Developments in the percutaneous treatment of obstructive coronary artery disease

Pierfrancesco Agostoni

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PhD thesis Utrecht University, Faculty of Medicine, the Netherlands

Design: Pierfrancesco Agostoni

Lay-out and printed by: Gildeprint Drukkerijen – Enschede, The Netherlands

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Ontwikkelingen in de percutane behandeling van obstructief coronair lijden

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht op gezag van de rector magnificus,
prof. dr. J.C. Stoof, ingevolge het besluit van het
college voor promoties in het openbaar te verdedigen op
donderdag 3 december 2009 op 10.30 uur

door

Pierfrancesco Agostoni

geboren op 3 oktober 1975
te Trescore Balneario (Bergamo), Italie

Promotor: Prof. dr. P.A.F.M. Doevendans

Co-promotor: Dr. P.R. Stella

To my fantastic family: Pa, Ma and Rosy

To all the extraordinary friends I was lucky to meet all over Europe on my way till here

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Introduction

INTRODUCTION

Coronary artery disease is one of the leading causes of mortality and morbidity in the industrialized world and its incidence is steadily increasing also in the third world countries. The main cause of coronary artery disease is atherosclerosis, a chronic-degenerative inflammatory disease, which has the potential to affect the wall of almost all the arteries of the human body (1).

Coronary atherosclerosis, together with superimposed thrombo-embolic events, determines stenoses and occlusions of the coronary arteries, leading, according to the progressive or sudden nature of the process, to clinical syndromes such as stable angina, acute coronary syndromes (unstable angina and myocardial infarction) and sudden cardiac death (2).

Medical therapy is the main treatment of atherosclerotic disease, in order to reduce the symptoms, to control the progression and to decrease the acute complications of this disease. However, as the morphologic appearance of atherosclerosis in the coronary arteries takes the form of the aforementioned stenoses, mechanical therapies have been successfully introduced in the last decades. Specifically, two techniques have been developed in this direction: coronary artery bypass graft surgery and percutaneous coronary intervention. The fist is an open-heart major surgical intervention in which new arterial or venous conduits are used to "bypass" the stenoses. The second, using a less invasive approach at the level of a superficial artery in the periphery of the human body as way to reach the coronary arteries by means of dedicated catheters, allows dilatation of the stenoses directly from inside the vessel itself. While a direct comparison of the benefits and drawbacks of the two techniques lies besides the goals of the current thesis (3), our focus will be on the current and future developments of the percutaneous treatment of coronary artery disease.

The percutaneous treatment of coronary arteries began in 1977, when Andreas Gruentzig treated the first patient by means of a balloon, which was tracked at the level of the coronary stenosis and inflated while in steady position. This allowed mechanical reduction of the stenosis itself and reestablishment of adequate flow in the artery downstream and relief of the symptoms of the patient. The technique was

called “percutaneous transluminal coronary angioplasty” (4). However, it became soon evident that this technique had drawbacks, specifically restenosis, which is a iatrogenic process leading, usually in the first 6 months, to new formation of a stenosis in the same place where the dilatation occurred (5).

Almost ten years later, Ulrich Sigwart and Jacques Puel introduced a new device to treat stenoses in the coronary arteries: the stent (6,7). This device, a metallic cylindrical net-shaped prosthesis left in place during the dilatation of the artery, proved to be superior to balloon-only angioplasty in reducing the occurrence of restenosis from around 40-50% to around 20-25%, as it provided additional scaffolding to the dilated vessel wall (8). Broad use of these stents began worldwide. Moreover, with the technical development of stent design, leading to stents with lower crossing profile, more flexible and more easily trackable in the coronary vasculature, interventional cardiologists progressively treated more complex anatomical settings. However restenosis was not abolished and still remained an issue. Moreover, another problem peculiar of the metallic stent arose: stent thrombosis, i.e. the formation of a clot inside the stent, potentially leading to its occlusion. Its impact could be devastating due to the acute occurrence of life-threatening occlusions of the coronary arteries of patients, with subsequent myocardial infarctions and potentially sudden arrhythmic death. Aggressive antiplatelet therapy with both aspirin and a thienopyridine for a specific period of time after implantation of the stent, using high inflation pressure (at least 12-14 atm), allowed limiting the incidence of this ominous complication to around 1-2% (9).

In the beginning of this millennium, the adjunct of drugs directly onto these metallic stents opened the way to the current drug-eluting stent development. Stents were not only used to scaffold the vessel, but also to elute drugs with the potential to inhibit the processes leading to restenosis and thus to limit its occurrence. In particular, two stents, eluting two different drugs, sirolimus and paclitaxel, entered the market after proving, according to the dictates of evidence-based medicine, strongly significant superiority in reducing restenosis as compared to bare metal stents in well conducted randomized clinical trials (10-13). A restenosis rate of less than 10% was reached. A “drug-eluting stent euphoria” led to the use of these devices in up to 90% of all percutaneous coronary interventions, following the release of these

pivotal trials. However these trials were performed in selected lesions and patients, thus strong evidence was missing for several clinical and anatomical settings. In particular, patients with diabetes, chronic renal insufficiency, multi-vessel disease, lesions located in bifurcations, chronic occlusions, left main coronary artery, bypass grafts, in-stent restenosis, small vessels and diffusely diseased vessels were poorly assessed. Moreover, the first long-term data of drug-eluting stents raised some concerns related to the safety of these devices and linked to the possibly higher rate of stent thrombosis (specifically occurring late after stent implantation –even more than 1 year after stent deployment) after drug-eluting stents as compared to bare metal stents (14,15).

AIMS OF THIS THESIS

Our work started at this point, when sirolimus- and paclitaxel-eluting stent began to be used extensively, also in "off-label" indications, i.e. those indications that fell out of the "instructions for use" of these devices based on the inclusion/exclusion criteria of the pivotal trials that allowed these stents to be released in the worldwide market. Specifically, in the first part of our thesis, we focused our attention on three subsets of lesions, excluded from the aforementioned pivotal trials, and usually excluded also from several other randomized trials subsequently performed, in order to assess extended efficacy and safety of drug-eluting stents also in these settings.

The first lesion subset was the left main coronary artery. Severe stenoses localized at this level of the coronary anatomy has been always considered surgical, however with the promising data of drug-eluting stents, several operators began these lesions treating percutaneously. We were able to investigate mid-term results of this strategy in one of the first large series of patients treated with drug-eluting stents for severe left main coronary artery disease (16).

The second lesion subset was the saphenous vein bypass graft. This lesion has always been considered high risk, for its inherent risks of acute embolization with distal myocardial damage and of restenosis, higher than in native arteries. While percutaneous intervention with bare metal stent is considered nowadays the gold-

standard treatment for this type of lesion (seen also the additional risks linked to Re-Do bypass surgery), the use of drug-eluting stents in this setting needed proper validation with specifically dedicated studies. We were able to conduct the first randomized trial comparing bare metal and sirolimus eluting stents in saphenous vein graft (17).

The third lesion subset was the complex, “real-life”, “routine-practice” anatomy, with “all-comer” patients often presenting with multi-vessel disease, long lesions requiring multiple overlapping stents, involving frequently bifurcations and chronic occlusions, and frequently also with severe co-morbidities. We could assess advantages and drawbacks of sirolimus- and paclitaxel-eluting stents in two large registries of all-comers (18,19). Alongside the clinical data relative to these patients, by using the same data, we could also focus our attention on the possible values and disadvantages of several surrogate endpoints routinely used in interventional cardiology as primary endpoints of randomized studies, such as the angiography based late lumen loss (20).

Besides our focus on the extension of the indication of drug-eluting stents to off-label indications, we also concentrated in the second part of the thesis on the potential advantages of new drug-eluting stents that were progressively introduced in the clinical arena. These devices were expected to further improve efficacy and/or safety as compared to “first-generation” drug-eluting stents. Specifically we could conduct a randomized multicenter international trial comparing stents eluting paclitaxel versus pimecrolimus versus the combination of both drugs. All these drugs were placed in a newly designed cobalt-chromium stent, with a reservoir-based platform, eluting the drugs in a controlled way via a bioresorbable polymer from specifically designed reservoir wells. The novelty of this trial, beside the new drug that was tested (pimecrolimus), relied also on the fact that for the first time a stent eluting two different drugs at the same time was used in the clinical setting. Finally, we investigated the possible improvements given by self-expanding drug-eluting stents, specifically designed for selected anatomies (21). In particular, we studied, in a prospective multicenter international registry, a novel self-expanding biolimus-eluting nitinol stent with a design dedicated for bifurcation lesions. In addition, we reported a case of a patient treated for a lesion in a small vessel (with a reference

vessel diameter <2.5 mm) with a dedicated self-expanding sirolimus-eluting nitinol stent directly loaded into a “conventional” coronary guidewire with a diameter of 0.014 inches.

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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 – vs. – without intravascular ultrasonic guidance.

Pierfrancesco Agostoni, Marco Valgimigli, Carlos A.G. van Mieghem, Gaston A. Rodriguez Granillo, Jiro Aoki, Andrew T. L. Ong, Keiichi Tsuchida, Eugène P. McFadden, Jurgen M. Ligthart, Pieter C. Smits, Peter de Jaegere, George Sianos, Willem J. Van der Giessen, Pim De Feyter, Patrick W Serruys.

Erasmus Medical Center, Thoraxcenter, Rotterdam, The Netherlands.

Published in the *American Journal of Cardiology* 2005;95:644-647

ABSTRACT

Aim of our 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, employed in 41% of the procedures, was not associated to additional clinical benefit with respect to angiography-assisted stent deployment.

INTRODUCTION

Intra-vascular 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 (DES) are used.[2,3] No definitive evidence for such a practice in LM treatment, exists. Indeed, 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, in patients referred for LM percutaneous revascularization with DES, the differential impact of IVUS guidance on short-and mid-term clinical events.

METHODS

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 a 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 procedure, both sirolimus-eluting stents (Cypher, Johnson & Johnson-Cordis unit, Cordis Europa NV) and paclitaxel-eluting stents (Taxus, Boston Scientific Corp.) have been used, as part, respectively, of the RESEARCH (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) and the T-SEARCH (Taxus-Stent Evaluated At Rotterdam Cardiology Hospital) registries. 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 maintain aspirin lifelong. Clopidogrel (300 mg loading dose prior to the procedure and 75 mg/day) was prescribed for 6 months.

Using a validated on-line quantitative coronary angiography system (CAAS II, Pie Medical), 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 intra-coronary injection of nitrates, using commercially available IVUS systems (30 MHz Ultracross or 40 MHz Atlantis, both from Boston Scientific Corp., or 20 MHz Eagle Eye from Volcano Inc.) and motorized pullback (0.5 or 1 mm/sec). All the 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 non-cardiac), non-fatal myocardial infarction, or target vessel revascularization. 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 (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 and/or circumflex artery.

Continuous variables are shown as mean ± standard deviation 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 angiography and

IVUS results in Table 3, in order to identify independent predictors of adverse events. A p-value <0.05 was considered to indicate statistical significance. All statistical tests were 2-tailed.

RESULTS

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

The overall rate of major events was 15% at a median follow-up of 433 days (range 178-780). At 30 days, the rates of mortality and major adverse events were, respectively, 3% and 7%. There were 2 peri-procedural 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 procedure, in a patient with severe left ventricular dysfunction due to a previous myocardial infarction and diffuse three vessel disease, who developed cardiogenic shock during the intervention, initially stabilized with a left ventricular assist device, but 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 following 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, while the others were surgically revascularized. Overall, the mortality rate was 5%, the myocardial infarction rate 3%, and the target vessel revascularization rate 7%.

Table 1. Baseline characteristics of the study population

Variable	Intravascular Ultrasonic Imaging		P-value
	Yes (N=24)	No(N=34)	
Age (years)	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 Smoke	4 (17%)	7 (21%)	0.75
Previous percutaneous coronary intervention	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

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

Table 2. Angiographic and Procedural Characteristics of the study population.

Variable	Intravascular Ultrasonic Imaging		P-value
	Yes (N=24)	No(N=34)	
Lesion location			
Ostial	7 (29%)	3 (9%)	0.08
Mid-shaft	7 (29%)	9 (26%)	0.9
Distal	10 (42%)	22 (65%)	0.08
Three vessel coronary disease	11 (46%)	25 (73%)	0.03
Right coronary occluded	3 (12%)	9 (26%)	-
Number 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
Pre-dilatation	12 (50%)	21 (62%)	0.37
Post-dilatation	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

Data are presented as mean $\pm$ standard deviation or number (percentage). *Considering only patients with distal LM disease.

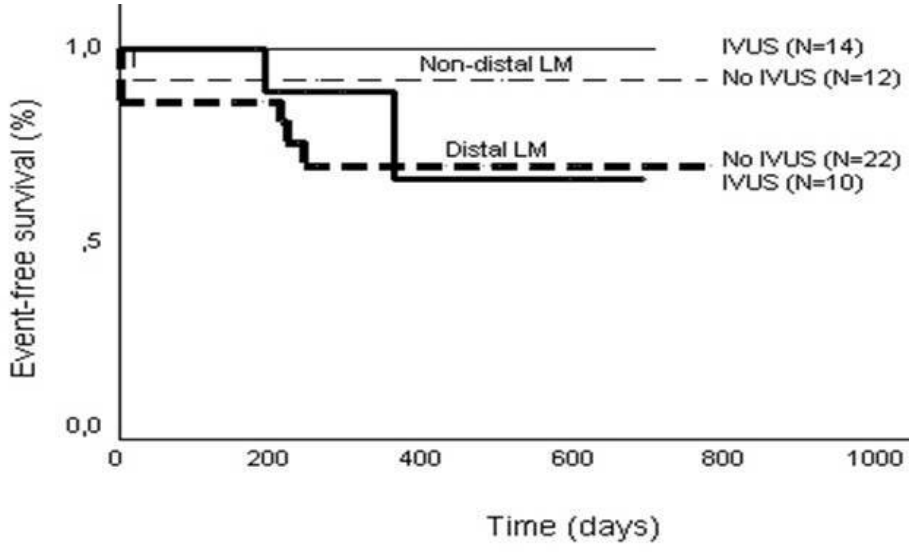
Table 3 Quantitative Coronary Angiography and Quantitative Coronary Ultrasound results of the study population.

Variable	Intravascular Ultrasonic Imaging		P-value
	Yes (N=24)	No(N=34)	
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	-	-

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

The incidence of major adverse events was 2/24 (8%) in the IVUS group and 7/34 (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 remained a significant predictor of adverse events with an hazard ratio of 7.7 (95% confidence interval: 1-62.6) (p=0.05). To test the effect of IVUS guidance in different anatomical LM subsets, we stratified the patients in two groups: non-distal vs. distal LM involvement. In the former, IVUS was used in 14 out of 26 patients (54%) and the rate of events was low, only one non-cardiac death (4%) after a non-IVUS guided procedure. In the latter, IVUS was used less frequently (p=0.08), i.e. in 10 out 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 out of 10 patients (20%) vs. 6 out of 22 (27%), respectively (Figure 1).

Figure 1



Kaplan-Mayer mayor adverse events – free survival curves of intra-vascular ultrasound (IVUS) vs. non-IVUS guided procedures, stratified according to the anatomical location of atherosclerotic disease in the left main (LM).

DISCUSSION

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. Indeed the rate of events did not differ significantly between IVUS and angiography 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 was the only independent predictor of events at follow-up, further strengthening this observation. Indeed, when ostial or mid LM disease is treated with DES, the rate of cardiac events is particularly low. Thus, routine IVUS does not confer any benefit in this sub-population with an excellent outcome. In patients with distal LM involvement, the rate of events was significantly higher,

but also in this case, no significant clinical benefit occurred in the IVUS sub-group. However, as IVUS was used in a smaller number of patients with respect to the group with non-distal LM involvement, it is possible that routine IVUS guidance may be useful when distal LM is diseased, and such a strategy warrants further evaluation.

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2

Randomized double-blind comparison of sirolimus-eluting stent versus bare metal stent implantation in diseased saphenous vein grafts: 6-month angiographic, intravascular ultrasound and clinical follow up of the RRISC (Reduction of Restenosis In Saphenous vein grafts with CypherTM sirolimus-eluting stent) trial.

Paul Vermeersch*, Pierfrancesco Agostoni*, Stefan Verheye, Paul Van den Heuvel, Carl Convens, Nico Bruining, Frank Van den Branden, Glenn Van Langenhove.

Antwerp Cardiovascular Institute Middelheim, AZ Middelheim, Antwerp, Belgium and Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands

*Drs. Agostoni and Vermeersch contributed equally to this work.

Published in the *Journal of the American College of Cardiology 2006;48:2423-2431*.2005;95:644-647

ABSTRACT

Objectives: To compare, in a randomized fashion, sirolimus-eluting stents (SES) versus bare metal stents (BMS) in saphenous vein grafts (SVG).

Background: SES reduce restenosis and repeated revascularization in native coronary arteries compared to BMS. However, randomized data in SVG are absent.

Methods: Patients with SVG lesions were randomized to SES or BMS. All were scheduled to undergo 6-month coronary angiography. Primary end point was 6-month angiographic in-stent late lumen loss. Secondary end points included: binary angiographic restenosis, neointimal volume by intravascular ultrasound and major adverse clinical events (death, myocardial infarction, target lesion and vessel revascularization).

Results: 75 patients with 96 lesions localized in 80 diseased SVG were included: 38 patients received 60 SES for 47 lesions, while 37 patients received 54 BMS for 49 lesions. In-stent late loss was significantly reduced in SES (0.38±0.51 vs. 0.79±0.66 mm in BMS, p=0.001). Binary in-stent and in-segment restenosis were reduced, respectively 11.3% vs. 30.6% (relative risk: 0.37 [95% confidence interval: 0.15-0.97], p=0.024) and 13.6% vs. 32.6% (relative risk: 0.42 [0.18-0.97], p=0.031). Median neointimal volume was 1 mm^3 [interquartile range: 0-13] in SES vs. 24 [8-34] in BMS (p<0.001). Target lesion and vessel revascularization rates were significantly reduced, respectively 5.3% vs. 21.6% (relative risk: 0.24 [0.05-1.0], p=0.047) and 5.3% vs. 27% (relative risk: 0.19 [0.05-0.83], p=0.012). Death and myocardial infarction rates were not different.

Conclusions: SES significantly reduce late loss in SVG as opposed to BMS. This is associated with a reduction in restenosis rate and repeated target lesion and vessel revascularization procedures.

INTRODUCTION

Saphenous vein grafts (SVG) remain the most frequently used conduits in coronary artery bypass graft surgery (1). However, within a decade after surgery, half of the SVG develop significant atherosclerotic disease and recurrent angina after bypass surgery is a common clinical problem (2). Repeated bypass surgery is technically more challenging than the first operation and it is associated with higher morbidity and mortality, thus currently percutaneous coronary intervention (PCI) is the preferred treatment for SVG lesions (3,4). Specifically, the implantation of bare metal stents (BMS) is the actual strategy to treat these patients (5,6). However, the results of BMS in SVGs are less favorable than those in native vessels, with restenosis rates exceeding 30% (5,7).

The introduction of sirolimus-eluting stents (SES) has recently reduced the occurrence of angiographic restenosis and repeated revascularization with respect to BMS in native coronary artery disease (8,9). Despite the growing evidence of the benefits of SES in several subsets of lesions (10-14) and patients (15,16), SVG have always been excluded from these randomized trials, and currently available registries on SES in SVG offer inconsistent results (17-21).

Thus, the aim of our study was to assess whether SES improves angiographic and clinical outcomes when compared to BMS in diseased SVG.

