacute of laatijdige vormen van stent-thrombose (hoofdstuk 12). Grotere studies met een langere follow-up duur zijn noodzakelijk om hierover meer duidelijkheid te verschaffen. DES zijn bijna 3 maal zo duur als traditionele bare metal stents (BMS): deze hoge kostprijs is een belangrijke limiterende factor voor het gebruik van DES in landen waar geen specifieke terugbetaling is voorzien. Het gebruik van tirofiban in combinatie met SES is een veelbelovende strategie bij de behandeling van patienten met myocardinfarct die een primaire PCI ondergaan aangezien ze op een kosten-effectieve manier de outcome verbetert (hoofdstuk 12).

De mate van bloedplaatjes activatie in de initiele fase van het myocardinfarct, blijkt gecorreleerd te zijn met de graad van angiografisch en electrocardiografisch herstel na behandeling, evenals de mate van cardiale beschadiging. De graad van bloedplaatjes activatie is een voorspellende factor voor het optreden van majeure cardiale events na 1 jaar (hoofdstuk 13). Nieuwe studies moeten aantonen of inhibitie van de bloedplaatjes aggregatie via specifieke of systemische therapie de prognostische implicaties van deze inherente bloedplaatjes activatie in gunstige zin kan beinvloeden.

De lage mate van restenose middels gebruik van DES ook bij de behandeling van complexe coronaire lesies, heeft het concept van lokale plaque sealing gebruik makende van DES ter preventie van plaque ruptuur en de geassocieerde klinische manifestaties ervan nieuw leven ingeblazen. Alhoewel de factoren die een rol spelen bij het ontstaan van de vulnerabele plaque inwerken op de ganse coronaire circulatie, is de distributie van vulnerabele plaques en geruptureerde plaques niet uniform verdeeld over de coronaire arteries en blijkt dit zich voor te doen op specifieke plaatsen. Uit onze studies blijkt dat coronaire plaques op deze specifieke plaatsen voor een relatief groot percentage bestaan uit necrotisch en/of vetrijk materiaal (hoofdstukken 9 en 10). Inzicht in de relatieve plaque samenstelling zal in de toekomst vermoedelijk een belangrijke rol spelen bij het bepalen van de behandelingsstrategie zowel wat betreft primaire als secundaire preventie.

Het gebruik van SES bij electieve PCI's voor meervats coronair lijden is veilig en heeft een lage incidentie van stent thrombose (hoofdstukken 14, 15, 16). Instabiel coronair lijden is niet geassocieerd met een slechtere outcome in deze patientengroep (hoofdstuk 14). Verder is er een tendens om gemakkelijker glycoproteine IIb/ IIIa receptor antagonisten toe te dienen in functie van de uitgebreidheid van het coronair lijden bij de behandeling van complexe lesies. Onze subanalyse van de ARTS II studie, waar het gebruik van glycoproteine IIb/ IIIa receptor antagonisten op individuele basis werd voorgeschreven door de arts die de procedure deed, toont aan dat deze krachtige bloedplaatjesaggregatie remmers de prognose op korte en lange termijn niet gunstig beinvloeden wanneer ze worden gebruikt in aanwezigheid van complexe coronaire lesies in plaats van in functie van het klinisch karakteristieken van de patient (hoofdstuk 15). In hoofdstuk 16 tonen we aan dat het gebruik van SES voor de behandeling van proximale LAD lesies bij patienten met meervats