METHODS

The RRISC (Reduction of Restenosis In Saphenous vein grafts with Cypher™ sirolimus-eluting stent) trial is a randomized double blind non-industry-sponsored trial performed in a single center with large experience in the percutaneous treatment of SVG disease (22,23). The trial design was approved by the local Ethics Committee.

Patient population

Patients were included if they were 18 to 85 years-old, had a history of previous coronary artery bypass surgery, had stable or unstable angina, and had one or more "de novo" target lesions (>50% diameter stenosis by visual estimate) localized in one or more diseased SVG with a reference vessel diameter (RVD) >2.5 and <4.0 mm. Exclusion criteria were: myocardial infarction (MI) within the previous 7 days

(with creatine kinase-MB elevation >2 times the upper limit of normal), documented left ventricular ejection fraction <25%, impaired renal function (creatinine >3.0 mg/dl), distal graft anastomotic stenosis, totally occluded SVGs, previous brachytherapy treatment in the index vessel, allergy to aspirin, clopidogrel, heparin, stainless steel, contrast agent or sirolimus. Aorto-ostial location and thrombotic and/or calcified lesions were not considered exclusion criteria. All enrolled patients provided written informed consent prior to the index procedure.

Procedural protocol

After percutaneous access was obtained, heparin was administered to maintain an activated clotting time >250 seconds. Glycoprotein IIb/IIIa receptor blockers were given at operator's discretion. The use of a distal protection device (GuardWire, Medtronic, Minneapolis, MN) was strongly recommended. After successful crossing of the target lesion with the guide-wire, patients were randomly allocated in a 1:1 ratio to treatment with Cypher™ SES or BX-Velocity BMS (both from Cordis, Johnson & Johnson, Warren, NJ). In case of treatment of more than one lesion the stent type remained the same. Direct stenting was promoted. In case of dissection or incomplete lesion coverage, the use of additional stents of the same type as the assigned stent was mandated. Angiographic success was defined as implantation of the study device with residual diameter stenosis <30% and normal (TIMI 3) coronary blood flow. Aspirin (100-300 mg/day) was given daily and clopidogrel (loading dose of 300 mg, 6 to 48 hours before the procedure and 75 mg/day thereafter) was administered for 2 months in all patients. Serial blood samples for creatine kinase, creatine kinase–MB and cardiac troponin I were routinely obtained before the procedure, and 8, 16, 24 hours after the intervention.

Randomization and blinding process

The randomization process was unblocked and non-stratified. The randomization list was generated by a computer. Randomization was performed by means of opaque envelopes (concealed until the operator successfully wired the target vessel) containing a letter: "A" or "B". Since the standard package of the stents is the only visible difference between the two stent types, additional external packages,

labeled respectively with “A” or “B” and the specific stent measure, were used. The appearance of the two stent types, once the standard package was opened, was the same, as the delivery system, the shaft, the stent design and the measures available are the same for both. After randomization, the interventional staff left the catheterization laboratory, and an independent nurse opened the package of the stent selected from randomization, and left the stent on the catheterization table. Thus, the operator (and his staff) and the patient were unaware of the stent type.

Clinical, angiographic and intravascular ultrasound follow up

Patients were evaluated clinically 1 and 6 months after the procedure. Coronary angiography was repeated at 6 months (± 15 days) and intravascular ultrasound (IVUS) analysis was recommended in every SVG treated with a study stent. IVUS was performed after injection of 0.2 mg of nitroglycerin with a 30 MHz ultrasound probe (Ultracross 2.9F, Boston Scientific Corporation, Natik, MA), connected to the Galaxy ultrasound console (Boston Scientific Corporation), and a motorized pullback (speed: 0.5 mm/sec). Angiography was performed earlier if there were recurrent symptoms, but if restenosis was not found during this repeated angiography, a new angiography was done at 6 months.

Quantitative coronary angiographic analysis

Digital coronary angiograms were analyzed offline by an expert operator blinded to the procedure (with an intraobserver variability for QCA measurements of <5% [range 2.4-9.2%]), using a validated automated edge detection system (CAAS II, PIE Medical, Maastricht, The Netherlands). Matched views were selected for angiograms recorded before and immediately after the intervention and at 6-month follow up. Angiographic measurements were made both in the stent and in the stented segment (defined as the stent plus the 5 mm edges proximal and distal to the stent) during diastole using the contrast-filled guiding catheter for magnification calibration. In case overlapping stents were placed, a single in-stent value was measured, and the segment was considered as the entirely stented part plus the 5 mm proximal to the more proximal stent and the 5 mm distal to the more distal stent implanted. Lesion RVD, minimal luminal diameter (MLD), percent diameter stenosis and length were

obtained at baseline. RVD, MLD and diameter stenosis were evaluated at the end of the procedure and at follow up, for the in-stent, proximal edge, distal edge and in-segment sections (24). Acute gain was defined as the difference between the in-stent MLD at the end of the intervention and the MLD at baseline. Late lumen loss was calculated as the difference in MLD between measurements immediately after the procedure and at follow up. Binary angiographic restenosis was defined as diameter stenosis >50% by quantitative coronary angiography, at the follow up angiogram (25). Restenosis patterns were assessed using the Mehran classification system (26).

IVUS analysis

IVUS data were stored on S-VHS videotape. The videotapes were transformed into the DICOM medical image standard. Quantitative coronary ultrasound analysis was performed using a validated software (Curad, version 4.32, Wijk bij Duurstede, The Netherlands), allowing semi-automated detection of luminal and stent boundaries in reconstructed longitudinal planes (27). In order to obtain a smooth appearance of the vessel wall structures in the longitudinal views, the Intelligate™ image-based gating method was applied (28-30). This validated technique retrospectively selects end-diastolic frames, allowing more reliable volumetric measurements. Volumetric quantitative coronary ultrasound analysis was obtained for stent and lumen. Neointimal volume was computed as the difference between the stent volume and the lumen volume.

End points and definitions

The primary end point of the study was 6-month in-stent late lumen loss. Secondary angiographic end points included in-segment late loss, and in-stent and in-segment binary restenosis rate. Secondary IVUS end point was in-stent neointimal volume. Secondary clinical end points were in-hospital, 30 days and 6 months major adverse cardiac events (MACE) rates. MACE included death, all non-fatal major MI (also periprocedural) and target vessel revascularization (TVR). Major periprocedural MI was defined as an elevation of creatine kinase enzyme-MB activity >3 times above the upper limit of normal (16 U/l in our institution). Non-periprocedural MI was defined as a new ischemic event with creatine kinase-MB >2 times the upper limit

of normal, or the electrocardiographic presence of new pathological Q-waves. We also recorded minor periprocedural myocardial damage, defined as a elevation of cardiac troponin I >0.4 ng/dl (31) or, if pre-procedural cardiac troponin I was already positive (in unstable patients), doubling of its value at any of the post-procedural samples, without fulfillment of the criteria for major periprocedural MI. Target lesion revascularization (TLR) was defined as a repeated revascularization procedure (either PCI or coronary bypass surgery), due to restenosis in the stented segment. TVR was defined as a new revascularization procedure in the target vessel, including also TLR. Target vessel failure (TVF) was defined as a composite of TVR, treated vessel-related MI and cardiac death. Stent thrombosis was defined according to Iakovou et al. (32). All the clinical events were adjudicated by an independent clinical events committee unaware of the patients' treatment assignment.

Statistical analysis

Sample size was calculated on the assumption that the mean per-lesion in-stent late loss in the BMS group would be 1±0.9 mm. To detect a decrease in mean late loss in the SES group of 0.6 mm, with an 80% power and a two-tailed type I (alpha) error of 0.05, 35 patients per group were required. Considering a 10% rate of patients with >1 lesion intervention (22,23) and a 15% rate of drop-outs, the number of enrolled patients was increased by 8%.

All analyses were conducted according to the intention-to-treat principle. The quantitative angiographic and IVUS results were analyzed on a per-lesion basis, while the clinical events were assessed per-patient. Continuous data are expressed as means ± standard deviations or as medians [interquartile range] as appropriate, whereas dichotomous data are summarized as frequencies. Student's *t* or Mann Whitney U test (as appropriate) and chi-square or Fisher's exact test (as appropriate) have been employed, respectively, for continuous and categorical variables, to analyze differences between the two study arms. A linear regression analysis with the primary end point (in-stent late loss) as dependent variable and all the baseline clinical and angiographic characteristics known to influence late loss as independent variables (stent type, maximum balloon diameter, maximum inflation pressure, post-dilatation performed, total stent length per lesion, diabetes, age of CABG, baseline

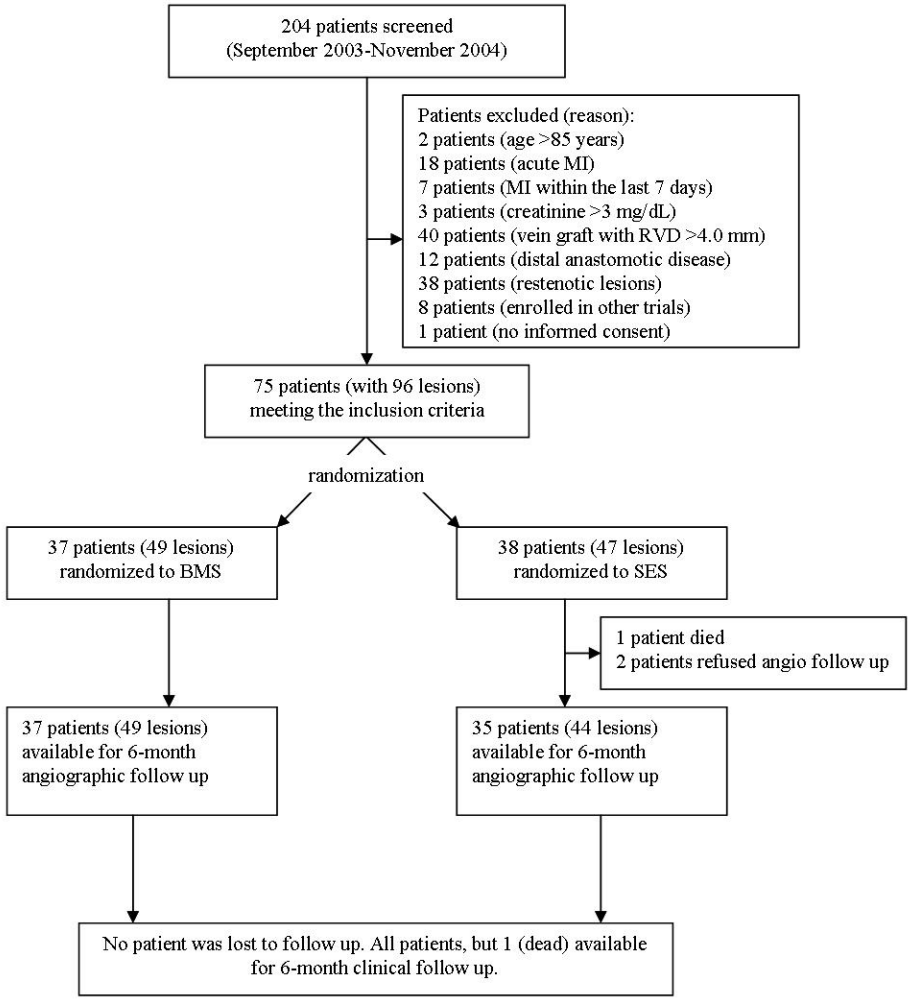
lesion length, baseline RVD) was also performed, to confirm the results of our analysis. Relative risks (RR) with their 95% confidence interval (CI) were computed for dichotomous variables. Computation of the number-needed-to-treat (with 95%CI), extrapolated from the absolute risk difference, was made for clinical variables. A two-sided p-value <0.05 was considered significant for all tests.

RESULTS

Study population and procedural outcomes

Between September 2003 and November 2004, 75 patients with 96 lesions localized in 80 SVG were enrolled (Figure 1). Baseline clinical characteristics of the patients, as well as the angiographic and procedural characteristics of the lesions treated are shown in table 1. The 2 groups were well balanced for all the variables considered. Out of a total of 114 stents deployed, 54 were BMS and 60 SES. Angiographic success was achieved in all the lesions treated. The use of glycoprotein IIb/IIIa inhibitors was very low (only in 1 SES patient). Distal protection devices were employed in more than 80% of the lesions treated. Only in case of distal position of the stenosis in the vein graft (not enough space for the placement of the device), suboptimal back up of the guiding catheter, or presumed low risk of embolization (very focal lesions), distal protection was not used.

Figure 1. Complete flow-chart of the patients enrolled in the RRISC trial.



BMS: bare metal stent; MI: myocardial infarction; RVD: reference vessel diameter; SES: sirolimus-eluting stent.

Table 1. Baseline clinical and procedural characteristics of the patients and the lesions in the two groups.

	BMS patients=37 grafts=41 lesions=49 stents=54	SES patients=38 grafts=39 lesions=47 stents=60	P-value
Age (years)	72 ± 8	73 ± 7	0.36
Men	33 (89%)	31 (82%)	0.36
Risk factors:			
Family history	29 (78.4%)	25 (65.8%)	0.23
Hypertension	21 (56.8%)	22 (57.9%)	0.84
Hypercholesterolemia	31 (83.8%)	33 (86.9%)	0.74
Current smoker	4 (10.8%)	2 (5.3%)	0.46
Diabetes Mellitus	5 (13.5%)	6 (15.8%)	0.78
Body mass index (Kg/m^2)	26.4 ± 3.9	26.4 ± 3.1	0.97
History of heart failure	7 (18.9%)	6 (15.8%)	0.72
Prior myocardial infarction	15 (40.5%)	17 (44.7%)	0.71
Prior coronary angioplasty	15 (40.5%)	12 (31.6%)	0.42
Unstable angina pectoris	19 (51.4%)	23 (60.5%)	0.41
Ejection Fraction (%)	72 ± 12	68 ± 18	0.37
Age of the grafts	12.6 ± 5.9	12.4 ± 4.6	0.92
Number of grafts treated per patient			0.20
1	33 (89.2%)	37 (97.4%)	
2	4 (10.8%)	1 (2.6%)	
Degenerated saphenous vein grafts*	17 (41.5%)	19 (48.7%)	0.51
Number of lesions treated per patient			0.55
1	26 (70.3%)	29 (76.3%)	
2	10 (27%)	9 (23.7%)	
3	1 (2.7%)	0 (-)	
Recipient native vessel territory			0.11
Left anterior descending/diagonal	6 (12.2%)	9 (19.2%)	
Circumflex/obtuse marginal	26 (53.1%)	15 (31.9%)	
Right coronary artery	17 (34.7%)	23 (48.9%)	
Lesion location in the graft			0.73
Aorto-Ostial	11 (22.4%)	12 (25.5%)	
Proximal	13 (26.5%)	12 (25.5%)	
Mid	16 (32.7%)	18 (38.3%)	
Distal	9 (18.4%)	5 (10.7%)	
Angiographic evidence/suspect of thrombus	12 (24.5%)	17 (36.2%)	0.21

Moderately/heavily calcified lesions	9 (18.4%)	8 (17%)	0.86
TIMI flow pre-procedure			0.19
1	2 (4.1%)	2 (4.3%)	
2	2 (4.1%)	7 (14.9%)	
3	45 (91.8%)	38 (80.9%)	
Number of stents per patient	1.46 ± 0.7	1.58 ± 0.7	0.45
1	24 (64.9%)	20 (52.6%)	
2	9 (24.3%)	14 (36.8%)	
3	4 (10.8%)	4 (10.6%)	
Number of stents per lesion	1.11 ± 0.3	1.28 ± 0.5	0.14
1	44 (89.8%)	36 (76.6%)	
2	5 (10.2%)	9 (19.1%)	
3	0 (-)	2 (4.3%)	
Total stent length per patient (mm)	33.4 ± 18.2	36.9 ± 17.6	0.39
Range	8-79	18-89	
Total stent length per lesion (mm)	25.2 ± 11.9	29.9 ± 15.6	0.11
Range	8-66	8-89	
Use of distal protection device per lesion	41 (83.7%)	37 (78.7%)	0.53
Median [IQR] time of occlusion with distal protection balloon (sec)	140 [120-168]	165 [130-260]	0.08
Successful direct stenting	44 (89.8%)	44 (93.6%)	0.50
Post-dilatation	7 (14.3%)	14 (29.8%)	0.09
Stent length (mm)	22.9 ± 8.0	23.4 ± 7.0	0.28
Stent diameter (mm)	3.36 ± 0.26	3.41 ± 0.19	0.72
Maximal balloon diameter (mm)	3.44 ± 0.38	3.56 ± 0.37	0.09
Maximal inflation pressure (atm)	18.8 ± 2.2	18.7 ± 2.8	0.85

Data are presented as numbers (percentages) or means ± standard deviation, unless otherwise specified. * Degenerated saphenous vein grafts are defined as grafts with luminal irregularities involving >50% of their total length. BMS: bare metal stent; IQR: interquartile range; SES: sirolimus-eluting stent; TIMI: Thrombolysis In Myocardial Infarction.

6-month angiographic and IVUS outcomes

None of the patients was lost to follow up. At 6 months, 3 SES patients did not receive angiographic follow up. An 83-year-old diabetic man died 5 months after the procedure because of severe progressive cardiac failure. The other 2 patients refused the control angiography. Both were completely symptom-free and without inducible

ischemia at the 6-month clinical visit. Thus, 6-month angiography was performed in 37 (100%) BMS patients and in 35 (92%) SES patients (p=0.24). IVUS analysis was performed in 59 patients (81.9% of all the patients receiving angiographic follow up). Overall, 39 lesions were analyzed in the BMS group, while 34 lesions were analyzed in the SES group (p=0.40). Reasons for lack of IVUS follow up in 13 patients included: occlusive or sub-occlusive in-stent restenosis that prevented a safe passage of the IVUS probe or poor trackability of the IVUS probe in the SVG due to the tortuosity of vessel itself. Patients' demographics were not different between those patients with versus without IVUS at follow up.

Angiographic and IVUS data are presented in table 2. The primary end point of the study, lesion-based in-stent late loss reduction, was met. Also the linear regression analysis showed that the only adjusted predictor of in-stent late loss remained the type of stent used (p=0.001). Accordingly, SES showed a significant reduction in all other secondary angiographic and IVUS end points on a per-lesion analysis. The RR of in-stent or in-segment restenosis occurrence after SES versus BMS was 0.37 (95% CI: 0.15-0.97) and 0.42 (95% CI: 0.18-0.97), respectively. Among the 6 in-segment binary restenoses after SES, 1 occurred in the distal edge, while the others were in-stent. Five out of 6 were focal (83.3%), one was diffuse (16.7%). No SES-restenotic occlusion was detected. Four restenoses (66%) occurred when multiple SES were deployed to cover one lesion. All the 16 in-segment binary restenoses after BMS were in-stent, apart form one that occurred in the proximal edge. After BMS implantation, most restenoses (62.5%) had a non focal pattern: 7 diffuse (43.8%), 1 proliferative (6.3%) and 2 occlusive (12.5%).

Table 2. Quantitative coronary angiography and intravascular ultrasound volumetric analysis of the lesions treated in the two groups.

	BMS	SES	P-value
Quantitative coronary angiography			
Pre-procedure	(n=49)	(n=47)	
Reference vessel diameter (mm)	3.34 ± 0.72	3.28 ± 0.57	0.63
Minimal luminal diameter (mm)	1.14 ± 0.51	1.05 ± 0.51	0.35
Diameter stenosis (%)	66 ± 13	68 ± 13	0.33
Lesion Length (mm)	16.2 ± 9	18.6 ± 11	0.27
Post-procedure	(n=49)	(n=47)	
In-segment			
Minimal luminal diameter (mm)	2.60 ± 0.54	2.76 ± 0.51	0.15
Diameter stenosis (%)	16 ± 8	17 ± 6	0.37
Proximal edge			
Minimal luminal diameter (mm)	3.08 ± 0.61	3.29 ± 0.60	0.08
Diameter stenosis (%)	7 ± 7	6 ± 8	0.48
In-stent			
Minimal luminal diameter (mm)	2.77 ± 0.44	2.88 ± 0.42	0.18
Diameter stenosis (%)	12 ± 11	14 ± 7	0.12
Acute gain (mm)	1.62 ± 0.58	1.83 ± 0.53	0.06
Distal edge			
Minimal luminal diameter (mm)	2.83 ± 0.71	2.99 ± 0.68	0.26
Diameter stenosis (%)	8 ± 10	9 ± 11	0.58
Follow up	(n=49)	(n=44)	
In-segment			
Minimal luminal diameter (mm)	1.90 ± 0.87	2.33 ± 0.68	0.010
Diameter stenosis (%)	39 ± 23	28 ± 16	0.008
Proximal edge			
Minimal luminal diameter (mm)	2.91 ± 0.79	3.10 ± 0.68	0.21
Diameter stenosis (%)	10 ± 12	10 ± 10	0.83
In-stent			
Minimal luminal diameter (mm)	1.97 ± 0.89	2.49 ± 0.67	0.002
Diameter stenosis (%)	38 ± 23	23 ± 18	0.001
Distal edge			
Minimal luminal diameter (mm)	2.59 ± 0.82	2.79 ± 0.71	0.22
Diameter stenosis (%)	13 ± 16	13 ± 13	0.99
Late loss (mm)			
In-segment	0.70 ± 0.61	0.40 ± 0.51	0.015
Proximal edge	0.17 ± 0.55	0.17 ± 0.48	0.97
In-stent	0.79 ± 0.66	0.38 ± 0.51	0.001
Distal edge	0.24 ± 0.50	0.19 ± 0.51	0.61
Binary angiographic restenosis			
In-stent	15 (30.6%)	5 (11.3%)	0.024
In-segment	16 (32.6%)	6 (13.6%)	0.031
Intravascular ultrasound volumetric analysis			
Follow up	(n=39)	(n=34)	
Stent length (mm)	21.2 [17.1-30.9]	23.4 [18.8-31.6]	0.14
Stent volume (mm^3)	211 [143-282]	214 [174-325]	0.23
Lumen volume (mm^3)	175 [125-243]	205 [174-310]	0.023
Neointimal volume (mm^3)	24 [8-34]	1 [0-13]	<0.001

Data are presented as numbers (percentages), means ± standard deviation, or medians [interquartile range]. BMS: bare metal stent; SES: sirolimus-eluting stent.

In-hospital, 1-month and 6-month clinical outcomes

Clinical events are presented in table 3. No deaths or urgent revascularizations occurred during hospitalization. The rate of major periprocedural MI was 4%, while minor myocardial damage occurred in 17.3% of the patients, without differences between BMS and SES patients (see table 3 for details). Between the end of the hospitalization and the first month after treatment no further events were recorded. After 35 days, 1 MI occurred in a SES patient, due to the occlusion of a vein graft different from the one treated in the index procedure. After 5 months a SES patient died, as previously described. The rates of TLR and TVR (all ischemia-driven PCI, namely PCI performed because of anginal complains or evidence of myocardial ischemia at exercise or pharmacological stress test) were significantly reduced after SES with respect to BMS: 5.3% vs. 21.6% (p=0.047) and 5.3% vs. 27% (p=0.012), respectively. The RR for TLR was 0.24 (95% CI: 0.05-1.0), while for TVR it was 0.19 (95% CI: 0.05-0.83). Number-needed-to-treat calculation showed that assigning 6 (3-175) patients to SES prevents a TLR with respect to BMS. Moreover, 5 (2-19) patients should be treated with SES to prevent a TVR. All TVR occurred at 6 months apart from 2 in the BMS group (one at 2 months and one at 4 months), furthermore 2 BMS patients underwent TLR in 2 lesions each. Indeed, on a per-lesion analysis the RR of TLR was 0.21 (95% CI: 0.05-0.90). Cumulative MACE rate was not different between the 2 groups. No stent thrombosis was recorded.

Table 3. In-hospital, 30-days and 6-month clinical events in the two groups.

	BMS (n=37)	SES (n=38)	P-value
In-hospital			
Death	0	0	
Repeat revascularization	0	0	
Major periprocedural myocardial infarction	1 (2.7%)	2 (5.3%)	0.99*
Minor periprocedural myocardial damage	4 (10.8%)	9 (23.7%)	0.14
Median cardiac troponin I rise (ng/dl) [range]	4.71 [0.43-5.33]	2.18 [0.54-9.01]	0.82
From discharge to 30-days			
Death	0	0	
Repeat revascularization	0	0	
Myocardial infarction	0	0	
Between 1 and 6 months			
Death	0	1 (2.6%)	0.99*
Myocardial infarction	0	1 (2.6%)	0.99*
TLR (per-patient)	8 (21.6%)	2 (5.3%)	0.047*
TVR (per-patient)	10 (27%)	2 (5.3%)	0.012*
Cumulative 6-month MACE	11 (29.7%)	6 (15.8%)	0.15
TVF (per-patient)	11 (29.7%)	5 (13.2%)	0.08
TLR (per-lesion)	10/49 (20.4%)	2/47 (4.3%)	0.017
TVR (per lesion)	12/49 (24.5%)	2/47 (4.3%)	0.005
TVF (per-lesion)	13/49 (26.5%)	5/47 (10.6%)	0.046

Data are presented as numbers (percentages), unless otherwise specified. * Fisher's exact test. BMS: bare metal stent; SES: sirolimus-eluting stent; MACE: major adverse cardiac events (death, any major myocardial infarction and TVR); TLR: target lesion revascularization; TVF: target vessel failure (cardiac death, target vessel-related myocardial infarction, TVR); TVR: target vessel revascularization.

DISCUSSION

Recurrent angina after coronary artery bypass surgery is a common clinical problem. Within 10 years after the operation, half of all SVGs are totally occluded or have severe atherosclerotic disease (2). Although the implantation of BMS is the actual

percutaneous strategy to treat patients with SVG lesions, the incidence of angiographic restenosis and repeated revascularization remains high (5,7,19). Implantation of SES has the potential to become the new therapeutic approach (19,20), but there has been no prospective comparison of BMS and SES in SVGs.

Our study is the first randomized comparison of SES versus BMS in patients with diseased SVGs. Our data show that in this challenging setting SES effectively reduce late lumen loss when compared to BMS. Late lumen loss has been extensively used in interventional cardiology trials as a reliable end point for two reasons. First, late lumen loss is a surrogate for in-stent neointimal hyperplasia (which is the pathological process that can lead to in-stent restenosis) (33). Accordingly, our IVUS data demonstrate that SES efficiently inhibit neointimal hyperplasia in SVG: a complete absence of neointimal growth was evident in 47% of the SES lesions versus only 2.5% of the BMS lesions. Second, recent data have shown that late lumen loss is a robust parameter to compare different types of stents and to predict binary angiographic and clinical differences (33,34). Although our study was underpowered to assess clinical end points, the beneficial angiographic and IVUS outcomes translated into a significant advantage in terms of binary restenosis, TLR and TVR. This suggests a clinical benefit for SES over BMS also in diseased SVGs, mainly for a reduced revascularization procedure rate. The finding of relative risk reductions of around 60% for restenosis and of around 80% for repeated revascularization further substantiates this benefit, as these values compare well with those obtained in trials performed in native coronary arteries (8-16).

Our trial is the first randomized study to date performed in de novo SVG lesions to show a significant angiographic benefit. Neither the pivotal Saphenous Vein De novo trial nor the recent Venestent trial were able to show a significant reduction in binary angiographic restenosis (which was the primary end point of both studies) of BMS versus balloon angioplasty (5,6). Furthermore, in these two trials the late loss of BMS was comparable to that of balloon angioplasty, if not worse. Other devices have been recently tested in diseased SVG, with disappointing results (35,36). Membrane-covered stents have been proposed as new option to reduce the restenotic process (35), but results from several randomized trials failed to show a significant benefit over standard BMS (36-38). In percutaneous SVG treatment, only the WRIST SVG

study showed a significant reduction of all the angiographic and clinical end points adding radiation therapy to conventional treatment (39). However, this trial assessed only in-stent restenotic SVG lesions, thus its results can not be extrapolated to de novo SVG lesions.

External validity

Several issues remain to be evaluated. First, the possible risk of late stent thrombosis, that has been already shown for native coronary arteries (40,41), should be considered also in a potentially favorable milieu such as SVG. Indeed, plaques in SVGs are lipid-rich, soft and more prone to rupture than plaques in native coronary arteries (42). Additionally, the histopathology of SVG after stent implantation is a mixture of cellular hyperplasia, progression of atherosclerosis, local inflammatory reaction to metallic stent struts and thrombosis (43,44). Second, longer term outcomes may be compromised also by late SES restenosis, a phenomenon that was recently described in native coronary arteries (45) and that can be potentially exacerbated by the specific pathology of SVGs. Finally, due to the exclusion criteria of our trial, our data do not apply to large SVG (with RVD >4.0 mm), to in-stent restenotic lesions, to occluded vein grafts, to lesions localized in the distal vein graft anastomosis and to patients treated for acute MI related to a sudden SVG occlusion.

Limitations

The main limitations of our study are inherent to the mono-centric design and the small sample size, which was underpowered for major clinical end points and lead to broad confidence intervals for the assessment of the relative risks and the number needed to treat for repeated revascularization procedures. Therefore, the possible existence of type I (alpha) or II (beta) error for all the secondary end points should not be dismissed. In particular, the rate of periprocedural myocardial damage (as assessed by troponin elevation) was more than double after SES, despite this increase was non significant.

In light of the non definitive clinical results of this trial, we welcome future larger trials, with a multi-center design, to unquestionably show a clinical benefit of SES in SVG with respect to BMS. In particular, these trials should mainly focus on potentially harmful events, such as late restenosis and stent thrombosis.

Conclusions

Our study has shown that, in diseased SVGs, SES significantly reduce 6-month angiographic late lumen loss as opposed to BMS. This is associated with a reduction in binary restenosis rate and repeated target lesion and target vessel revascularization procedures.

ACKNOWLEDGMENT

Participating RRISC (Reduction of Restenosis In Saphenous vein grafts with Cypher™ sirolimus-eluting stent) Investigators:

Steering Committee: Paul Vermeersch, MD (principal investigator); Stefan Verheye, MD, PhD; Glenn Van Langenhove, MD, PhD.

Data Monitoring: Christine Jacobs, RN; Nancy Aerts, RN; Anne-Rose Gustin (BVBA Incubate, Cardiac Solutions).

Clinical Events Adjudication Committee: Giuseppe M. Sangiorgi, MD; Giuseppe G.L. Biondi-Zoccai, MD.

Angiographic Data Evaluation Committee: Pierfrancesco Agostoni, MD.

Intravascular ultrasound Evaluation Committee: Nico Bruining, PhD.

Statistical Analysis: Glenn Van Langenhove, MD, PhD; Pierfrancesco Agostoni, MD.

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3

Intravascular ultrasound comparison of sirolimus-eluting stent versus bare metal stent implantation in diseased saphenous vein grafts (from the RRISC [Reduction of Restenosis In Saphenous vein grafts with Cypher sirolimus-eluting stent] trial).

Pierfrancesco Agostoni, Paul Vermeersch, Oscar Semeraro, Stefan Verheye, Glenn Van Langenhove, Paul Van den Heuvel, Carl Convens, Frank Van den Branden, Nico Bruining.

Antwerp Cardiovascular Institute Middelheim, AZ Middelheim, Antwerp, Belgium and Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands

Published in the *American Journal of Cardiology* 2007;100:52-58.

ABSTRACT

The randomized Reduction of Restenosis In Saphenous vein grafts with Cypher sirolimus-eluting stent (SES) trial aimed at comparing angiographic outcomes of SES versus bare metal stents (BMS) in saphenous vein grafts (SVG). Using intravascular ultrasound (IVUS), performed during 6-month follow-up angiography, we compared the vascular effects of the 2 types of stent on SVG. Among 75 patients (96 lesions) included, 59 patients underwent IVUS in 61 SVG: 29 patients received 40 SES for 34 lesions, while 30 patients received 42 BMS for 39 lesions. IVUS parameters (diameters, areas, volumes) were compared in the two groups. A specific analysis was performed for overlapping SES. Median neointimal volume was 1.3 mm^3 [interquartile range: 0-13.1] in SES versus 24.5 [7.8-39.5]in BMS ($p<0.001$). Minimal incomplete stent apposition was detected only at 3 stent edges (2BMS, 1 SES) next to ectatic regions of the SVG. As compared to single SES, overlapping SES showed significant increase of the neointimal reaction, with a neointimal volume/mm stent of 0.6 mm^3/mm [0.1-1.8] versus 0 [0-0.4] in single SES ($p=0.03$), and this phenomenon was mainly localized in overlapping SES segments where neointimal volume/mm stent was 1.1 mm^3/mm [0.6-4.4] versus 0 [0-1.3] in non-overlapping segments ($p=0.05$). In conclusion, SES effectively inhibit neointimal hyperplasia volume vs. BMS in diseased vein grafts, without evidence of increased incomplete apposition risk. The neointimal response to overlapping SES layers seems higher than to a single SES layer.

As compared to bare metal stents (BMS), sirolimus-eluting stents (SES) have reduced the occurrence of angiographic restenosis and repeated revascularization in native coronary artery disease (1,2). In the Reduction of Restenosis In Saphenous vein grafts with Cypher SES (RRISC) trial, we have recently shown that the reduction of the restenotic process (as assessed by angiography) after SES versus BMS is maintained also in saphenous vein grafts (SVG) (3). In light of the peculiar pathological process of SVG disease (4,5), and to evaluate the vascular effect of SES implantation on diseased SVG, we aimed in the present study to perform a comprehensive analysis of the intravascular ultrasound (IVUS) findings of the RRISC trial. We focused specifically on the extent and behavior of neointimal hyperplasia (NIH), and on the presence of incomplete stent apposition (ISA).

METHODS

The RRISC is a randomized, double blind, non-industry-sponsored, single center trial. The study was approved by the local Ethics Committee, and its design and main results have been previously described (3). Briefly, patients, with a history of previous coronary artery bypass grafting and with one or more "de novo" target lesions (>50% diameter stenosis by visual estimate) localized in one or more diseased SVG with a reference vessel diameter >2.5 and <4.0 mm were enrolled. Overall, 75 patients with 96 lesions in 80 SVG were included. All enrolled patients provided written informed consent prior to the index procedure. After successful crossing of the target lesion with the guide wire, patients were randomly allocated in a 1:1 ratio to treatment with Cypher SES or BX-Velocity BMS (both from Cordis, Johnson & Johnson, Miami Lakes, FL). Details on the randomization process have been described (3). In case of treatment of more than one lesion the stent type remained the same. In case of dissection or incomplete lesion coverage, the use of additional stents of the same type as the assigned stent was mandated. Aspirin (100-300 mg/day) was given daily and clopidogrel (loading dose of 300 mg, 6 to 48 hours before the procedure and 75 mg/day thereafter) was administered for at least 2 months in all patients. Clinical follow-up was scheduled at 1 and 6 months. Coronary angiography was mandated at

6 months (± 15 days) and a pre-specified IVUS analysis was strongly recommended in every SVG treated with a study stent. IVUS was performed after injection of 0.2 mg of nitroglycerin with a 30 MHz ultrasound probe (Ultracross 2.9F, Boston Scientific Corporation, Natik, MA), connected to the Galaxy ultrasound console (Boston Scientific Corporation), and a motorized pullback (speed: 0.5 mm/sec).

IVUS data were stored on S-VHS videotape. The videotapes were digitized on a computer system, transformed into the DICOM medical image standard and stored on an IVUS Picture Archiving and Communications System. Qualitative and quantitative IVUS analysis was performed by an independent operator (N. Bruining) blinded to treatment allocation. The analysis was executed using a validated software (Curad, version 4.32, Wijk bij Duurstede, The Netherlands), allowing semi-automated detection of luminal and stent boundaries in reconstructed longitudinal planes (L-mode views) (6). Due to catheter motion during the cardiac cycle, non-gated IVUS pullbacks result in a saw-tooth-appearance of the coronary segment on the longitudinal views and thus interfere with the contour detection algorithms used in most IVUS software packages. This phenomenon can also lead to inaccurate measurements. In order to obtain a smooth appearance of the vessel wall structures in the longitudinal views, the Intelligate image-based gating method was applied (7,8). This validated technique eliminates catheter-induced image artifacts by retrospectively selecting end-diastolic frames, thus resulting in more reliable volumetric measurements. Assuming a heart rate of 60 beats per minute and given a pullback speed of 0.5 mm/sec, the Intelligate method selects 2 IVUS frames/mm for data analysis. This method has been expanded by introducing the so-called Intelliview, which shows during the analysis of the end-diastolic L-mode view the corresponding complete cardiac cycle of the IVUS images made at that particular position on a second computer screen. This enhances the capabilities to determine, for the observer, the blood-intima interface with more certainty, which can in some cases be hard to identify on still IVUS images especially when there is a high blood speckling and a relatively echo lucent vessel wall. By detecting the borders of the stent struts and the lumen-intima interface, volumetric quantitative coronary ultrasound analysis was obtained for stent and lumen. The intra- and inter-observer variability of this methodology has been reported (9).

The primary end point of this sub-study was the tri-dimensional NIH volume, computed as the difference between the stent volume and the lumen volume. Secondary IVUS end points included lumen volume and stent volume and all the bi-dimensional data derived from the tri-dimensional reconstruction of the stent-lumen IVUS image, including:

- stent, lumen and NIH indexes defined respectively as stent, lumen and NIH volumes divided by the length of the stent,
- stent, lumen and NIH cross sectional areas and diameters (minimum, maximum and mean),
- percentage area and diameter stenosis (minimum, maximum and mean) defined respectively as the percentage ratio between stent and lumen area and as the percentage ratio between stent and lumen diameter,
- ISA, defined as the presence of at least 1 stent strut clearly separated from the vessel wall with evidence of blood speckling behind it.

A particular focus was put in the analysis of overlapping SES, with supplementary comparisons of the IVUS parameters between lesions treated with overlapping SES and lesions treated with single SES and also between the overlapping part and the non-overlapping part of SES used in the same lesions. No specific investigation for overlapping BMS was performed because the number of lesions treated with overlapping BMS (only 3) was too low to allow a reliable analysis.

No sample size computation was done for this IVUS study as the power analysis was formally performed for the RRISC trial and it was based on angiographic late loss, the primary end point of the trial (3). The IVUS results were analyzed on a per-lesion and a per-stent basis. Continuous data are expressed as means ± standard deviations or as medians [interquartile range] as appropriate, whereas dichotomous data are summarized as frequencies. Parametric Student's *t* or non-parametric Mann Whitney U test (as appropriate) and chi-square or Fisher's exact test (as appropriate) have been employed, respectively, for unpaired continuous and for categorical variables, to analyze differences between the two study arms. In case of paired continuous variables (overlapping versus non-overlapping part of the same SES), the comparison was performed with the non-parametric Wilcoxon signed-rank test. A two-sided p-value <0.05 was considered significant for all tests.