coronair lijden het aantal majeure cardiale events in belangrijke mate reduceert in vergelijking met een historische controle groep waarbij BMS werden gebruikt. Bovendien bleek de outcome na 1 jaar vergelijkbaar te zijn met een historische controle groep van chirurgische patienten die gerevasculariseerd werden met 1 enkele arteriele graft en verschillende veneuse grafts (hoofdstuk 16).
Ook in de situatie waarbij onbeperkt van SES gebruik gemaakt wordt, blijkt de uitgebreidheid/ complexiteit van het coronair lijden een duidelijke en onafhankelijke voorspeller van de outcome bij patienten die een electieve PCI ondergaan voor 3-vats coronair lijden. De Syntax score is een veelbelovend hulpmiddel bij de berekening van de uitgebreidheid en de complexiteit van het coronair lijden (hoofdstuk 17).
Als gevolg van een belangrijke afname in de incidentie van restenose, laat het gebruik van DES toe ook patienten met uitgebreide coronaire ziekte te behandelen. In deze patientenpopulatie vormt de aanwezigheid van linker ventrikel dysfunctie evenwel een belangrijke beperking om op een veilige manier een percutane revascularisatie uit te voeren. De beschikbaarheid van een veilig en effectief percutaan circulatoir ondersteuningssyteem zou een belangrijke vooruitgang zijn bij op het gebied van hedendaagse PCI's. Het Impella RECOVER LP 2.5 systeem is een miniatuur bloedpomp model dat percutaan via retrograde weg over de aortaklep wordt gepositioneerd. De pomp aspireert bloed uit het linker ventrikel en drijft het uit in de aorta ascendens. Preliminaire bevindingen tonen de waarde aan van de pomp voor wat betreft hemodynamische ondersteuning (hoofdstuk 18). Aangezien er in een daaropvolgende studie problemen waren op het gebied van efficaciteit en veiligheid, blijft het gebruik ervan vooralsnog gelimiteerd tot het onderzoeksdomein (hoofdstuk 19).

In conclusie kunnen we stellen dat de introductie van DES het ontstaan van neointimahyperplasie, dat ontstaat als gevolg van schade aan de vaatwand, in belangrijke mate afremt en zodoende een belangrijke plaats heeft verworven binnen de wereld van interventionele cardiologie. In een vroegere fase bleek het gebruik van BMS voor de behandeling van hoofdstamlesies of uitgebreid meervatslijden obsoleet aangezien de resultaten in vergelijking met cardiale heelkunde suboptimaal waren. DES bieden het perspectief in de nabije toekomst deze specifieke groep van coronaire lesies op een effectieve manier te kunnen behandelen.
Het gebruik van beeldvormingstechnieken in-vivo voor de evaluatie van plaque compositie in combinatie met DES, die de noodzaak tot herinterventie in belangrijke mate reduceren, biedt nieuwe perspectieven om na te gaan of een lokale behandeling ter preventie van plaque ruptuur effectief is.
Aangezien DES toelaten meer complexere vormen van coronair ziekte te behandelen, is er een toenemende nood aan risico stratificatie vóór de behandeling. De uitgebreidheid van coronair lijden kan berekend worden volgens een bepaalde score (Syntax score model) en deze score laat een risico-stratificatie toe van patienten met uitgebreide coronaire ziekte vooraleer een PCI te ondergaan. Bij de behandeling van het ST-segment elevatie myocardinfarct zijn bepaalde merkers van bloedplaatjes activatie veelbelovend aangezien zij de mogelijkheid bieden de intensiteit en het type van bloedplaatjes remmende farmacologische therapie te sturen in functie van de individuele patient.
Er bestaat een grote behoefte om via percutane weg op een effectieve manier de circulatie te kunnen ondersteunen en het linker en rechter hart te kunnen ontlasten. Initieel moet de veiligheid, effectiviteit en gebruiksgemak worden aangetoond bij electieve hoog-risico interventies om het vervolgens te kunnen gebruiken in acute situaties. Deze 3 voorwaarden konden tot op heden nog niet worden bewerkstelligd, doch eenmaal hieraan voldaan zou dit percutaan ondersteuningssysteem de vierde revolutie kunnen betekenen op het gebied van percutane coronaire interventies.

Acknowledgment

Art is "I"; science is "we"
(Claude Bernard)