RESULTS

Among the 75 patients (with 96 lesions localized in 80 SVG) enrolled, 59 patients (73 lesions) underwent IVUS analysis at follow up angiography (78.6% of the patients, 76% of the lesions). Reasons for lack of IVUS follow up in 16 patients included: death (1 patient, at 5 months), lack of consent for angiographic follow-up (2 patients), IVUS not attempted because of an occlusive/sub-occlusive in-stent restenosis that prevented a safe passage of the IVUS probe (5 patients) or presumed poor trackability of the IVUS probe in the SVG due to tortuosity of vessel itself (8 patients). Patient demographics were not different between patients with versus without IVUS at follow up. Overall, 30 patients received 42 BMS for 39 lesions in 32 SVG, while 29 patients received 40 SES for 34 lesions in 29 SVG (p=0.40). The 2 groups were well balanced for all the baseline clinical, angiographic and procedural characteristics (Table 1). Among the 15 patients with angiographic in-stent restenosis after BMS implantation, 5 did not undergo IVUS examination: 2 had occlusive restenosis, 1 had proliferative sub-occlusive restenosis and 2 had focal sub-occlusive restenosis. All the 5 patients with in-stent restenosis after SES underwent IVUS.

Table 1. Baseline clinical characteristics of the patients enrolled and angiographic variables of the lesions treated.

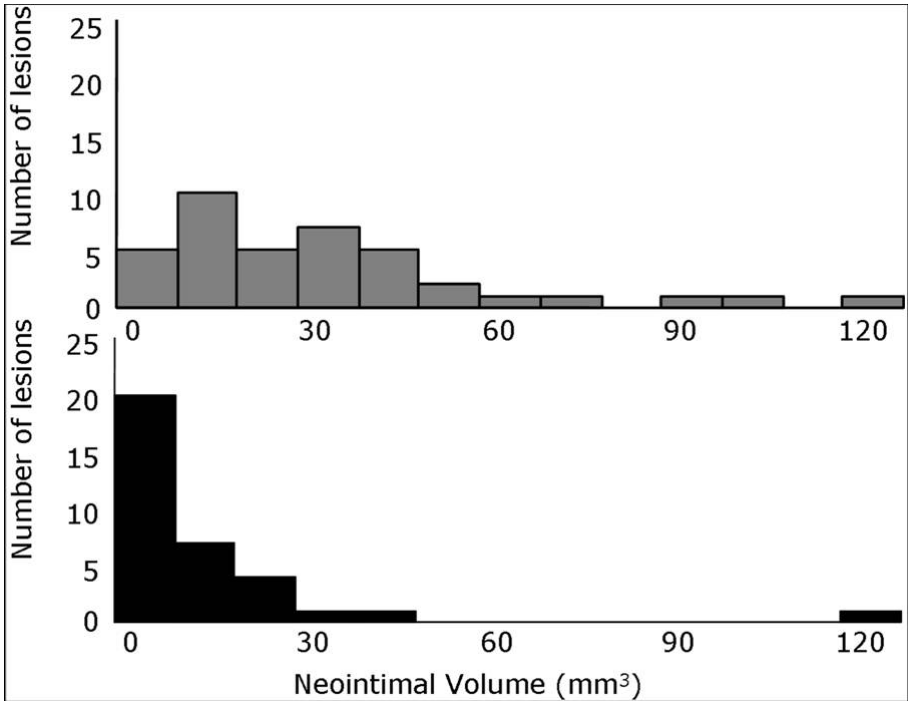
	BMS patients=30 grafts=32 lesions=39 stents=42	SES patients=29 grafts=29 lesions=34 stents=40	P-value
Age (years)	72 ± 8	73 ± 7	0.48
Men	26 (87%)	23 (79%)	0.50
Hypertension	18 (60%)	20 (69%)	0.30
Hypercholesterolemia*	25 (83%)	25 (86%)	0.91
Current smoker	4 (13%)	1 (3%)	0.39
Diabetes Mellitus	5 (17%)	4 (14%)	0.99
Body mass index (Kg/m^2)	26.1 ± 3.6	26.5 ± 3.1	0.67
History of heart failure	4 (13%)	5 (17%)	0.73
Prior myocardial infarction	12 (40%)	13 (45%)	0.79
Prior coronary angioplasty	12 (40%)	8 (28%)	0.41
Unstable angina pectoris	15 (50%)	17 (59%)	0.62
Ejection Fraction (%)	73 ± 12	66 ± 19	0.15
Age of the grafts (years)	13.0 ± 6.0	12.8 ± 4.7	0.88

Number of grafts treated per patient			0.49
1	28 (93%)	29 (100%)	
2	2 (7%)	0 (-)	
Degenerated saphenous vein grafts	12 (37%)	11 (38%)	0.99
Number of lesions treated per patient			0.50
1	22 (74%)	24 (83%)	
2	7 (23%)	5 (17%)	
3	1 (3%)	0 (-)	
Recipient native coronary vessel territory			0.12
Left anterior descending/diagonal	5 (13%)	4 (12%)	
Circumflex/obtuse marginal	20 (51%)	10 (29%)	
Right	14 (36%)	20 (59%)	
Lesion location in the graft			0.53
Aorto-Ostial	8 (20%)	7 (21%)	
Proximal	10 (26%)	8 (23%)	
Mid	12 (31%)	15 (44%)	
Distal	9 (23%)	4 (12%)	
Angiographic evidence/suspect of thrombus	9 (23%)	12 (35%)	0.30
Moderately/heavily calcified lesions	7 (18%)	6 (18%)	0.99
TIMI flow pre-procedure			0.98
1	1 (3%)	1 (3%)	
2	2 (5%)	2 (6%)	
3	36 (92%)	31 (91%)	
Number of stents per patient			0.75
1	21 (70%)	20 (69%)	
2	6 (20%)	7 (24%)	
3	3 (10%)	2 (7%)	
Number of stents per lesion			0.34
1	36 (92%)	29 (85%)	
2	3 (8%)	4 (12%)	
3	0 (-)	1 (3%)	
Total stent length per patient (mm)	31.6 ± 17.1	34.9 ± 15.6	0.44
Range	8-66	18-74	
Total stent length per lesion (mm)	23.0 ± 9.8	27.8 ± 12.6	0.07
Range	8-56	13-61	
Use of distal protection device per lesion	34 (87%)	28 (82%)	0.74
Successful direct stenting	37 (95%)	33 (97%)	0.99
Post-dilatation	6 (15%)	7 (21%)	0.76
Stent length (mm)	21.3 ±7.9	23.0 ± 6.8	0.31
Stent diameter (mm)	3.38 ± 0.27	3.41 ± 0.19	0.54
Maximal balloon diameter (mm)	3.47 ± 0.40	3.52 ± 0.36	0.59
Maximal inflation pressure (atm)	19.1 ± 1.8	18.4 ± 3.1	0.25

* Hypercholesterolemia: total cholesterol >200 mg/dL or known statin therapy. Data are presented as means ± standard deviations or numbers (percentages), unless otherwise specified. BMS: bare metal stent, SES: sirolimus-eluting stent.

The IVUS results are presented in Table 2 and Figure 1. As evident, SES determined a significant reduction of NIH volume when compared to BMS and consistently reduced all the other bi-dimensional parameters indicative of neointimal proliferation (maximum NIH area and diameter, maximum percentage area and percentage diameter stenosis), without significant differences in stent dimensions, thus leading to larger lumen diameters, areas and volume. Lack of NIH volume was evident in 47% SES versus 2.5% BMS lesions ($p<0.001$). NIH volume <30 mm^3, NIH volume between 30 and 60 mm^3, NIH volume >60 mm^3 were respectively 47%, 3% and 3% after SES, versus 56.5%, 28% and 13% after BMS (p for trend <0.001).

Figure 1.



Distribution of the degree of neointimal hyperplasia volume in bare metal stents (top graph, gray bars) and in sirolimus eluting stents (bottom graph, black bars).

Table 2. Intravascular ultrasound tri-dimensional and bi-dimensional parameters evaluated in lesions treated with bare metal stents versus those treated with sirolimus-eluting stents.

	BMS lesions=39	SES lesions=34	P-value
Stent length (mm)	21.2 [17.1-31.0]	23.4 [18.8-31.6]	0.13
Luminal volume (mm^3)	175.2 [124.9-243.3]	205.0 [174.3-310.6]	0.02
Stent volume (mm^3)	211.3 [142.7-282.3]	214.8 [174.6-325.2]	0.23
NIH volume (mm^3)	24.5 [7.8-39.5]	1.3 [0-13.1]	<0.001
Mean lumen area (mm^2)	7.5 [5.8-10.7]	9.4 [8.2-10.7]	0.13
Maximum lumen area (mm^2)	10.8 [8.6-13.9]	11.4 [9.6-12.4]	0.63
Minimum lumen area (mm^2)	5.3 [3.9-8.0]	7.2 [5.7-8.7]	0.02
Mean stent area (mm^2)	9.2 [7.4-11.1]	9.6 [8.4-11.0]	0.82
Maximum stent area (mm^2)	10.8 [8.9-14.6]	11.7 [10.0-12.5]	0.93
Minimum stent area (mm^2)	7.8 [6.0-9.0]	8.4 [6.9-9.4]	0.41
Mean NIH area (mm^2)	0.9 [0.4-2.0]	0.1 [0-0.5]	<0.001
Maximum NIH area (mm^2)	3.1 [2.0-4.5]	0.4 [0-2.4]	<0.001
Minimum NIH area (mm^2)	0 [0-0]	0 [0-0]	0.10
Mean area stenosis (%)	10.0 [4.1-21.2]	0.8 [0-5.8]	<0.001
Maximum area stenosis (%)	32.6 [17.8-47.4]	5.3 [0-23.0]	<0.001
Minimum area stenosis (%)	0 [0-0]	0 [0-0]	0.10
Mean luminal diameter (mm)	3.1 [2.7-3.7]	3.4 [3.2-3.7]	0.12
Maximum luminal diameter (mm)	3.7 [3.3-4.2]	3.8 [3.5-4.0]	0.6
Minimum luminal diameter (mm)	2.6 [2.2-3.2]	3.0 [2.7-3.3]	0.02
Mean stent diameter (mm)	3.4 [3.1-3.8]	3.5 [3.3-3.7]	0.80
Maximum stent diameter (mm)	3.7 [3.4-4.3]	3.9 [3.6-4.0]	0.93
Minimum stent diameter (mm)	3.2 [3.0-3.4]	3.3 [3.0-3.5]	0.40
Mean NIH diameter (mm)	0.2 [0.1-0.4]	0 [0-0.1]	<0.001
Maximum NIH diameter (mm)	0.6 [0.4-1.0]	0.1 [0-0.4]	<0.001
Minimum NIH diameter (mm)	0 [0-0]	0 [0-0]	0.04
Mean diameter stenosis (%)	5.4 [2.0-11.4]	0.4 [0-2.7]	<0.001
Maximum diameter stenosis (%)	17.9 [9.1-27.4]	2.6 [0-12.0]	<0.001
Minimum diameter stenosis (%)	0 [0-0]	0 [0-0]	0.04
Projected mean MLD (mm)	3.0 [2.6-3.5]	3.3 [3.0-3.5]	0.09
Projected maximum MLD (mm)	3.5 [3.0-3.9]	3.6 [3.4-3.8]	0.56
Projected minimum MLD (mm)	2.4 [2.0-3.0]	2.7 [2.5-3.1]	0.03

Data are presented as medians [interquartile ranges]. BMS: bare metal stent, MLD: minimal luminal diameter, NIH: neointimal hyperplasia, SES: sirolimus-eluting stent.

Incomplete stent apposition was never documented in the body of the stent. Three cases (4.1% of the lesions treated) of very short and focal ISA were detected: 2 after BMS (5.1%) and 1 after SES deployment (2.9%). All occurred at the very proximal or very distal edge of the stent and in all cases the stent was positioned just next to an ectatic segment of the SVG treated. Thus, they all occurred at the "boundary" between the end or the beginning of the ectatic vessel wall and, respectively, the beginning or the end of the stent itself.

In the SES group, 5 lesions were treated with overlapping stents: 4 lesions received 2 SES each, while 1 lesion received 3 SES. Thus, in total 11 stents were put in overlap and the overlapping segments were 6. The comparison of the IVUS findings between overlapping and single SES is shown in Table 3. While stent dimensions remained similar (apart from length, longer for overlapping stents), a significant increase of the neointimal response in overlapping stents was noted. We further evaluated the overlapping segments versus the non overlapping segments of the SES used for the same lesions. Tri-dimensional IVUS results are shown in Table 4: interestingly, the degree of NIH volume per mm of stent was significantly higher in the overlapping part of the SES, suggesting an augmented neointimal reaction localized where 2 SES layers were present.

Table 3. Intravascular ultrasound tri-dimensional and bi-dimensional parameters evaluated in lesions treated with single SES versus those treated with overlapping SES.

	Single SES lesions=29; stents=29	Overlapping SES lesions=5; stents=11	P-value
Stent length (mm)	22.5 [18.3-25.9]	48.6 [32.6-50.0]	<0.001
Luminal volume (mm^3)	193.4 [169.6-266.8]	399.2 [278.4-465.6]	0.005
Stent volume (mm^3)	193.4 [173.5-276.1]	450.9 [294.4-513.2]	0.004
NIH volume (mm^3)	0 [0-9.7]	29.0 [1.7-83.3]	0.015
Lumen volume index (mm^3/mm)	9.4 [8.2-10.8]	9.0 [7.0-11.2]	0.68
Stent volume index (mm^3/mm)	9.5 [8.4-11.0]	9.7 [7.8-12.2]	0.83
NIH volume index (mm^3/mm)	0 [0-0.4]	0.6 [0.1-1.8]	0.03
Mean lumen area (mm^2)	9.4 [8.3-10.8]	8.6 [7.0-10.7]	0.48
Maximum lumen area (mm^2)	11.7 [9.5-12.5]	10.9 [8.7-13.1]	0.58
Minimum lumen area (mm^2)	8.0 [6.1-9.1]	5.6 [3.8-6.4]	0.02
Mean stent area (mm^2)	9.5 [8.3-11.0]	9.7 [7.7-12.0]	0.94
Maximum stent area (mm^2)	11.7 [9.9-12.5]	11.6 [8.9-13.7]	0.75
Minimum stent area (mm^2)	8.5 [7.0-9.5]	7.0 [5.7-10.2]	0.71
Mean NIH area (mm^2)	0 [0-0.4]	0.6 [0.1-2.1]	0.02
Maximum NIH area (mm^2)	0 [0-1.9]	2.6 [0.8-6.4]	0.02
Minimum NIH area (mm^2)	0 [0-0]	0 [0-0.1]	0.14
Mean area stenosis (%)	0 [0-5.1]	9.8 [1.7-18.7]	0.01
Maximum area stenosis (%)	0 [0-16.4]	42.2 [10.6-56.0]	0.007
Minimum area stenosis (%)	0 [0-0]	0 [0-0.7]	0.14
Mean luminal diameter (mm)	3.5 [3.2-3.7]	3.3 [3.0-3.7]	0.48
Maximum luminal diameter (mm)	3.9 [3.5-4.0]	3.7 [3.3-4.2]	0.62
Minimum luminal diameter (mm)	3.2 [2.8-3.4]	2.6 [2.2-2.8]	0.02
Mean stent diameter (mm)	3.5 [3.3-3.7]	3.5 [3.1-3.9]	0.90
Maximum stent diameter (mm)	3.9 [3.5-4.0]	3.8 [3.4-4.2]	0.73
Minimum stent diameter (mm)	3.3 [3.0-3.5]	3.0 [2.7-3.6]	0.73
Mean NIH diameter (mm)	0 [0-0.1]	0.1 [0-0.4]	0.02
Maximum NIH diameter (mm)	0 [0-0.3]	0.7 [0.2-1.3]	0.01
Minimum NIH diameter (mm)	0 [0-0]	0 [0-0]	0.02
Mean diameter stenosis (%)	0 [0-2.4]	5.0 [0.9-10.5]	0.02
Maximum diameter stenosis (%)	0 [0-8.3]	23.8 [5.5-33.7]	0.007
Minimum diameter stenosis (%)	0 [0-0]	0 [0-0.3]	0.02
Projected mean MLD (mm)	3.3 [3.0-3.5]	3.2 [2.8-3.5]	0.51
Projected maximum MLD (mm)	3.7 [3.4-3.8]	3.6 [3.2-4.0]	0.63
Projected minimum MLD (mm)	2.8 [2.5-3.2]	2.5 [2.0-2.6]	0.02

Data are presented as medians [interquartile ranges]. MLD: minimal luminal diameter, NIH: neointimal hyperplasia, SES: sirolimus-eluting stent.

Table 4. Intravascular ultrasound tri-dimensional parameters evaluated in the non-overlapping segment versus the overlapping segment of overlapping sirolimus-eluting stents.

	Non overlapping SES segment (n=11)	Overlapping SES segment (n=6)	p-value
Region length (mm)	17.8 [12.4-20.2]	2.8 [1.7-6.8]	0.005
Luminal volume (mm^3)	148.8 [107.0-234.4]	19.6 [13.7-52.2]	0.003
Stent volume (mm^3)	148.8 [122.2-258.8]	26.5 [18.4-59.5]	0.005
NIH volume (mm^3)	0.3 [0-23.6]	6.5 [2.1-9.5]	0.61
Lumen volume index (mm^3/mm)	9.4 [7.7-12.2]	6.9 [6.0-9.3]	0.16
Stent volume index (mm^3/mm)	9.8 [7.8-12.0]	10.4 [7.3-11.4]	0.99
NIH volume index (mm^3/mm)	0 [0-1.3]	1.1 [0.6-4.4]	0.05

Data are presented as medians [interquartile ranges]. NIH: neointimal hyperplasia, SES: sirolimus-eluting stent.

DISCUSSION

This IVUS sub-study of the RRISC trial evaluates the vascular effects of SES versus BMS in diseased SVG. The main findings are the following: 1) SVG lesions treated with SES showed a marked reduction of NIH as compared to lesions treated with BMS, 2) overlapping SES layers produced an increased neointimal reaction than single SES layers in SVG, 3) no evidence of increased incomplete apposition of the stent was noted after SES, and this phenomenon was overall rare and localized only at the stent edges.

SES efficiently inhibit neointimal hyperplasia in SVG: of interest, a complete absence of neointimal growth was evident in 47% of the SES lesions evaluated versus only 2.5% of the BMS lesions. This total lack of neointimal formation in approximately half of the SES analyzed in this trial is consistent with other previous reports. In particular, previous data have already shown that de novo and in-stent restenotic lesions treated with SES did not develop any neointimal hyperplasia at follow-up in half of the cases (10), and the same held true for lesions in diabetic patients (11). Even

more interestingly, in the first series of post-coronary artery bypass surgery patients treated in the USA as part of the SES compassionate use (SECURE) registry, half of the SVG lesions treated with SES showed absence of neointimal hyperplasia at follow up (12). Focusing in particular on the vascular reaction to SES deployment, we observed a greater degree of neointimal formation specifically at overlapping SES segments. Previous IVUS data in native coronary arteries have shown no differences in terms of neointimal hyperplasia between overlapping and single layer SES segments (13). However, angiographic analyses, always performed in native coronary arteries, revealed a potentially increased risk of restenosis exactly at the overlapping SES segment (14,15). Despite our findings derive from a secondary post-hoc analysis and thus must be considered as "hypothesis-generating", they are at odds with the IVUS data in native coronary arteries previously mentioned (13), but in agreement with the angiographic data (14). The findings of our study can be associated to an increased neointimal response to overlapping SES, specifically related to SVG. Indeed, in this lesion subset, it is possible that the increased quantity of metal and/or of polymer deployed leads to a more pronounced inflammatory and neointimal reaction, that can outweigh the double dose of sirolimus present. In particular, all biocompatible polymers are associated with some degree of inflammatory reaction and data from animal models have shown a more pronounced inflammatory response after polymer stent implantation with a high polymer mass versus low polymer mass (16,17). These data suggest a potentially increased inflammatory reaction which can be related to the amount of polymer, and can be relevant in case of SES overlap. In any case our study, along with the others previously mentioned (13-15), confirmed the lack of toxicity of multiple SES layers on the vessel wall.

Incomplete apposition of the stent to the vessel wall at follow-up was an infrequent event and not different between the 2 types of stent. It never occurred in the body of the stent but only at the edges in proximity of ectatic SVG segments. Our IVUS data have the intrinsic inability to describe whether malapposition was already present after stent deployment or developed at follow-up, as no serial IVUS assessment was done. However the proximity with ectatic SVG regions let us presume that this minimal malapposition was already present immediately after stent deployment. The absence of malapposition in the body of the stents is extremely remarkable,

particularly in a specific lesion subset such as SVG, known to develop plaques that are richer in lipids, softer and more prone to embolize and to develop thrombosis than those in native coronary arteries (18). A potential explanation for this finding can be related to our stent deployment strategy. Some authorities have suggested that stent deployment in SVG should follow 2 rules: slight undersizing of the stent and low pressure inflations (19). These technical measures may avoid plaque dislodgement and distal embolization, events that can lead to periprocedural complications, and may "entrap" the plaque between the vessel wall and the stent without squeezing it out (19). At odds with these hints (proposed, in fact, before the routine use of distal protection devices), we always deployed stents with a stent/artery ratio >1 and high pressure inflations (the mean deployment pressure was >18 atm in this cohort of patients), and with non compliant balloon post-dilatation, if needed (around 18%). Actually, the low rate of periprocedural adverse events in our trial (only 4% myocardial infarctions) confirmed the feasibility of our approach (3).

There are limitations in our study. First, the sample size of the lesions analyzed with IVUS is small. Second, IVUS evaluation was performed at a single time point, while serial IVUS assessment is considered the actual gold standard for an optimal measurement of stent performance. Indeed, in the RRISC trial IVUS was only performed at follow-up, but not immediately after stent deployment, thus losing the possibility to compare post-procedural immediate and long-term results.

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4

Increased late mortality after sirolimus-eluting stents versus bare metal stents in diseased saphenous vein grafts: results from the randomized DELAYED RRISC trial.

Paul Vermeersch,* Pierfrancesco Agostoni,* Stefan Verheye, Paul Van den Heuvel, Carl Convens, Frank Van den Branden, Glenn Van Langenhove; the DELAYED RRISC (Death and Events at Long-term follow up AnalYsis: Extended Duration of the Reduction of Restenosis In Saphenous vein grafts with Cypher stent) investigators.

Antwerp Cardiovascular Institute Middelheim, AZ Middelheim, Antwerp, Belgium

* Drs. Agostoni and Vermeersch contributed equally to this work.

Published in the *Journal of the American College of Cardiology* 2007; 50:261-267.

ABSTRACT

Objectives: To provide long-term follow-up data of sirolimus-eluting stents (SES) versus bare metal stents (BMS) in saphenous vein grafts (SVG), from the "Reduction of Restenosis In Saphenous vein grafts with Cypher" (RRISC) trial.

Background: We have previously shown that in SVG, SES reduce 6-month restenosis and repeated revascularization procedures versus BMS. These data are consistent with trials in native coronary arteries. However, recently published long-term follow-up data of these trials have revealed an increased risk of adverse events (particularly, very late stent thrombosis) after SES.

Methods: 75 patients with 96 SVG lesions were randomized to SES versus BMS. All patients underwent clinical follow-up up to 3 years. Specific outcomes assessed in this secondary post-hoc analysis were all-cause mortality, myocardial infarction and target vessel revascularization.

Results: 38 patients received 60 SES for 47 lesions, while 37 patients received 54 BMS for 49 lesions. At a median follow-up time of 32 months [interquartile range:26.5-36], 11 deaths (7 cardiac, of which 1 due to very late stent thrombosis and 3 sudden) occurred after SES (29% [95% confidence interval: 17-45%]) versus 0 after BMS (0% [0-9%]) with an absolute difference of 29% [14-45%] ($p<0.001$). The rates of myocardial infarction and target vessel revascularization were not different: respectively, 18% and 34% after SES versus 5% and 38% after BMS (respectively $p=0.15$, and $p=0.74$).

Conclusions: In this secondary post-hoc analysis, BMS were associated with lower long-term mortality than SES for SVG disease. Also the 6-month reduction in repeated revascularization procedures with SES was lost at longer-term follow-up.

INTRODUCTION

Sirolimus eluting stents (SES) have been shown to reduce 6-month to 1-year major adverse cardiac events (MACE) as compared to bare metal stents (BMS) in native coronary arteries, mainly by considerably dropping the rate of repeated revascularization procedures caused by the restenotic process in the stent (1-5). Conversely, recent data on long-term (>2 years) clinical follow-up have raised the issue of an increased rate of "hard" end points, such as death and myocardial infarction (MI), after SES, potentially due to an augmented risk of late stent thrombosis (6-10), and to an increase also in non cardiac-related deaths (11).

Despite this large body of evidence, lesions in saphenous vein grafts (SVG) have been poorly represented if not totally excluded in pivotal drug eluting stent trials. However this lesion subset represents a consistent proportion of lesions in which percutaneous procedures are performed, up to 10-15% in most centers (12), and effective and satisfactory therapies are still lacking, as periprocedural complications and long-term events remain elevated (12,13).

We have recently shown that SES are effective in reducing 6-month angiographic and clinical parameters of restenosis with respect to BMS in SVG (14). However, due to the lack of long-term data in patients with this type of lesion and in order to offer additional information to the current debate on the safety of SES, we performed a clinical follow-up evaluation of the patients enrolled in the Reduction of Restenosis In Saphenous vein grafts with Cypher sirolimus-eluting stent (RRISC) trial up to 3 years, focusing specifically on all-cause mortality.

METHODS

The RRISC trial is a randomized study approved by the local Ethics Committee, and its design and main results have been previously described (14). The study was double blind till the moment of primary analysis (14). Blinding was maintained in the follow up period only for patients and referring clinical cardiologists and general practitioners, but not for the interventional cardiologists performing the index procedure and analyzing the data. Thus the current analysis is single blind.

Between September 2003 and November 2004, 75 patients with a history of previous coronary artery bypass surgery and with 96 “de novo” target lesions localized in 80 diseased SVG with a reference vessel diameter >2.5 and <4.0 mm were enrolled. They all provided written informed consent prior to the index procedure.

Patients were randomly allocated in a 1:1 ratio to treatment with Cypher SES or BX-Velocity BMS (both from Cordis, Johnson & Johnson, Miami Lakes, FL). Details on the randomization process have been described (14). Acetylsalicylic acid (100-300 mg/day) was given daily and clopidogrel (loading dose of 300 mg, 6 to 48 hours before the procedure and 75 mg/day thereafter) was administered for at least 2 months in all patients. Prolonged therapy with clopidogrel or ticlopidine (250 mg x 2 times/day) instead of clopidogrel was left to the decision of the physician taking care of the patient (who was also blinded to the type of stent implanted, as previously mentioned). Clinical follow-up was scheduled at 1 and 6 months. Coronary angiography was repeated at 6 months.

Long-term follow-up

In September 2006, we obtained a new Ethics Committee approval to prolong the follow-up duration of the RRISC trial, in order to know directly from the patients their status and the occurrence of further events after the initial 6 months. We mailed an additional informed consent to every patient (or to the relatives), to obtain permission to use their data. Once we received back all the signed informed consents, from November 2006 we contacted by phone every patient and we investigated the occurrence of events such as death, MI, repeated revascularizations, new hospitalizations, and additional ambulatory visits, using a pre-specified questionnaire. In case a positive result for any of the aforementioned events was obtained, we asked the patient (or relatives) to send us the records related to each event. If the patient was hospitalized in our institution, we reviewed our internal clinical records. In case of hospitalization in other hospitals, we formally requested the clinical records of interest. To ascertain survival status, the National Civil Registry was further contacted for final confirmation of the occurred events.

End points and definitions

The new post-hoc main end point of this secondary long-term follow-up analysis was all-cause mortality. Additional end points were MACE rates, which included death, all non-fatal major MI (also periprocedural) and target vessel revascularization (TVR). All deaths were considered cardiac unless a clear non-cardiac cause could be established. Specifically, any unexpected or unwitnessed death was considered of cardiac origin. Periprocedural MI was defined as an elevation of creatine kinase enzyme-MB activity >3 times above the upper limit of normal (16 U/l in our institution). Non-periprocedural MI was defined as a new ischemic event with creatine kinase-MB >2 times the upper limit of normal, or the electrocardiographic presence of new pathological Q-waves. Target lesion revascularization (TLR) was defined as a repeated revascularization procedure (either percutaneous coronary intervention or coronary bypass surgery), due to restenosis in the stented segment. TVR was defined as a new revascularization procedure in the target vessel, including also TLR. Stent thrombosis was defined as early (<30 days), late (<1 year) and very late (>1 year) and as definite, probable or possible. Definite stent thrombosis required an acute coronary ischemic event associated to angiographic or autopsy documentation of partial or total stent occlusion or thrombosis. Probable stent thrombosis included any unexplained death within 30 days after the index procedure and any target vessel MI (also without angiographic documentation) anytime during follow-up. Possible stent thrombosis included any unexplained death occurring >30 days after the index procedure (15). All the clinical events were adjudicated by an independent clinical events committee unaware of the patients' treatment assignment.

Statistical analysis

Continuous data are expressed as means ± standard deviations or as medians [interquartile range] as appropriate, whereas dichotomous data are summarized as frequencies. Parametric Student's *t* or non-parametric Mann Whitney U test (as appropriate) and chi-square or Fisher's exact test (as appropriate) have been employed, respectively, for unpaired continuous and for categorical variables, to analyze differences between the two study arms. Additionally, survival analysis was also graphically represented with the Kaplan-Meyer technique and groups were

compared with the log rank test. A two-sided p-value <0.05 was considered significant for all tests. We also calculated the 95% confidence limits for the single rates found and the 95% confidence intervals (CI) for the absolute differences computed, using the Confidence Interval Analysis software (CIA, version 2.0.0) (16). Number needed to treat/harm with 95% CI (extrapolated from the absolute difference) was computed for the occurrence of dichotomous events. Pierfrancesco Agostoni had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

RESULTS

Among the 75 patients (with 96 lesions localized in 80 SVG) enrolled in the RRISC trial, 38 patients received 60 sirolimus-eluting stents for 47 lesions, while 37 patients received 54 bare metal stents for 49 lesions. The baseline clinical characteristics of the 2 groups are shown in Table 1 and are not different.

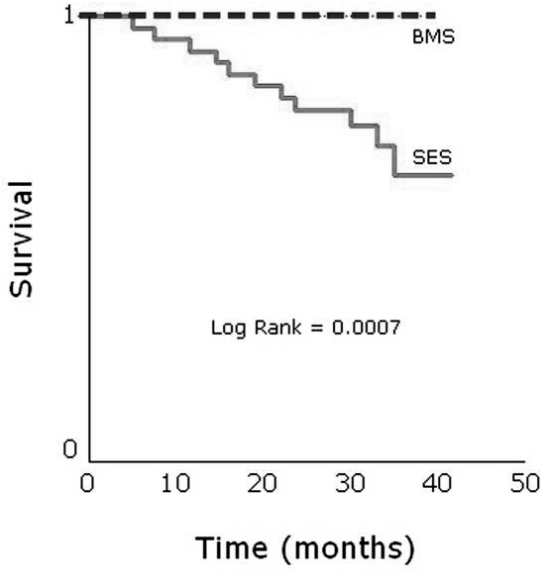
All the patients were contacted between November and December 2006. The median follow-up was not different between the 2 groups: 30.5 months [24-36] for patients treated with SES, versus 32 months [29-35.5] for patients treated with BMS (p=0.24). Death occurred in 11 patients after SES (29% [95% confidence limits: 17-45%]) versus 0 after BMS (0% [0-9%]) with an absolute difference of 29% (95% CI: 14-45 %, p<0.001, figure 1). According to the number needed to harm analysis, in our trial the treatment of 3.4 patients (95% CI: 2.2-7.3) with SES resulted in 1 additional death with respect to treatment with BMS.

Table 1. Baseline clinical and procedural characteristics of the patients in the two groups.

	BMS (n=37)	SES (n=38)	P-value
Age (years)	72 ± 8	73 ± 7	0.36
Men	33 (89%)	31 (82%)	0.36
Risk factors:			
Family history	29 (78%)	25 (66%)	0.23
Hypertension	21 (57%)	22 (58%)	0.84
Hypercholesterolemia	31 (84%)	33 (87%)	0.74
Current smoker	4 (11%)	2 (5%)	0.46
Diabetes Mellitus	5 (14%)	6 (16%)	0.78
Body mass index (Kg/m^2)	26.4 ± 3.9	26.4 ± 3.1	0.97
History of heart failure	7 (19%)	6 (16%)	0.72
Prior myocardial infarction	15 (41%)	17 (45%)	0.71
Prior coronary angioplasty	15 (41%)	12 (32%)	0.42
Unstable angina pectoris	19 (51%)	23 (60%)	0.41
Ejection Fraction (%)	72 ± 12	68 ± 18	0.37
Age of the grafts	12.6 ± 5.9	12.4 ± 4.6	0.92
Number of vein graft lesions treated per patient			0.55
1	26 (70%)	29 (76%)	
2	10 (27%)	9 (24%)	
3	1 (3%)	0 (-)	
Number of stents per patient	1.46 ± 0.7	1.58 ± 0.7	0.45
1	24 (65%)	20 (53%)	
2	9 (24%)	14 (37%)	
3	4 (11%)	4 (10%)	

Data are presented as numbers (percentages) or means ± standard deviation. BMS: bare metal stent; SES: sirolimus-eluting stent.

Figure 1. Survival curves

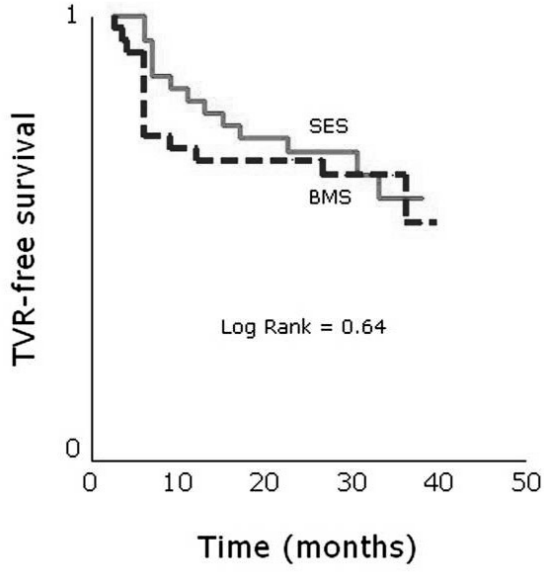


Kaplan Meyer estimates for survival by type of randomized stent (dotted line = BMS: bare metal stent; continuous line = SES: sirolimus-eluting stent).

Specifically, there were 7 cardiac deaths of which 3 were sudden, thus possibly related to late or very late stent thrombosis according to our definition, and one was caused by an angiographically documented very late stent thrombosis 13 months after stent implantation, which caused a large MI leading to death. Other details on the deceased patients are presented in tables 2 and 3. Another additional very late angiographically documented SES thrombosis caused a non fatal MI 30 months after the index procedure, and it was successfully treated percutaneously. The patient was on acetylsalicylic acid, while he stopped clopidogrel 6 months after the index procedure. Thus the overall rate of definite angiographically documented stent thrombosis was 5% in the SES group (2 out of 38, both very late) vs. 0% in the BMS group (p=0.49), while the rate of any possible stent thrombosis was 13% (5 out of 38, 2 late and 3 very late) after SES vs. 0% after BMS (Fisher's exact test 2-sided p-value=0.054; log rank test=0.022).

Table 4 shows the overall rate of events that occurred in the 2 groups at long-term follow-up and the medical therapy taken by the patients at the moment of last follow-up. As evident, a non-significant trend toward an increased rate of lesion- and vessel-related revascularization procedures is evident in the SES group after 6-month follow-up, neutralizing the initial 6-month benefit of SES in terms of TLR and TVR (figure 2). Potential confounding factors such as additional revascularization procedures not TLR/TVR-related or the anti-platelet/hypocholesterolemic therapy, were not significantly different and well balanced between the 2 groups.

Figure 2. Target vessel revascularization-free survival curves



Kaplan Meyer estimates for target vessel revascularization (TVR)-free survival by type of randomized stent (dotted line = BMS: bare metal stent; continuous line = SES: sirolimus-eluting stent).

Table 2. Clinical and angiographic details on the SES patients who died.

Patient number	Age* (years)	Sex	Diabetes*	Ejection Fraction* (%)	Type of angina*	Age of the grafts (years)*	Number of lesions treated	Number of SES implanted	Total length of SES implanted (mm)
17	81	M	no	70	unstable	10	2	2	51
30	60	M	no	70	unstable	14	2	2	51
37	79	M	yes	56	unstable	21	1	3	49
39	72	M	no	72	unstable	11	1	2	31
42	83	M	yes	40	unstable	15	1	2	51
44	72	M	yes	32	stable	18	2	3	74
46	69	F	no	75	unstable	12	1	1	23
50	83	F	yes	75	stable	9	1	2	51
52	66	M	no	45	stable	14	1	2	61
56	69	M	no	51	unstable	20	1	1	33
58	61	F	no	NA	stable	11	1	1	23

*At enrollment. F: female; M: male; NA: not available; SES: sirolimus-eluting stent.

Table 3. Details on the specific time-courses and reasons of death in the sirolimus-eluting stent patients.

Patient number	Time of death (months)	Cause of death	Anti-thrombotic therapy at the moment of death
17	35	sudden out-of-hospital death	ASA, TP
30	33	progressive multiple organ failure after ReDo CABG (documented late in-stent restenosis and additional progression of other lesions)	ASA, TP
37	30	progressive Parkinson disease	ASA, TP
39	19	metastatic colon carcinoma	- (suspended 2 months before death because of cachexia and anorexia)
42	5	progressive heart failure	TP
44	11.5	sudden out-of-hospital death	ASA, TP
46	7.5	sudden out-of-hospital death	TP, W
50	23.5	post-operative (aortic valve replacement and ReDo CABG for progression of disease not in the stented segment) infection (decubitus)	ASA, TP
52	16	metastatic urothelial carcinoma	- (suspended 1 month before death for severe anemia requiring transfusion)
56	14.5	progressive heart failure after MI due to stent thrombosis of the index stent (angiographically documented)	- (suspended 1 week before MI for planned knee operation)
58	22	progressive heart failure after peri-operative (acute limb ischemia) MI (no stent thrombosis of the index stent, but late stent thrombosis of a paclitaxel eluting stent implanted 15 month before in the left main)	- (suspended 1 week before MI for planned AICD change)

AICD: automatic implantable cardioverter defibrillator; ASA: acetylsalicylic acid, CABG: coronary artery bypass surgery, MI: myocardial infarction, TP: thienopyridine (ticlopidine or clopidogrel), W: warfarin.