Being a fellow at the Thoraxcenter *per se* is not *easy* nor *nice*…this goes by definition. Nevertheless, it is definitively a great and worthwhile experience, which becomes memorable in cases like mine, where so many people help and support you during this endeavour. They make the PhD experience so valuable. They make this section of the book the most important one.
The first time I came across the word *Thoraxcenter* was during the second year of residency. I had just started my training in the cath-lab in Brescia when my mentor Salvatore Curello asked me: do you know the Thoraxcenter? I candidly replied "not really"…that was a big mistake because I had to try hard before I could regain his esteem afterwards.
April 2002, back to Ferrara's cath-lab, where a salesman from a statin company offers me the possibility to attend a full immersion course on IVUS imaging at the Cleveland clinic: FANTASTIC! But three weeks before the scheduled departure, the plan of the trip changes slightly: the course will focus on non-invasive cardiology and it will be held at the Thoraxcenter. Rotterdam, which had been described to me like a grey, rainy industrial city, appeared incredibly sunny in the three days I spent there (typical example of the sampling error due to a low number of observations…) and the Erasmus MC appeared to me like a piece of US in Europe. The typical personal-based medicine approach, characterised by "I think….; in my practice…." disappeared all of a sudden in favour of the NEJM-, JAMA-, Circulation-, JACC-based approach. Marcel van der Brand was in charge of the interventional cardiology section of the course (finally some invasiveness was luckily kept in). He is among the wisest, most balanced, friendly (i.e. PimdeFeyter-like) and tanned interventional cardiology I have ever met. He guided some of us inside the sliding doors of the "Interventie Cardiologie". That day started with a seminar on stem cells at 08:00. We obviously arrived late, and we broke into the room when Dr. Pieter Smits was just about to show some in vitro data supporting the concept that the skeletal myoblasts do not up-regulate connexin 43, and as such it remained unclear how they could participate to the heart contraction once injected (dear Pieter, thank you for showing me afterwards that they simply do not contract…that's it, the mystery is over). The seminar finished and I thought "nice to see that interventional cardiologists are dedicating so much attention to basic science stuff"…well, you cannot imagine my reaction when Marcel informed me that this seminar was held for nurses and technicians…not doctors!!!
We then moved to the viewing room, where we went through some PCI cases…the two square metre plasma screen impressed me a lot…but no as much as the lesions that were routinely treated there. I could not resist the temptation to pose hundreds of questions to Marcel, who finished giving me David Foley's PhD book where most of the answers I was looking for were indeed available. However, to address my request on…*how to become a fellow of the Thoraxcenter*, he asked "Pedro" to provide me with some insights. Pedro…yes, I really mean *Pedro Lemos!* He was running from one room to the other with pen and paper in his hand…I was witnessing the early days of the great RESEARCH registry. He is the rare kind of great researcher who is well aware that a smile can often serve you more than an impact factor of 20. I was firstly impressed by his kindness: "it would be really nice if you could join us as fellows…we have a lot of work to be done here" and afterwards, in the few months I spent with him at the Thorax, by his knowledge in statistics, clinical trials and philanthropy. I regret to have spent only a few months close to you but I bet our paths will cross again, Pedro.
Standing in the Interventie Cardiologie corridor, with David Foley's PhD book in my hands, Prof Serruys appeared. He was in a very good mood, he looked at me for two seconds and said: "I see you are interested in good literature" and disappeared well before I could formulate an answer that was worthy of being said to the living legend of the interventional cardiology. At that stage, I did not predict that around 18 months after I would be sitting in his room in front of him for the traditional screening-fellows interview. All the "senior" interventional cardiologists are supposed to do the same. That was a very important moment since it was the only occasion I had to speak to Wim van der Giessen for more than 5 seconds. Wim is the kind of very rare person who is really able to summarise things: in three, maybe four words he explained to me that in the Netherlands it is common habit to *formally* share decisions and this process of interviewing fellows was fitting this basic principle…it is a pity I cannot recall the 3 or 4 words he put together to clearly express this concept! Thank you Wim for showing me some tips and tricks on *how to survive at the Thoraxcenter* and best of luck with your ongoing research on stem cells.

Fifteen days after the interview, Prof Serruys called me on my mobile and informed me that my request to become fellow of the Thoraxcenter had been accepted, and that I was supposed to start on 1st of January. The first thought was…Professor Serruys is calling me on my mobile, incredible!! The second, wow, I will become a fellow of the Thorax…the third…but he said 1st of January…this means I have to travel the last day of the year, i.e. Yes Thoraxcenter, then really NO party!
The second interview with Prof Serruys occurred around the end of January, while the meaning of being a fellow was becoming progressively clear to me. The objective of the meeting was to find an answer to the question: what do you want to do here? After 60 minutes of discussion I had a complex flow-chart tree in my hands (which I jealously keep among my most important files) where any topic possibly related to the field of interventional cardiology was listed, including drug eluting stent, vulnerable plaque, stem cells and in light of my past work in the *basic science*…also some experimental

lab!...I was indeed forgetting the biomarkers and the PV loop technology, they were also listed. I spent hours on that flow-chart trying to find an invisible connection between all of these topics. Later on I understood two concepts: these topics are not given to you straight away…you have to try hard to *conquer* them day by day…, secondly, I was supposed to choose ONE of those and to be focused on that…not try to deal with ALL of them at the same time!!!