Table 4. Clinical events and medical therapy in the two groups at longest available follow-up.

	BMS (n=37)	SES (n=38)	P-value
In hospital			
Periprocedural myocardial infarction	1 (3%)	2 (5%)	0.99*
From discharge to 6 months			
Death	0	1 (3%)	0.99*
Myocardial infarction	0	1 (3%)	0.99*
TLR	8 (22%)	2 (5%)	0.047*
TVR	10 (27%)	2 (5%)	0.012*
After 6 months			
Death	0	10 (26%)	0.001*
Myocardial infarction	1 (3%)	4 (10%)	0.35*
TLR	3 (8%)	7 (18%)	0.30*
TVR	4 (11%)	11 (29%)	0.05
Cumulative events			
Death	0	11 (29%)	<0.001*
Myocardial infarction	2 (5%)	7 (18%)	0.15*
TLR	11 (30%)	9 (24%)	0.55
- TLR lesion based	13/49 (26%)	9/47 (19%)	0.39
TVR	14 (38%)	13 (34%)	0.74
- TVR lesion based	20/49 (41%)	17/47 (36%)	0.64
MACE (without double counting)	15 (41%)	22 (58%)	0.13
Other PCI not TLR/TVR-related	14 (38%)	12 (32%)	0.57
Medical therapy at follow-up			
Double anti-platelet therapy	19 (51%)	19 (50%)	0.91
Single anti-platelet therapy	14 (38%)	15 (39%)	0.88
No anti-platelet therapy	4 (11%)	4 (10%)	0.97
Aspirin	26 (70%)	26 (68%)	0.86
Thienopyridine (clopidogrel or ticlopidine)	26 (70%)	27 (71%)	0.94
Statin	27 (73%)	29 (76%)	0.74

Data are presented as numbers (percentages). * Fisher's exact test. BMS: bare metal stent; SES: sirolimus-eluting stent; MACE: major adverse cardiac events (death, any myocardial infarction and TVR); PCI: percutaneous coronary intervention; TLR: target lesion revascularization; TVR: target vessel revascularization.

DISCUSSION

This extended analysis of the randomized double-blind RRISC trial evaluates the long-term clinical effects of SES versus BMS in patients with diseased SVG. The main findings are: 1) patients treated with SES showed a significant increase in total mortality, and 2) the benefit of SES in terms of reduced revascularization procedures shown at 6 months (14) was no longer evident up to 3 years.

Great focus has been recently put on the evaluation of long-term follow-up of drug-eluting stents in native coronary arteries, mainly after publication of original and meta-analytical studies showing a possible increase in "hard" adverse events, specifically very late stent thrombosis, after drug-eluting stent deployment with respect to BMS (6-11). In light of these data, in December 2006 the U.S. Food and Drug Administration (FDA) has set up a panel in order to thoroughly assess the long-term values and drawbacks of drug-eluting stents. A final statement was made, in which the FDA deemed the on-label use of drug eluting stents safe but warned against an increased risk of adverse events with off-label use (17,18). As percutaneous SVG treatment with SES is currently off-label, and also in light of the results of our trial, potential advantages and drawbacks of the implantation of SES (or other drug-eluting stents) versus BMS in SVG should be carefully evaluated before the procedure and discussed personally with every patient.

Our trial suggests also that in SVG there can be a potential late "catch-up" phenomenon, as a non significant trend toward more repeated revascularization procedures occurred in the SES group after 6 month with respect to the BMS group, thus leading to a lack of benefit of SES over BMS also in reduction of clinical restenosis. A percutaneous treatment with a clear additional benefit over BMS in SVG lesions, that account for up to 10-15% of the lesions treated percutaneously in the majority of the catheterization laboratories (12), is still missing. Of interest, other recent studies assessing the clinical impact of drug-eluting stent vs. BMS in diseased SVG failed to show benefits of the former over the latter (19,20).

A clear patho-physiological explanation for these findings is lacking. It is well established that the long-term prognosis of patients with diseased SVG is mainly impacted by progression of disease in non intervened SVG segments (21,22).

However, also the specific anatomic and pathological response of diseased SVG to stent implantation can lead to processes that conduct to late/very late thrombosis and late restenosis in a more pronounced way than what occurs in native coronary arteries. Indeed, SVG lesions, which are more lipid-rich, softer and more prone to rupture than plaques in native coronary arteries, can induce progression of atherosclerosis and may lead to an enhanced inflammatory and thrombotic reaction after deployment of stents and this can potentially be more pronounced with devices coated with drugs and polymers (23-25).

Thus far, BMS should be still considered the reference percutaneous treatment of SVG and the correct control arm for future SVG randomized trials, which should also be designed bearing in mind the potential occurrence of very late (>1 year) thrombosis and late (>6 months) restenosis.

Limitations

There are major limitations in our study. First, the sample size of this cohort of patients is small, thus the results can be underpowered to appropriately address specific questions, and can be prone to type I and type II statistical error. Second, the recommended duration of double anti-platelet therapy was only mandatory for at least 2 months in our study (though half of the population was still taking acetylsalicylic acid and a thienopyridine up to 3 years, as evident in table 4). Recent evidence has shown that double anti-platelet therapy should be recommended in all patients receiving drug-eluting stents for at least 12 months (26). On the other hand, the RRISC trial was started in 2003 and at that period patients in whom SES were implanted routinely received 2 to3-month double anti-platelet therapy, also in other trials (1-4). We cannot exclude however that some of the events described in the current study could be explained by “premature” discontinuation of dual anti-platelet therapy. Third, this manuscript presents a secondary post-hoc analysis, thus the current main end point (death) was not pre-specified at the moment of the beginning of the trial (which was powered for a 6-month difference in angiographic late loss analysis). Death was selected as end point after the recent concerns related to an increase in long-term mortality after SES treatment in native coronary arteries (6-10). However, like in the Basel Stent Kosten Effektivitats LAte Thrombotic Events

(BASKET-LATE) trial (6), the use of a previously randomised study cohort for a long-term observational study can preserve some of the internal validity of a randomized comparison (27). Because most of the effort and resources go into the organization and conduct of the original trial, adding a second question and extending follow-up can be logistically efficient and scientifically helpful (27). Moreover, no drug-eluting stent trial to date has been powered to assess long-term mortality (1-4), thus preliminary data on long-term results of the currently available trials can be useful for future directions.

Conclusions

Our study has shown that the use of BMS was associated with lower long-term mortality than the use of SES for SVG disease. Also the 6-month reduction in repeated revascularization procedures shown with the use of SES was lost at longer-term follow-up. Because the observations seen in this secondary post-hoc analysis may have arisen from the play of chance or other clinical factors unrelated to stent type, further studies are required before conclusions can be made about the safety or harm of using SES for SVG lesions.

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5

Drug eluting stent versus bare metal stent in the treatment of saphenous vein graft disease: a systematic review and meta-analysis.

Luca Testa, Pierfrancesco Agostoni, Paul Vermeersch, Giuseppe GL Biondi-Zoccai, William J van Gaal, Ravinay Bhindi, Emmanouil S Brilakis, Roberto A Latini, Maria-Luisa Laudisa, Samuele Pizzocri, Stefania Lanotte, Nedy Brambilla, Adrian P Banning, Francesco Bedogni.

Interventional Cardiology Department, S. Ambrogio Clinical Institute, Milan; Institute of Cardiology, University of Turin, Turin; all in Italy. John Radcliffe Hospital, Oxford, UK. Department of Cardiology, University Medical Center, Utrecht, The Netherlands. Antwerp Cardiovascular Institute Middelheim, Antwerp, Belgium. Institute of Cardiology, University of Melbourne, Melbourne; Department of Cardiology, Royal North Shore Hospital, University of Sydney; all in Australia. University of Texas Southwestern Medical Center, Dallas, TX, USA.

Submitted.

ABSTRACT

Aims. Treatment of saphenous vein graft (SVG) disease is still a matter of debate given the uncertainty of available conflicting data. Our aim was to assess, by means of meta-analytic approach, the risk/benefit profile of drug eluting stent (DES) versus bare metal stent (BMS) in the treatment of SVG disease.

Methods and result. Search of relevant studies in several databases was performed. End points of interest such as major adverse events [MAE: combination of overall death and non fatal myocardial infarction (AMI)], target vessel revascularisation (TVR), and target lesion revascularisation (TLR)] have been calculated in-hospital and at the longest follow up. Single end-points and the rate of stent thrombosis (ST) were also assessed.

Three randomised controlled trials and 15 registry studies were appraised, totalling 3294 patients. During hospitalisation, there was no difference in the risk of MAE, overall death, AMI and TVR. No data were available to calculate TLR rate. At a mean follow up of 19.8 months, no significant differences were found in the risk of MAE and AMI. BMS were associated with a trend towards a higher risk of overall death [OR 1.32 (1,00-1.74),p=0.05,number needed to treat (NNT)=55]. DES showed superiority in terms of TVR [OR 1.86 (1.33-2.61),p=0.0003,NNT=16], and TLR [OR 1.77 (1.27-2.48),p<0.0001,NNT=25]. According to pre-specified subgroup analyses, these effects seem less evident at long-term follow up. DES were not associated with an increased risk of ST.

Conclusions. Use of DES in SVG substantially reduces both TVR and TLR. These data also demonstrate that using DES in SVG is safe and contradict previous reports of potential risks.

INTRODUCTION

Coronary artery bypass grafting surgery (CABG) dramatically changed the management of patients with ischemic heart disease as it proved to improve symptoms and life expectancy in particular in those patients with multivessel disease. Despite the superiority of arterial over venous conduits, saphenous vein grafts (SVG) are still the most commonly used [1] even though they have a rate of long term failure of almost 50% at 10 years [2]. Significant atherosclerotic disease of SVG, despite optimal medical therapy, may result in recurrence of angina and higher risk of major adverse events [1]. The treatment of patients with evidence of SVG failure is still a matter of debate for both interventional cardiologists and cardiac surgeons. Given the high risk of a further surgical treatment [3] and the availability of new technologies including protection devices and ad hoc catheters, percutaneous coronary intervention (PCI) is currently the preferred approach [4,5].

The superiority of bare metal stents (BMS) over balloon angioplasty is widely accepted even in this particular setting [6]. On the other hand, the encouraging data about the beneficial effect of drug eluting stents (DES) over BMS in terms of risk of restenosis and repeat revascularization when deployed in native coronary arteries acted as a spur for the utilization of such devices also for "off label" indications like SVG disease [7]. Notably, along with several study registries reporting disparate results, there are very few data concerning a randomised comparison of BMS vs DES in SVG treatment [8-11]. Of note, data from the RRISC trial, while showing a consistent superiority of DES at the short term follow up [8], reported a puzzling increase of death and stent thrombosis in the DES arm at 3 year follow up [9] which were not confirmed by the SOS trial [10] and the recently published SVG subgroup analysis of the BASKET trial [11]. Thus, a general consensus over this topic is still lacking. By means of meta-analytic approach we aimed at summarizing current evidences in order to provide thoughtful insights in such an unclear scenario.

METHODS

Study Selection

BioMedCentral and PubMed were searched without language restrictions (updated to March 2009), according to an established method using as key words “saphenous vein graft” and “stent”(see Appendix) [12]. Pertinent studies were also searched in major recent international cardiology meetings. References of original and review articles were cross-checked.

Data extraction and Endpoints of interest

Two trained and independent reviewers (TL, AP) performed data abstraction blindly. Divergences were resolved by consensus or by a third reviewer. The endpoints of interest were the combined rate of major adverse events (MAE, defined as the cumulative risk of all cause death and nonfatal acute myocardial infarction), target vessel revascularization (TVR) and target lesion revascularization (TLR). Additional analyses were carried out according to single end points and the rate of stent thrombosis. End point assessment was performed both for in-hospital and longest follow up available.

Primary analyses included all the available studies. Secondary analyses were performed by sub grouping studies according to follow up duration of 6 months, 6 to 12, 12 to 24 and more than 24 months. Separate analyses were also performed pooling data from registries and randomised controlled trials.

Moreover, we assessed whether there are distinctive effects of sirolimus- (SES) and paclitaxel- (PES) eluting stent compared to BMS by sub grouping studies according to the type of stent used.

Data Synthesis and Analysis

Review Manager 4.2.5 [13] was used. Review Manager is a comprehensive statistical and reviewing program, developed and maintained by The Cochrane Collaboration, which includes ad hoc statistical tools for pooled estimate calculations, according to several methods.

Statistical analyses

Odds ratios with 95% confidence intervals (95%CI) were used as summary statistics. Binary outcomes from individual studies were combined with both Der Simonian and Laird random-effect model and fixed-effect model, according to an intention to treat analysis. We also carried out the "z" test where z = estimated effect size / standard error of the estimated effect size, and the odds ratio considered on the log scale. As log (OR) has a unimodal distribution, the reported z values were analyzed to obtain a two-tailed "p", and hypothesis testing results were considered statistically significant at the 0.05 level [14]. We also calculated the number needed to treat (NNT) to prevent a MAE as the inverse of absolute risk reduction (ARR): NNT=1/ARR. We computed Cochrane Q heterogeneity test (H) by summing the squared deviations of each study's estimate from the overall meta-analytic estimate, weighting each study's contribution in the same manner [14]. We used the Q together with the resulting degrees of freedom (df) to calculate the proportion of variation due to heterogeneity [Inconsistency: (I^2)=(Q-df)/Q]. The degree of inconsistency among studies (I^2) was estimated with scores of <25%, between 25% and 75%, and >75% representing, respectively, low, moderate or high inconsistency [15].

Sensitivity analysis was performed by excluding trials one at time in order to assess the contribution of each study to the pooled estimates [14].

The likelihood of publication bias was assessed graphically by generating a funnel plot for the combined endpoint of MAE and mathematically by means of Egger's test (p for significant asymmetry <0.1) [16].

This study is inspired by good practice guidelines [17], including those from the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group [18] and the Cochrane collaboration Newcastle-Ottawa scale for assessing quality of cohort study [14].

RESULTS

Search result

The search algorithm resulted in 220 citations. We eventually appraised 18 studies, three randomised controlled trials [8,9,10,11] and 15 registries [19-33] totaling 3294 patients with a mean follow up of 19.8 months (range 6-48) (Figure 1). Main characteristics of included studies are shown in the table 1. Five studies compared BMS versus sirolimus eluting stents (SES) [8,9,22,24,26,29], three BMS versus paclitaxel eluting stent (PES) [10,20,23], nine BMS versus both PES and SES [11,19,21, 25,27,30,31,32,33]. Only one study included also tacrolimus eluting stents [28]. Baseline characteristics of the enrolled patients and the incidence of the common cardiovascular risk factors were similar across studies. The percentage of patients admitted with ST-elevation myocardial infarction was reported only in five studies where it ranged between 2% and 11% [11, 20,24,29,31,33]. The relative percentage of patients with stable and unstable angina was highly variable across studies as well as the use of distal protection devices and IIb/IIIa inhibitors. Definitions of end-points were fairly homogeneous thus allowing the pooling of dichotomous data.

In-hospital end points.

Few studies reported in hospital end-points. Pooling data with either “random-effect” or “fixed-effect” model yielded similar results, which are shown according to the former. There was no difference in the risk of MAE [0.90 (0.49-1.67), p=0.74, p for H=0.44, I^2 = 0%] as well of overall death [0.98 (0.22-4.47), p=0.98, p for H=0.45, I^2 = 0%], AMI [0.97 (0.57-1.67), p=0.92, p for H=0.52, I^2 0%] and TVR [3.70 (0.66-20.72), p=0.14, p for H=0.83, I^2 = 0%]. No data were available to calculate TLR rate.

Table 1. Main features of included studies.

	N	Follow up (months)	Comparison	Allocation process	UA (%)		IIb/IIIa (%)		DPD (%)		Dual antiplatelet therapy duration (months)	
					BMS	DES	BMS	DES	BMS	DES	BMS	DES
Vermeersch et al[8,9]	75	32 (median)	BMS vs SES	random	51	60	0	2.6	83.7	78.7	2	2
Brilakis et al[10]	80	18 (median)	BMS vs PES	random	36	39	13	10	56	51	1	6
Jeger et al[11]	47	18	BMS vs DES	random	54	27	46	21	NA	NA	6	6
Ge et al[19]	150	6	BMS vs DES	historical matching	36	18	19	9	22.5	31.1	1	3-6
Hoffman et al[20]	120	6	BMS vs PES	historical matching	31	28	NA	NA	28	34	1	6
Lee et al[21]	223	9	BMS vs DES	contemporary	25	31	12	8	19	15	NA	NA
Chu et al[22]	105	12	BMS vs SES	historical matching	NA	NA	NA[#]	NA[#]	100	100	≥6	≥6
Whorle et al[23]	39	12	BMS vs PES	historical matching	NA	NA	19.2	15.4	0	0	6	6
Ellis et al[24]	350	12	BMS vs SES	historical matching	78.6	72	83.9	52.3	25.1	35.1	NA	NA
Vignali et al[25]	360	14	BMS vs DES	contemporary	22.9	26.4	NA[#]	NA[#]	NA	NA	1	6
Minutello et al[26]	109	20	BMS vs SES	historical matching	72	62.7	64	49.2	48	71.2	1	3
Bansal et al[27]	109	33	BMS vs DES	contemporary	NA	NA	53	39	27	39	NA	NA
Gioia et al[28]	225	24	BMS vs DES[*]	contemporary	52	40	21	16	21	26	1	6
Ramana et al[29]	311	34	BMS vs SES	contemporary	36	55	&	&	NA	NA	3	3
Applegate et al[30]	148	24	BMS vs DES	propensity score matching	34	31	#	#	47	53	1	>3
Assali et al[31]	111	24	BMS vs DES	historical matching	77	74	33	52	22	27	1	>6
van Twisk et al[32]	250	48	BMs vs DES	contemporary	53	50	41	21	4.7	1.6	1	>3
Okabe et al[33]	482	12	BMS vs DES	contemporary	61	60	48	15	21	26	1	6

***Sirolimus, Paclitaxel and Tacrolimus eluting stents; **#:** discretional; &: administered as default in the absence of contraindication; BMS: bare metal stent, DES: drug eluting stent (paclitaxel and sirolimus); DPD: distal protection devices; NA: not available; PES: paclitaxel eluting stent; SES: sirolimus eluting stent, UA: unstable angina.

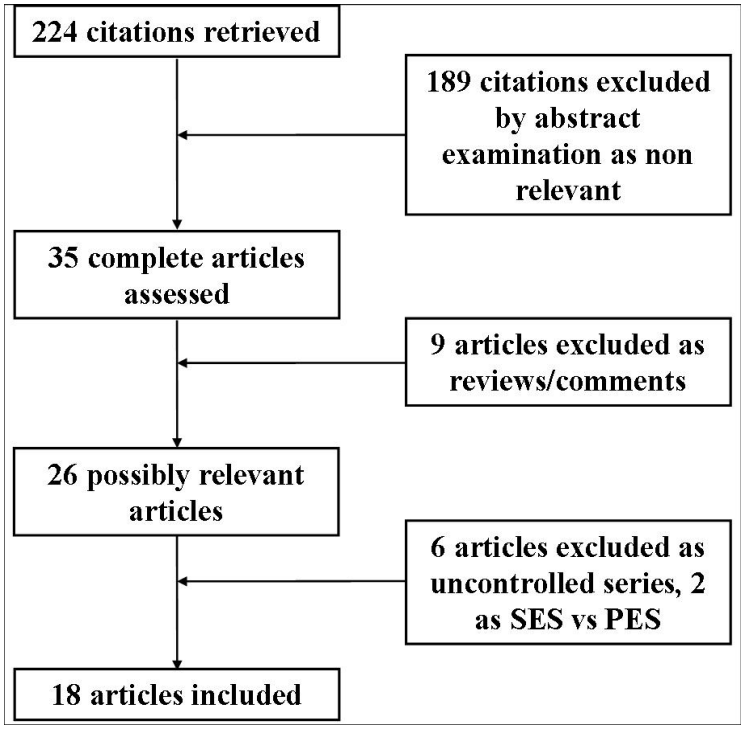
Table 1. Main features of included studies (continued).