The first months of Rotterdam were quite tough, I was still sleeping in a Hotel, trying to find a decent but cheap apartment where to live, attending a full immersion course on Dutch while attempting to start some research activity at the Thorax.
Josè Ruiz Cantador, who had just arrived from Spain, shared with me hopes and fears along with evenings and week-ends during this period (he unfortunately left after three months). I am profoundly indebted to Josè for his sense of humour, sensibility and great cleverness (and Spanish ham as well). Patrizia and I should come to Barcelona more often to visit you, Eva and your friends!

During the first year of fellowship, my office was located at 1200, which means third floor in the Thoraxcenter language (I never understood the sense of it) with Carlos van Mieghem and Jurgen Ligthart as room mates.
Carlos was listening to my ItalEnglish for hours, trying to figure out where to go and what to do there, sharing advice, impressions and opinions. In other words we established that kind of sincere friendship between peers which revealed to be stronger than all the negative influences which are naturally around the corner in a place where people go to prove themselves (…the Thoraxcenter is often playing new episodes of *Star Wars)*. Carlos, I cannot avoid thanking you for the day that while I was warning you that Prof. Serruys was investigating who, among the fellows, was supposed to be writing about the left main, you told me: "*Marco, would like to be in charge of that?*" That moment was a cornerstone to find "*my way at the thoraxcenter*". You stayed close to me in difficult moments and you have been enormously supportive. I really miss our conversations, especially when you were disappointed over something and I was always surprising you asking what was wrong with you just based on the expression of your face. The Multislice CT coronary angiography has a great future in your interventional cardiologist hands.
Jurgen, the "Guru" of the IVUS; who can see clearly beyond the greys that everybody see in IVUS cross sections, incredibly kind attitude and always available (which sometimes can be quite dangerous in such a place). It was a real pleasure to share the room and so many hours with you, thank you for lending me your eyes to understand the black and white of things.
Hei Jurg, I still have something to tell you (you are probably expecting this)… Dooooeeeei.

The first month finished. While getting desperate for the fact that the Home hotel (more the latter than the former actually) was draining my budget, Giorgios *George* Sianos conquered my gratitude suggesting to get in touch with Marcoen Scholten, who was seeking a tenant after Akis left. Marcoen is a Dutch –even if his sense of hospitality makes him appear a typically south European– - gentleman. Thanks a lot Marcoen for everything, my bike is always ready for you in Italy and do not forget that Italian wines are definitively much better than those sold as such in Albert Heijn. Dear George, I wish I could reach one day part of your attitude towards the catheter and wires, which is an incredible cocktail of rare technical skills, (self)-determination and …some unconsciousness.
Eugene McFadden had arrived as senior cardiologist 13 months before me. The first time I saw him I thought he was a grown up fellow due to his humble way of speaking and interacting with people.
It took me some time to know him a little bit better: I am always too shy especially with shy people. When he left the Thorax at the end of March 2005, I thanked God for the privilege of knowing him. Eugene taught me the ins and outs of the cath-lab, including the way to reach the major medical journals and how to think in big whilst remaining humble. Eugene, I owe you a lot (apart from probably 100 or more cigarettes!!), and I will always thank you for this. A bien tôt!

Working late every evening, including Saturday and Sunday, was my way to get to know a unique person the of the Thoraxcenter: Doctor Aki Balk. Her office was just behind my working station. Aki, also very hard worker, was frequently trying to push me to spend at least some hours of my life outdoors. Aki, thank you for all of your kindness, help and support, I have always regarded you as a real friend inside the Thoraxcenter.
The ACC congress 2005 was approaching. Prof. Serruys was invited to give (among the other 100 lectures of course!!) a 360 degrees lecture on interventional cardiology, the title was something like "interventional cardiology where are we heading?" This was my first occasion to get closer to The Professor (while you work with him on his presentations, he is able to weigh you from head to toe…) and to Jiro Aoki. Jiro was "The Japanese Fellow". The force from Japan is very strong at the Thoraxcenter and the list of successful interventional cardiologists who flew high after their prolonged visit at the Throaxcenter is very long. Jiro will definitively be among them: clever, humble, hard worker, is sometimes hiding some more western attitudes behind a typical Japanese appearance which altogether make Jiro an intriguing atypical Japanese. Jiro, thank you for everything that you taught to me, for letting us sample your wonderful Asato, and for your fantastic stories about fish…people who say Japanese lack imagination must be very confused.

After 4 months of pure research activity, my name finally appeared in the on-call roster. This pushed me inside the clinical side of cath-lab, which is an entity full of nurses and technicians who are only apparently separated from research, yet they actually constitute its real scaffolding by carrying it out, understanding it and often enjoying it. I am indebted to all of them for their help and patience, in particular to Anna-Marie, who taught me all the secrets of QCA with her Dutch-*Canadian* kindness, the smart and sensible Dick, Gio, Elco, Max, Maaike and John, who recorded kilometres of pressure tracings during the impella cases, and Emilie…well Emilie's story definitively deserves a separate paragraph.
The first time I met Emilie was immediately after my first interview with Prof Serruys. He approached me in the

viewing room and said "Prof Serruys told me to contact you for setting up a research protocol to evaluate whether machrophage activation in vitro produces an increase in temperature which is detectable by this catheter"…I started wondering whether the guy in front of me was a real technician or rather Kenneth Chien from la Jolla….. Emile, thank you for all your help with the terrible PV loop machine, I wish you all the best with your new activity in the industry, lucky them who can rely on your value now.
The word "PV loop" naturally leads me to Paul Steendijk, who brought me into the magic world of pressures and volumes. Well, actually if we imagine the PV loop entity as a room, I'd rather better say that while Paul was gently inviting me inside, I experienced a lot of attrition to completely cross the entrance…the disappointing "evaluation version only" software of the PV loop machine definitively played a role in this. Thank you Paul for all of your efforts in trying to give a sense to all the PV recordings I was bringing to you. Your corrections to my draft papers have always been of outstanding quality. Paul, I really admired your scientific rigor…but please convince yourself that respecting your own deadlines from time to time does not necessarily mean you do not have it!!
Thanks also to Folkert ten Cate for his patience (I hope we will see our common efforts soon finalised), Evelyn Regar, who was always very supportive and friendly, to Sjoerd Hofma, now working in Groningen, and to Martin van der Ent, who *indirectly* helped me to revise my priorities at the Thorax at the right moment, to Johannes Schaar, the pulpo chap, to Eric Duckers, the chosen one, to Koen Nieman, the future and to all secretarial staff, in particular to Anja who is probably still crying desperately after my departure. Among the arts assistenten, a special thanks to Martijn Akkerhuis and Jawed Polad. Peter de Jaegere, the clinical-head. Your help and comprehension were so nice, speaking or making jokes with you was always very pleasant; you were friendly and open to any request from my side (including your kind sponsorship to the TCT young investigator award). I enjoyed a lot working close to you (I actually performed more than 50% of my PCI cases under your supervision!) and I wish you and Sofie all the best. I am one of your fans.

"*One of the most valuable experiences of being at the Thoraxcenter is being part of the team of Fellows from around the world*" (From Angela Hoye, PhD book page 244).