	SVG Lesion location (%)						Graft Age (years, SD)		Stent length mm (mean, SD)		Stent diameter mm (mean, SD)	
	Prox		Body		Distal		BMS	DES	BMS	DES	BMS	DES
	BMS	DES	BMS	DES	BMS	DES						
Vermeersch et al[8,9]	48.9	51	32.7	38.3	18.4	10.7	12.6 (5.9)	12.4 (4.6)	22.9 (8.0)	23.4 (7.0)	3.36 (0.26)	3.41 (0.19)
Brilakis et al[10]	47	54	33	30	20	16	12 (6)	11 (6)	18 (6)	18 (6)	3.17 (0.42)	3.14 (0.35)
Jeger et al[11]	NA	NA	NA	NA	NA	NA	NA	NA	46 (30)	41 (25)	17*	29*
Ge et al[19]	43.3	50.7	22.5	26.1	34.2	23.2	92 (4.8)	9.7 (5.6)	20.4 (8.8)	29.4 (19.8)	3.83 (0.58)	3.35 (0.39)
Hoffman et al[20]	45	49	27	28	28	23	10.1 (4.5)	11.3 (5.7)	14.6 (4.4)	16.7 (3.7)	3.4 (0.6)	3.3 (0.3)
Lee et al[21]	NA	NA	NA	NA	NA	NA	7.6 (3.8)	7.7 (2.8)	NA	NA	2.96 (0.65)#	2.94 (0.23)#
Chu et al[22]	58	60	28	18	14	22	9 (7)	10 (8)	23.1 (10.6)	20.8 (7.5)	3.8 (0.8)	3.1 (0.4)
Whorle et al[23]	NA	NA	NA	NA	NA	NA	9.1 (5.1)	11.4 (7.1)	23.6 (14.1)	23 (12.4)	3.28 (0.82)	3.06 (0.7)
Ellis et al[24]	45.1	40.1	48.9	42	16.1	17.8	NA	NA	21.61 (11.8)	20.6 (8.1)	3.37 (0.37)	3.33 (0.34)
Vignali et al[25]	13.8	9	NA	NA	NA	NA	10 (4)	9 (2)	18.7 (6.2)	19.7 (6.4)	3.5 (0.7)	3 (0.4)
Minutello et al[26]	42	37.3	46	50.8	0	1.7	9.4 (5.5)	12.9 (6.4)	NA	NA	3.43 (0.48)	3.12 (0.37)
Bansal et al[27]	NA	NA	NA	NA	NA	NA	NA	NA	17.9 (0.76)	17.1 (1)	3.8 (0.07)	3 (0.07)
Gioia et al[28]	NA	NA	NA	NA	NA	NA	11 (5)	11 (6)	24 (10)	21 (6)	3.9 (0.5)	3.3 (0.4)

Ramana et al[29]	NA	NA	NA	NA	NA	NA	12.9	11.5	29.3	28.3	4.2	3.3
Applegate et al[30]	NA	NA	NA	NA	NA	NA	NA	NA	25 (14)	26 (11)	NA	NA
Assali et al[31]	43.4	47	43.6	39	13	14	11.4 (4.5)	10.8 (5.1)	20.7 (13.1)	30.3 (18.5)	3.6 (0.7)	3.3 (0.4)
van Twisk et al[32]	NA	NA	NA	NA	NA	NA	NA	NA	31.9	32	3.5	3.1
Okabe et al[33]	§	§	§	§	§	§	10 (7)	9 (6)	20.3 (6.4)	19.8 (8.6)	3.09 (0.37)	3.84 (2.07)

§ unclear values from he original paper**; *** proportion of stents with diameter ≥ 3.5; **#** mean diameter of reference vessel; BMS: bare metal stent; DES: drug eluting stent; SD: standard deviation; SVG: saphenous vein graft.

Figure 1. Flow diagram according to QUOROM statement.



PES: paclitaxel eluting stent, SES: sirolimus eluting stent.

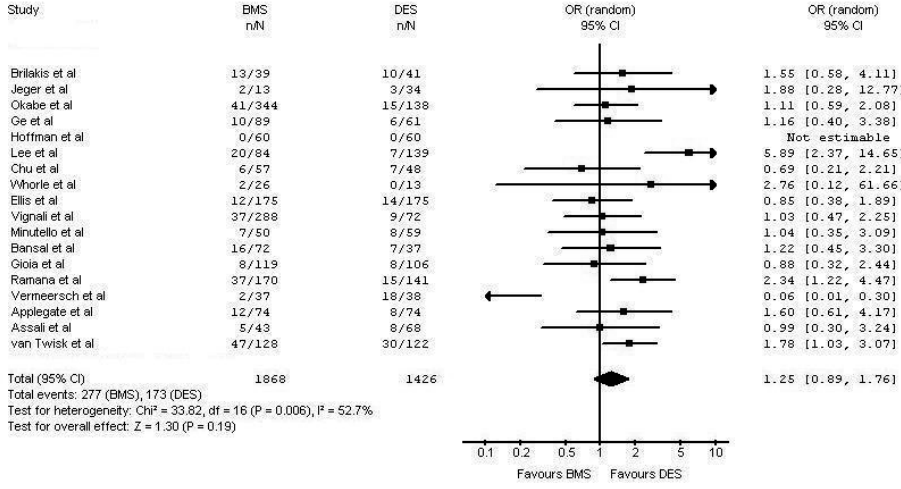
Longest follow up end points.

Pooling raw data according to "random-effect" model yielded different results with respect to the "fixed-effect" model. Because of the presence of heterogeneity and moderate inconsistency, results are shown and discussed according to the former. No significant differences were found according to the risk of MAE [1.25 (0.89-1.67), p=0.19, p for H=0.006, I^2 52%] and AMI [1.15 (0.69-1.92), p=0.6, p for H=0.02, I^2 47%] while there was a trend towards a beneficial effect of DES in terms of overall death [1.32 (1,00-1.74), p=0.05, p for H=0.44, I^2 0% ARR=0.02, NNT=50 (25-90)] (Figure 2). DES showed superiority in terms of a reduced risk of TVR [OR 1.86 (1.33-2.61), p=0.0003, p for H=0.0009, I^2 59%, ARR=0.06, NNT=16 (7-25)], and TLR [OR 1.77 (1.27-2.48), p<0.0001, p for H=0.13, I^2 0%, ARR=0.04, NNT=25 (10-100)] (Figure 3).

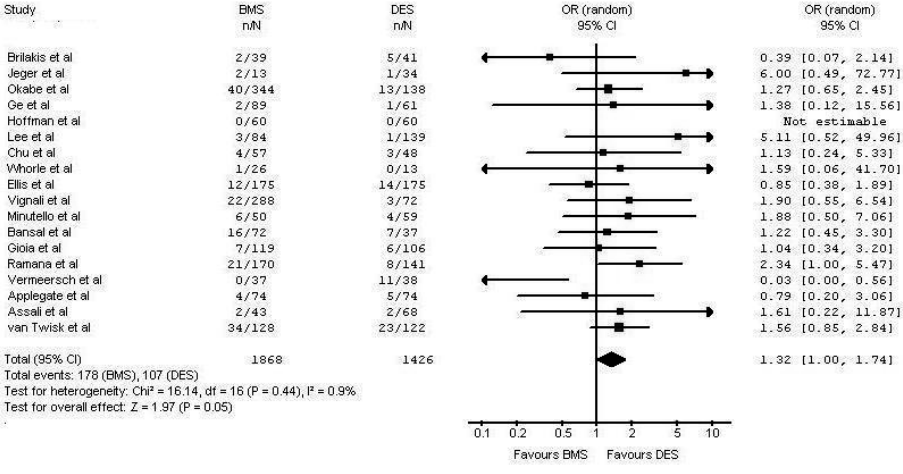
Absolute incidences of end-points across the included studies are shown in Table 2. Importantly, the risk of stent thrombosis was not different between DES and BMS [OR 1.86 (0.52-6.61), p=0.34, p for H=0.26, I^2 24%].

Figure 2.

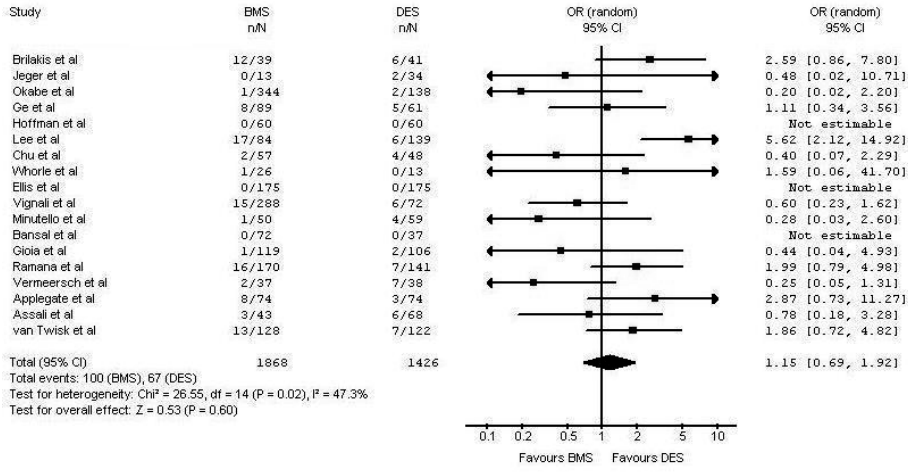
A



B



C

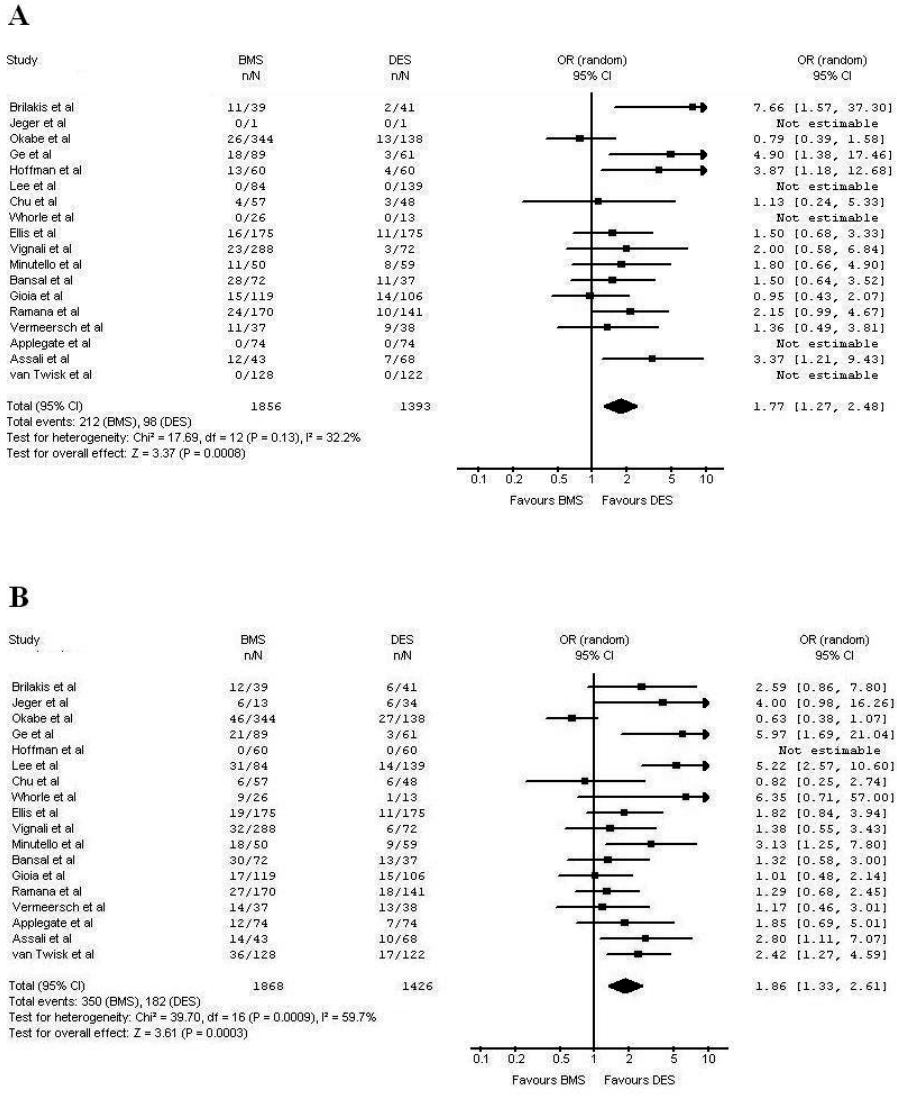


Overall analysis of the risk of (**A**) major adverse events (MAE), (**B**) overall death and (**C**) acute myocardial infarction at the longest follow up available. Single study odd ratios and 95% confidence intervals are shown by squares and lines. Overall odd ratios with 95% confidence interval are shown by diamonds.

Table 2. Pooled incidences of the end-points across included studies at the longest follow up available (mean: 19.9 months).

	BMS (%)	DES (%)
Major adverse events	14.8	12.1
Overall death	9.5	7.5
Acute myocardial infarction	5.3	4.6
Target lesion revascularization	11.4	7.0
Target vessel revascularization	18.7	12.7
Stent thrombosis	0.7	0.2

Figure 3.



Overall analysis of the risk of (**A**) target lesion revascularization and (**B**) target vessel revascularization at the longest follow up available. Single study odd ratios and 95% confidence intervals are shown by squares and lines. Overall odd ratios with 95% confidence interval are shown by diamonds.

Pre-specified sub-group analyses.

In the subgroup of studies with follow up duration of 6 months, no differences were observed for the risk of MAE, AMI and overall death. On the other hand, DES showed large superiority in terms of TVR [5.97 (1.69-21.04), p=0.0005, ARR=0.1, NNT=10 (7-25)] and TLR [4.32 (1.82-10.28), p=0.0009, ARR 0.14, NNT=7 (4-14)].

In the subgroups of studies with follow up duration of 6-12 months, as well as 12-24 months, no differences were found with respect to all the endpoints.

In the subgroup of studies with follow up duration of >24 months, DES were slightly significantly associated with a reduction of TVR [1.62 (1.16-2.25), p=0.04, ARR=0.07, NNT=15 (7-50)]. No differences were found for other end-points.

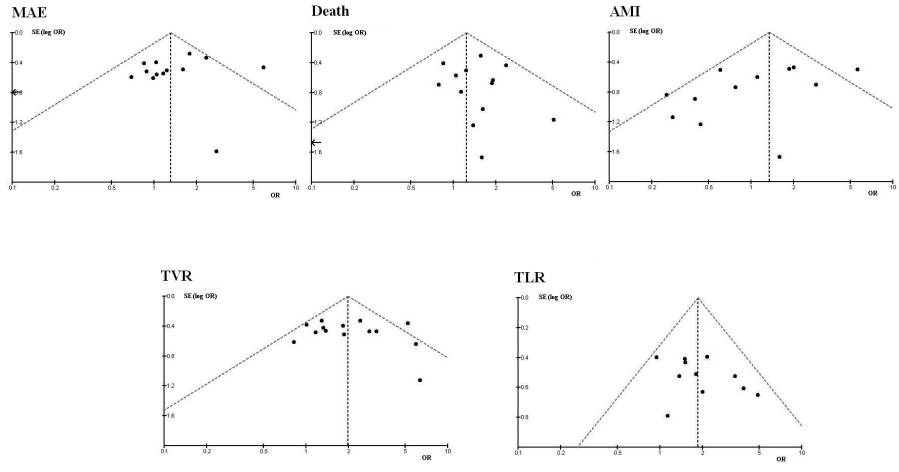
Sensitivity analysis

We performed explorative analyses initially excluding one study at a time and then pooling the randomised controlled trials and the registries separately. The exclusion of one study at a time did not significantly alter the pooled ORs. Of note, the pooled analysis of the randomised controlled trials showed superiority of the DES over BMS only in terms of TVR at the longest follow up with an OR of 1.95 (1.04, 3.67), p=0.04, ARR 0.14, NNT 7 (4-15). On the other hand, in the pooled analyses of the registries, DES were associated with a significant benefit in terms of MACE [1.45 (1.15-1.81), p=0.001, p for H=0.14, ARR 0.03, NNT 33 (19-60)], overall death [1.4(1.06, 1.85), p=0.02, p for H=0.95, ARR 0.03, NNT 33 (22-55)], TVR [1.7 (1.38, 2.10), p< 0.001, p for H=0.0004, ARR 0.07, NNT 14 (7-34)], and TLR [1.67(1.27, 2.20), p=0.0003, p for H=0.18, ARR 0.04, NNT 25 (16-48)] while showing only a trend in favor of DES for the risk of AMI. When comparing raw data from historical matched registries no difference in terms of MACE, overall death and AMI was found, while DES showed superiority over BMS in terms of reduced TVR [OR 2.48 (1.49-4.13), p=0.003] and TLR [2.3 (1.48-3.55), p= 0.02]. On the other hand, when pooling raw data from “contemporary” registries DES were associated with a reduced risk of MACE [OR 1.64(1.07-2.51), p=0.02] and death [OR 1.54 (1.10-2.14), p=0.03], while no difference was found in terms of AMI, TLR and TVR. Three studies specifically used PES [10,20,23] while 5 SES [9,22,24,26,29]. Overall consistency was found without apparent difference between each of the stents and the overall analyses.

Quality of included studies and assessment of possible biases

The assessment of possible sources of bias is reported in Table 3. Very good overall consistency has to be acknowledged among reviewers rating the quality of the studies (LT, PA). As for the study registries, discrepancies in the design of the study (see Table 1), the lack of a "sequence generation" for the "allocation process", which was not "concealed", along with the lack of "blinding" might have introduced possible biases. Nevertheless, included patients were well representative of the "real-world" scenario according to the incidence of risk factors and baseline characteristics. The presence of "incomplete data", whereas applicable, has been thoughtfully addressed, and no "selective reporting" has to be acknowledged. Overall the quality of the registries has to be acknowledged as poor (i.e. high likelihood of biases) while the randomised controlled trials had a good internal validity (i.e. low likelihood of biases). The Funnel plot for all studies according to the risk of MAE, death, AMI, TLR and TVR (Figure 4) showed an overall symmetry within the 95% confidence interval. Moreover, Egger's test for the risk of MAE further confirmed the absence of small study/publication bias as "p for asymmetry" was 0.13.

Figure 4.



Funnel plots of included studies according to the end points. Dotted lines represent 95% confidence interval.

Table 3. Assessment of potential sources of bias according to Cochrane Collaboration. **NA**: not applicable.