I totally agree with Angela (thanks Angela for this) regarding this statement. While you are at the Thoraxcenter you see the world as a surprisingly small entity, and Andrew from Australia contributed a lot to this feeling considering that he was able to teach me a lot about Europe, including Italy (I am serious)!!
The *dangerous* Vijay, from India will remain memorable to me for his capability to enjoy Rotterdam day and night with the same level of enthusiasm and dedication; it is a pity you could not stay longer to teach us how you managed it!
Gaston and his wife Ines were a real breakthrough for me: eating, chating, drinking, working with them was always fun. Ines, who could not hide her typical Italian temperament in the way she expressed herself…*Marco, que mieeeerda decis?*..was at the same time bringing to all of the conversations a spin of Argentinean laughs and good humour. Gato, in spite of his young age, which was almost offending us old fellows (thank you Andrew for being the eldest), is an amazing mature person, who has already clear in mind his real goals in life. Gato, I owe you a great deal, your "mountains" and your trust literally saved my…rear; knowing you has been a real cornerstone…even if my liver does not always agree with this statement! "*meditate on what you taught to me…I will*" . I hope to remain close to you and sorry for being a boring old Italian who needs to sleep after 12 hours of work and 2 litres of Argentinean wine!
When Jiro finally became a Jedi and left, Keiichi Tsuchida first and Shuzou Tanimoto afterwards took over to warrant continuity in the Japanese tradition of the Thoraxcenter. I will never forget the image of Keiichi reviewing angiograms till late in the viewing room every evening, searching for all possible bifurcations treated in the previous years at the Throaxcenter (…can you imagine how many they must be?). While reviewing ARTS II angiograms with him for the Syntax score, I realised he is the biggest expert of bifurcation in the world, and I am sure that Anthony would accept his sub-analysis of ARTS II on bifurcations if he knew his true value!
The force of Shuzou, proud disciple of Kenko Tanabe, also impressed me a lot when he could quietly (at least outside…) keep working as if nothing had happened while his sweet Yui came much prematurely to light to visit the foreign Dutch country.
Strange to say but the Thorax gave me the opportunity to get in contact with Elena Biagini, who lives and works just at few miles from me in Italy. She is really impressive; always laughing and down-regulating herself, she could have a tremendous amount of work done exploiting all possible infrastructures of the Erasmus MC and beyond. Elena, I am planning the PIADA trial and I hope that you cannot avoid being involved in such a pleasant piece of work. I am looking forward to it.
While wearing my orange plaster, in August 2005, Hector Garcia Garcia joined the group of the Thoraxcenter fellows. He soon revealed himself not only as smart and a valuable researcher, but also as an incredibly funny guy. Fond of statistics as well as world food (Hector, I cannot find one among the 100 pictures I have of you in which you are not eating!), Hector is the fellow everybody would like to work with (by the way, I look forward to seeing how you will manage to put all your topics together in your PhD book). Hector, thank you for all of your help and kindness, my house (when I own one of course, so take this as a metaphor for the time being!) will always be open to you, Lulu, Andres and all the south American Mafia!
I will miss Sophia Vaina a lot. After my upgrade to 1600 (fourth floor), she was my neighbour in the office. Sophia came to the Thoraxcenter with an impressive clear mind: to become an outstanding interventional cardiologist, no matter the price to get there! However, in between procedures, she loved to chat a little… Sophia, I think you and I were the two most stressed fellows (well, after Keiichi), while the big Hector was perfectly counterbalancing all of us. Sophia, Thank you very much for being so sweet and supportive, I am sure you will become the best Greek interventionalist very soon: I

know you still have problems in performing the double inverted super-crush technique in extensively calcified vessel without pre-dilation with a single hand during night call or the direct stenting a CTO with bridging collaterals...but it will come…do not worry!
It is a shame that I did not get the opportunity to work much with Joost Daemen…incredible but true…the only local guy among us. Generous, hard worker, he is in the lucky, but now also quite challenging, position of handling the magic Throaxcenter database: success!
Thanks a lot to Paul Cummins, now the great managing editor of Eurointervention and Arno Ruiter, the marathon racer, always very helpful and kind. Paul, the Irish-Dutch chap who always knew when to cover someone with insults along the corridors (this is the way he introduced himself to me….) or to offer you a cigarette and say: *yes, I know, you are right, I know... any news from Eugene?* Thanks a lot, Paul.

Part of the success of the Thoraxcenter is certainly due to Cardialysis. Cardialysis is the place of dreams for a researcher, where dozens and dozens of professionals do research not just for fun or for "just a period", rather for living.
Cardialysis played a major role during my fellowship in Rotterdam and I am indebted to the whole structure for their help: Marie-Angèle Morel, for her natural enthusiasm and kindness, always ready to help, Gerrit-Anne van Es, the smartest political statistician I have ever met, Jeroen Kleijne, with whom, going from skeletal myoblasts to Taxus stents was always a pleasure to work with, to the whole statistical department (Marco, Dick, Tessa, Jessica) for their patience, advice and never ending support, Janette Symons, for her wonderful and relaxing smile, to Yvonne for being so supportive and to Pascal.
I met Pascal Vranckx for the first time during a meeting in Cardialysis. The second time was in the office of The Professor. I do not remember the third time, but I do remember Pascal that I owe you a great deal (you have even helped me to get this book funded!!!). Pascal is a recombinant figure, being motivated and a hard worker as a fellow, but also wise and politically correct as a senior, he surely will be among the emerging European interventional cardiologists in the near future. But most importantly working with you Pascal was real fun and I look forward to seeing what the two of us can do together in the future.

I have no words to express my gratitude to my paranymphs, Patrizia and Pierfrancesco.
Pierfrancesco Agostoni joined the Thoraxcenter for just a few months in the summer 2004. He came to increase his knowledge in palpography. This was what he actually did for the first month, buried on the 23th floor. Then I met him and I could not resist the temptation to involve him in what I was working on. Surprisingly smart, born as "letter to the journal" writer and then as successful meta-analysis thanks to the influence of Beppe Biondi-Zoccai, he is now becoming a brilliant interventional cardiologist. He did a fantastic job in an extraordinary short time in our "IVUS paper" while he was busy retrieving the data from the surgical database…the missing paper(s) in this thesis. I am really sorry I could not defend his work as I wished! But this experience taught me a lot, and I promise you Ago this will not happen a second time: we have a lot to do in the future together, and I look forward to your enthusiasm, ideas and balance.
Patrizia, Patty, Malagutti, Malaguttona. My life. My favourite co-worker. My love. She joined me at the Thoraxcenter during the second year of my fellowship, and she changed everything (if you do not believe this, please ask Gato, he will mimic me before and after, very funny!).
She is an incredibly hard worker, precise and meticulous. With her spectacular QCA, we reached JAMA, JACC several times and AHJ. I sincerely hope nobody will discover how truly good you are at research otherwise, I may loose my secret. It is impossible to thank you properly for your outstanding contribution to this thesis, which belongs to you in the same proportion as it does to me.
Si dice sempre in questi casi..senza di te questo lavoro non sarebbe mai stato scritto, beh, questa frase è tutto meno che retorica in questa circostanza! Si contruisce sempre a piccoli passi. Non vedo l'ora di correre al tuo fianco.

Patty also introduced me in the multislice CT world. Pim, I will never stop thanking you for your understanding and support. You are a myth of the Thoraxcenter and the lucky ones who know you can fully understand why. Thank you Pim for accepting to be one of my promoters. Your dedication to research is perfectly balanced by your clinical sensibility. Thanks also to the whole Multi-slice CT group, including Manuel, the Master of PCs and the king of kindness, Giuseppe, The Sicilian, Alessandro and Ludovico who studied all of the available literature on the vulnerable plaque (!) and kept discussing its unravelled features for months during lunch time, to Francesca, The American who was born in Italy, Nico, the Dutch *co-boss*, Filippo, the Italian *co-boss* and the great Bob, whose hair style inspired Patty and I on how to name our favourite plant in Rotterdam.

A lot of people at the Thoraxcenter made my life much easier. Among them, I would like to mention Prof. Simoons for his understanding in the most critical moment of my PhD experience, Prof. de Jong, for his friendship, Ron van Domburg, with whom I regret not having spent more time, to Linda Smit and the magic Annet Louw, who made all PhD bureaucracy a smooth and enjoyable step, Jan Tuin and Paula Delfos for their professionalism and kindness.
I am deeply indebted to all of the committee members whose prestige and international credibility bring light and honour to this thesis.
The first time I saw William Wijns was during the annual congress of the Italian invasive cardiology society some years ago in Como. He was asked to speak about the role of PCI in stable coronary artery disease when he clearly stated the truth…medical treatment may be even better from a prognostic standpoint…the message was not well received by the audience…since then I kept appreciating his scientific rigor, his balance and smart attitude and…hey guys…what a style!
I should write a separate chapter about *my* Professor Ferrari. I betrayed your basic science to become an inverventional cardiologist…something you will never

forgive me for…Thank you for believing in me since the early days, thank you for supporting me when nobody was even in the mood to, a new challenge close to you is just about to start, I hope I will be able to show you how big is my gratitude towards you is in the following years.
Eric Boersma has always been a hero for me with his "reappraisal of the golden hour" much before I came to the Thorax. The truth is that knowing Eric a little bit more has led me to simply increase my appreciation towards him. Very busy but always surprisingly well organized he *significantly* contributed to the biggest successes of this thesis! I know it will be almost impossible to keep working with you in the future Eric…but I will give it a try anyhow!
Gabriel, I have never understood why, but I have felt as a friend of yours since the early days I met you in Capri, between stem cells and some mozzarella cheese. Subsequently, I had the privilege of knowing you better as part of the steering committee of the nameless "ex superiority trial" (by the way your High-Tech proposal was not bad at all!) and now I am even working with a true fan of yours…Prof Martial Hamon. It seems that destiny is pushing me towards you and your excellent work, I hope it will be highly successful, then!
A special thanks to Prof. Alfredo Rodriguez, who kindly accepted to be a member of my PhD committee and for his great and highly appreciated support in the MULTI-STRATEGY project and to Prof D. Poldermans, for his remarkable capability to go directly to the point.

Dulcis in fundo, it is time to focus on HIM, Prof PW Serruys, who in some way made the majority of the above mentioned interconnections possible, and acknowledging them is an indirect way to thank HIM as well. For an interventional cardiologist Patrick Serruys is the Thoraxcenter and the Thoraxcenter is Patrick Serruys…this is one of the first basic laws the fellow discovers. He wonderfully played the role of Obi-Wan Kenobi for several years and trained, with the help of his outstanding teams, dozens of Jedis around the world. I learned hundreds of things from HIM, the living legend of interventional cardiology, (starting from witnessing that this title is absolutely very well deserved!!): the way he tries hard every second of his life to push himself beyond any boundaries, to understand more and to do more than anybody else, how he fights everyday to reach and maintain his astonishing level of knowledge and international recognition in the field, the way he attracts and plays with industries in the full respect of science and the truth (which is something not too fashionable nowadays unfortunately!!). I will never stop thanking you PROFESSOR for all this and for the privilege to work close to and on behalf of you. Knowing you was my first priority coming to the Thorax. Getting a PhD with you is the second one. The third will be to stay in close contact with you and keep learning from you and your team beyond my fellowship. I will endeavour to achieve my third priority with the same of level of intensity and enthusiasm you have seen me doing for the first two.

Last, but not least, I would like to go back to my roots in cardiology. I was born as an internal medicine doctor in Bologna and becoming a cardiologist has not been so easy, thanks to the very flexible Italian University system. Prof Bruno Magnani was a key figure in this transition; he first stirred me with his scientific rigor wonderfully applied to patient care, and then he paved my way with his good-natured and paternal attitude. Dear Prof Magnani, your advice and two disciples (i.e. Prof Marco Bonvicini and Angelo Placci) took me to Ferrara, where I had the privilege of finding *my* professor Ferrari (…another disciple of yours actually, in a certain way). I wish I could grow up in line with his and your teachings even if…at a distance.

Elda, Bruno, Barbara, Stefano, Luca…adoro riconoscermi in tutti voi. Grazie.

Curriculum Vitae

Marco Valgimigli was born on 6th March 1972 in Forlì, Italy. He obtained his medical degree in 1997 with Summa cum Laude at the University of Bologna, Italy. He performed his training in internal medicine at the University of Bologna in 1997-1999 and completed the training in cardiology at the University of Ferrara in 2003. In January 2004, he started a clinical and research fellowship in the catheterisation laboratory of the Thoraxcenter, Erasmus Medical Centre in Rotterdam, under the supervision of Prof Patrick Serruys. In November 2005, he moved to Caen, Normandy, France to be trained in transradial approach under the supervision of Prof Martial Hamon.

Awards

- Winner of the "*Best Scientific contribution Award*" with a research project entitled: "*Apoptotic activity of serum is increased in patients with pancoronary syndrome*" October 2002, Verona, Italy, on behalf of GISE (Gruppo Italiano Studi di Emodinamica)

- Winner of the "*Scholarship from Italian society of Cardiology*" with a scientific contribution entitled: "*Pathophysiological and clinical implications of bone marrow stem cells spontaneous mobilisation in Acute Coronary Syndromes and Heart Failure*" Rome 2003, Italy, SIC (Italian Society of Cardiology)

- Finalist TCT Young Investigator Award, October 2005, Washington

Membership

Marco Valgimigli is a member of the European Society of Cardiology (ESC), of the Big Register, of the Società Italiana di Cardiolgia (SIC), and of the Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO).

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