	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting
Vermeersch et al[8,9]	Computerised	Adequate	Adequate	NO	NO
Brilakis et al[10]	Computerised	Adequate	Adequate	NO	NO
Jeger et al[11]	Computerised	Adequate	Adequate	NO	NO
Ge et al[19]	NA	NA	NA	NO	NO
Hoffman et al[20]	NA	NA	NA	NO	NO
Lee et al[21]	NA	NA	NA	NO	NO
Chu et al[22]	NA	NA	NA	NO	NO
Whorle et al[23]	NA	NA	NA	NO	NO
Ellis et al[24]	NA	NA	NA	NO	NO
Vignali et al[25]	NA	NA	NA	NO	NO
Minutello et al[26]	NA	NA	NA	NO	NO
Bansal et al[27]	NA	NA	NA	NO	NO
Gioia et al[28]	NA	NA	NA	NO	NO
Ramana et al[29]	NA	NA	NA	NO	NO
Applegate et al[30]	NA	NA	NA	NO	NO
Assali et al[31]	NA	NA	NA	NO	NO
van Twisk et al[32]	NA	NA	NA	NO	NO
Okabe et al[33]	NA	NA	NA	NO	NO

Sequence generation: describe the method used to generate the allocation sequence, if any. Allocation concealment: describe the method used to conceal the allocation sequence, if any. Blinding: describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Incomplete outcome data: describe the completeness of outcome data for each main outcome. Selective outcome reporting: state how the possibility of selective outcome reporting was examined by the review authors.

DISCUSSION

The result of this pooled analysis of all the available studies showed that the use of DES in the setting of SVG treatment does not increase the risk of death, infarctions and stent thrombosis, conversely to previous reports seriously addressing the safety of DES in SVG. Drug-eluting stents appear even to be beneficial compared to BMS by significantly reducing TVR and TLR.

According to this analysis, treating 100 patients with SVG disease with a DES would prevent, at a mean follow up of 19.8 months, 10 TVR and four TLR compared to BMS. Of note, such advantage seems mostly driven by the beneficial effect of DES on short term follow up, while at longer term the advantage seems much less evident if not absent at all.

The treatment of SVG disease represents about 5-10% of the cases of the catheterization laboratory [4]. Atherosclerotic process in SVG has several peculiarities which account for the poor outcome compared to coronary arteries. Lesions in SVG are generally associated with a higher plaque burden, more friable material and frequent superimposed thrombosis which conceivably relate to the higher risk of distal embolization and peri-procedural myocardial damage [34,35]. Plaque composition is also peculiar as it is lipid-richer, softer and, as a consequence, more prone to rupture [36].

As soon as the technology of BMS has been introduced, its advantage over balloon angioplasty was clear [6], however the outcome of BMS in SVG was still poor when compared to interventions in native coronaries as the rate of 30-days MACE was about 10% while the rate of 6-months restenosis was >30% [4]. These findings led to several studies investigating the in-stent restenosis phenomenon in SVG and eventually to the clarification that even the restenotic process was different as it was based on several distinct phenomena including intimal hyperplasia, progression of atherosclerosis, local inflammatory reaction and thrombosis [37] whilst the major process in the coronaries is intimal hyperplasia [38].

The idea behind the covered stent technology was intriguing. Covering the metallic stent struts with a layer of polytetrafluoroethylene looked like a sensible approach to entrap the friable material and the drug itself was meant to reduce the intimal hyperplasia. However, despite promising preliminary data, results from randomised controlled trials were indisputably negative [39-42].

On the other hand, following their consistently positive results when implanted in native arteries [43-45], DES have been thought able to overcome the limitations of BMS. Three randomised controlled trial has been published on this topic, providing both short and long term outcomes [8-11].

The short term data from the RRISC trial showed that DES (SES) were associated with a reduced in stent late loss, binary in stent and in segment restenosis. Moreover, TLR and TVR were also reduced with DES [8]. At long term, DES were associated with a significantly increased risk of death and stent thrombosis whilst the risk of MI and TVR was no longer different between DES and BMS [9]. Of note, long term data from SOS trial and Basket trial subgroup did not confirm such a puzzling finding [10,11].
The long term safety of DES is still a matter of debate [46-49] and it seems related to the delayed endothelialization and higher local inflammatory response compared to BMS, but also to an insufficient duration of dual antiplatelet therapy. In the registry studies, the duration of dual antiplatelet therapy ranged from 3 to >6 months (few registries also reported a significant percentage of patients in dual antiplatelet therapy well after 12 months), while in the randomised controlled trials it was two [8,9] or six months [10,11]. Overall, the incidence of stent thrombosis was very low in both BMS and DES arms.
Currently, after DES implantation dual antiplatelet therapy should be continued for at least 12 months if well tolerated [6], thus the answer to the question of long term safety still requires a properly designed trial.

Limitation of the present study

A limitation inherent to all meta-analyses is the potential heterogeneity among studies, in terms of protocols, patients, and sample sizes, and the unavailability of patient-level data. However, the primary disagreement that arises in meta-analyses is whether to incorporate between-study variation (heterogeneity and inconsistency) in estimating summaries of effect size. If there is little between-study variation (i.e. non significant heterogeneity), the choice between random effect and fixed effect models usually make little difference in the results. In presence of significant heterogeneity it may be more appropriate to analyze results using both methods. A statistically significant result with the fixed effect model indicates that there is an effect in at least one of the studies, and the overall result is an average measure of treatment effect of the studies in the analysis. On the other hand, the random effects approach relies on assumptions that the studies are a random sample from a hypothetical population of studies and that the heterogeneity between studies can be represented by a single

variance. The random effects model tends to give a more conservative estimate (i.e. with wider confidence intervals) which has to be preferred in the presence of significant heterogeneity. The retrospective designs of most of the included studies, the lack of adjusted ORs in some reports, some discrepancies in duration of dual antiplatelet therapy, follow up, use of protection devices and, ultimately, the use of different DES have to be acknowledged as possible limitations of this analysis. They are all impossible to overcome due to the design of the included studies. Ultimately, the potential risk of selection bias is unavoidable in registry studies.

Avenues for future research

The treatment of SVG disease is a complex scenario where the outcome still remains poor when compared to the treatment of native coronary disease. Despite the initial concerns about DES safety, the present systematic quantitative review does not confirm the issue of an increased mortality after DES. On the other side, the possible advantages of DES seem to be evident at short term follow up, while they tend to disappear at longer term and in any case they seem to be much less manifest (in terms of absolute and relative reduction) than in native arteries. Properly powered and specifically designed randomised trials, with extensive use of adjunctive devices and long term dual antiplatelet therapy are required in order to clarify such a complex matter. Moreover, the fact that the RRISC trial (with SES) was very negative while the SOS (with PES) was encouraging may lead to the concept that DES in SVG "are not created equal" therefore suggesting the need for a randomised controlled trial specifically assessing this issue.

Two multicenter studies are currently recruiting patients in Europe. The first one is the Prospective, Randomized Trial of Drug-Eluting Stents vs. Bare Metal Stents for the Reduction of Restenosis in Bypass Grafts (ISAR-CABG) trial (NCT00611910), which plans to enrol 600 patients in 2 centers in Germany. Patients will be randomized to either a DES arm (3 DES will be used, SES, PES or a local polymeric stent coated with rapamycin) or a bare metal stent arm. The primary endpoint is the composite of death, myocardial infarction and target lesion revascularization at one year after stent implantation. The estimated completion date is April 2009 [50]. The second is the BAsel Stent Kosten Effektivitäts Trial - SAphenous Venous Graft Angioplasty Using

Glycoprotein IIb/IIIa Receptor Inhibitors and Drug-Eluting Stents (BASKETSAVAGE) (NCT00595647). BASKETSAVAGE will randomize 240 patients to a paclitaxel-eluting stent (Taxus Liberte) vs. a similar bare-metal stent (Liberte). Enrollment will occur at one center in Switzerland and one center in Germany. The primary endpoint of the study is the composite of cardiac death, non-fatal myocardial infarction, and TVR and results are anticipated in April 2009 [51].

Conclusions

In our knowledge, there is no previous publication concerning a pooled analysis of all available data investigating the impact of DES compared to BMS in treating SVG disease. Limitations are present, however, pooling results from different observational and randomised studies, with different operators in independent centers can provide a reliable picture of the "real world" scenario. Furthermore, the evidence of some discrepancies with respect to the sensitivity analyses also support the utility of comprehensively pooling the data. Of note, our data are quite consistent with those coming from the comparison of DES vs. BMS in the setting of STEMI patients. This similarity with another high risk group strengthens the reliability of the data.

In conclusion, although an advantage in terms of repeated revascularizations seemed evident at short term, considering the nature of the available studies and the heterogeneity of the data, caution is required before advocating a routinely application of this technology to saphenous vein graft disease. Importantly, while waiting for higher quality data, the results of our analyses do not confirm previous reports on major issues related to safety of DES in this "off label" indication.

ACKNOWLEDGEMENTS

This study is part of a senior investigator project of the Meta-analysis and Evidence-based Medicine Training in Cardiology (METCardio), website: http://www.metcardio.com.

APPENDIX

Algorithm for electronic search on pubmed*

(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR (clinical trial[tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind[tw])) OR (latin square[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR evaluation studies[mh] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh]) NOT (comment[pt] OR editorial[pt] OR meta-analysis[pt] OR practice-guideline[pt] OR review[pt])) AND saphenous vein graft AND stent

*Biondi Zoccai G, Agostoni P, Abbate A, Testa L, Burzotta F. A simple hint to improve Robinson and Dickersin's highly sensitive PubMed search strategy for controlled clinical trials. Int J Epidemiol 2005;34:224-5.

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6

Appraising the effectiveness and safety of paclitaxel-eluting stents in over 1000 very high-risk patients: overall results of the Taxus in Real-life Usage Evaluation (TRUE) registry

Giuseppe M Sangiorgi, Giuseppe GL Biondi-Zoccai, Pierfrancesco Agostoni, David Antoniucci, Eberhard Grube, Carlo Di Mario, Bernard Reimers, Corrado Tamburino, John Cosgrave, Antonio Colombo, on behalf of the Taxus in Real-life Usage Evalutaion (TRUE) Investigators

EMO Centro Cuore Columbus and Interventional Cardiology Unit, and San Raffaele Hospital, both in Milan; Division of Cardiology, University of Turin, Turin; Division of Cardiology, Careggi Hospital, Florence; Cardiology Department, Mirano Hospital, Mirano; Clinical Division of Cardiology, Ferrarotto Hospital, Catania, all in Italy. Antwerp Cardiovascular Institute, AZ Middelheim, Antwerp, Belgium. Department of Cardiology, Heart Center Siegburg, Siegburg, Germany. Department of Cardiology, Royal Brompton Hospital, London, UK.

Published in *EuroIntervention* 2007;3:333-339.

ABSTRACT

Aims: Paclitaxel-eluting stents (PES) have been proved safe and effective in selected patients undergoing percutaneous coronary intervention (PCI). However, there is uncertainty on the performance of PES in real-world patients at higher risk for major adverse cardiovascular events (MACE) or restenosis. We conducted a multicenter registry enrolling very high-risk subjects treated with PES.

Methods and results: We enrolled 1065 consecutive patients undergoing PES implantation, provided that the target lesion treated with the PES was an unprotected left main (N=113), a true bifurcation (N=219), a chronic total occlusion (CTO, N=183), a long lesion (>28 mm, N=283), in a small vessel (<2.75 mm, N=417), or the patient had medically-treated diabetes mellitus (N=315). Clinical events were adjudicated at 1 and 7 months, and 4 to 8-month angiographic follow-up was recommended for core-lab quantitative coronary angiography. The primary end-point was the 7-month occurrence of MACE, ie the composite of cardiac death, non-fatal myocardial infarction (MI), coronary artery bypass grafting (CABG) and percutaneous target vessel revascularization (TVR). A total of 2116 lesions were treated with 2.0±1.2 Taxus per patient and 46.4±30.1 total Taxus length per patient. One-month MACE occurred in 4.3% of patients, with 0.4% cardiac death, 3.3% myocardial infarction (MI), 0.1% coronary artery bypass grafting (CABG), and 0.8% target vessel revascularization (TVR) PCI. Seven-month events were as follows: MACE 20.4%, cardiac death 1.2%, MI 4.2%, CABG 1.2%, TVR-PCI 15.4% and target lesion revascularization (TLR)-PCI 10.9%. Binary restenosis occurred in 20.7% out of the 1071 lesions undergoing follow-up angiography. Finally. stent thrombosis (ST) was reported with a 0.8% 12-month cumulative rate (0.3% acute, 0.3% subacute, and 0.2% <6 months, but no thrombosis >6 months).

Conclusion: This registry, enrolling 1065 high-risk patients treated with PES, confirms the satisfactory performance of this device, especially given the overall profile of enrolled subjects and the limited number of stent thromboses.

INTRODUCTION

There is now evidence on the effectiveness and mid-term safety of drug-eluting stents in comparison to bare-metal stents (BMS) in selected patients and lesions.[1] While new devices have been entering the market recently,[2] most data concern polymer-based sirolimus-eluting stents (Cypher, Cordis, Miami, FL) and polymer-based paclitaxel-eluting stents (PES, Taxus, Boston Scientific, Natick, MA), and, indeed, since the publication of the first human feasibility study in humans in January of 2003, PES have entered the mainstream of interventional cardiology.[3-6]

While randomized trials enrolling subsets of higher-risk patients and lesions treated with PES have reported encouraging results, and awaiting for the ongoing trials of coronary artery bypass grafting (CABG) vs PES in patients with multivessel triple vessel or unprotected left main disease, the interventional cardiology community still faces the challenge of either avoiding the potentially beneficial implantation of a PES in a patient not strictly fulfilling the stringent selection criteria of the available randomized trials, or deciding for implanting a PES despite the lack of a sound evidence base. In this context, we must rely on multicenter registries and non-experimental studies,[7-8] notwithstanding their inherent limitations.[9] Indeed, to date only registries can provide the opportunity to test the risk-benefit ratio of PES in very high-risk or complex lesions unlikely to be the object of randomized comparison with BMS, such as unprotected left main, bifurcation lesions, or safenous vein grafts.[10-13]

We thus conducted a multicenter registry enrolling high-risk patients and lesions treated with PES, with the goal of thoroughly appraising its mid-term risk-benefit profile both clinically and angiographically.[14]

METHODS

Patients.

Consecutive patients undergoing PES implantation, using the Taxus Express[2] device were prospectively enrolled provided that the target lesion treated with the PES was an unprotected left main, a true bifurcation, a chronic total occlusion, a long

lesion (>28 mm), in a small vessel (<2.75 mm), or the patient was diabetic. Exclusion criteria were: ongoing or recent (≤24 hours) ST-elevation acute myocardial infarction, impossibility to assume or continue to combined antiplatelet therapy (aspirin plus ticlopidine or clopidogrel) for ≥8 months following PES implantation), or allergy to paclitaxel. High-risk patients treated at participating centers were not treated universally with PES, but occasionally and at physician's discretion with other devices. Nonetheless, most high-risk procedures during the study period were performed with this device. All enrolled patients provided written informed consent. Given the observational design, Ethics Committee approval was obtained for data collection only.

Procedure.

Coronary angioplasty and PES implantation were performed according to standard practice. At the start of the procedure, unfractionated heparin was recommended at a dosage of 70-100 IU/kg to achieve an activated clotting time ≥250 seconds. Patients were started on aspirin and thienopyridines ≥3 days before the procedure and to continue for ≥8 months, while a loading dose of clopidogrel was used in those not previously taking thienopyridines.[15] Clinical follow-up was scheduled for all patients by means of direct visit or phone call at discharge, and at 1, and 7. Angiographic follow-up was recommended between 4 and 8 months or earlier if a non-invasive evaluation or the clinical presentation suggested the presence of recurrent myocardial ischemia.

Quantitative angiographic analysis.

Coronary angiograms were analyzed in a core laboratory (Mediolanum Cardio Research) according to standard methods (QCA CMS 5.2, Medis, Leiden, The Netherlands). Reference vessel diameter, minimum lumen diameter, diameter stenosis, lesion length and late loss were computed at the in-segment, proximal and distal (5 mm) edges, and in-stent. Binary angiographic restenosis was adjudicated in case of >50% diameter stenosis.

Outcomes.

The primary end-point was the 7-month rate of major adverse cardiovascular events, defined as the composite of cardiac death, non-fatal myocardial infarction, coronary artery bypass grafting (CABG) and percutaneous target vessel revascularization. As secondary end-points, we analyzed the individual 7-month occurrence of cardiac death, myocardial infarction, target vessel revascularization, target lesion revascularization, and stent thrombosis. Safety end-points were the rates of major and minor bleeding (defined according to the Thrombolysis In Myocardial Infarction [TIMI] scheme), stroke, and bone marrow toxicity due to thienopyridines. Myocardial infarction was defined as Q-wave or non–Q-wave (defined as elevation of total CK 2 times above the upper limit of normal with a positive MB fraction in the absence of pathological Q waves), will all patients having post-procedural blood draws until discharge. Target lesion revascularization was defined as any percutaneous revascularization performed on the treated segment, and target vessel revascularization as any percutaneous reintervention performed on the treated vessel. Stent thrombosis was adjudicated according to the definite and probable Academic Research Consortium definitions and distinguished in acute (occurring in the catheterization laboratory), subacute (≤1 month) and late (>1 month).[8]

Statistical analysis.

Continuous variables were reported as mean±standard deviation or median (interquartile range) and compared with Student t test or Mann-Whitney U or Wilcoxon tests, when appropriate. Categorical variables were reported as n/N (%) and compared with uncorrected chi-square or Fisher exact tests, when appropriate. The Kaplan-Meier method was employed for survival analysis. Multivariable logistic regression analyses were performed by concomitantly entering all significant ($p<0.05$) univariate predictors of adverse events in the final model. Similarly, we take into account time to event and censoring with Cox proportional hazard analyses. Computations were performed with BMDP (Saugus, MA, USA) and SPSS 11.0 (Chicago, IL, USA), with significance was set at the 2-tailed 0.05 level.

RESULTS

Baseline characteristics and in-hospital outcomes.

Patient, lesion and procedural characteristics are available in Tables 1-3. Specifically, enrollment according to the high-risk inclusion criteria is confirmed by occurrence of diabetes in 322 (30.2%), subjects, unprotected left main intervention in 115 (10.8%), true bifurcation stenting in 229 (21.5%), PES implantation in a chronic total occlusion in 191 (17.9%), in small vessels in 430 (40.4%), and in long lesions in 289 (27.1%). In-hospital major adverse cardiovascular events occurred in 40 (3.8%) patients, with 2 (0.2%) cardiac deaths, 32 (3.0%) myocardial infarctions, 5 (0.5%) target vessel revascularizations, and no CABG. In-hospital bleedings occurred in 15 patients (1.4%), with 4 (0.4%) major and 11 (1.1%) minor bleeds.

Table 1. Patient characteristics and high-risk features.

Patients	N=1065
Age (y)	64.2±10.2
Males	860 (80.8%)
Dyslipidemia	414 (38.5%)
Hypertension	731 (68.6%)
Unstable angina	427 (40.1%)
Prior acute myocardial infarction	494 (46.4%)
Prior percutaneous coronary intervention	433 (40.7%)
Prior coronary artery bypass surgery	184 (17.3%)
LVEF (%)	54.6±9.7
High-risk features	
Diabetes mellitus	322 (30.2%)
Unprotected left main stenting	115 (10.8%)
Small vessel (<2.75 mm) stenting	430 (40.4%)
Long lesion (>28 mm) stenting	289 (27.1%)
Chronic total occlusion stenting	191 (17.9%)
Bifurcation stenting	229 (21.5%)

Values are expressed as mean±standard deviation or n (%); LVEF=left ventricular ejection fraction.

Table 2. Lesion characteristics.

Lesions	N=2116
Target lesion distribution	
Left main	124 (5.9%)
Left anterior descending	824 (38.9%)
Left circumflex	627 (29.6%)
Right coronary artery	502 (23.7%)
Arterial or venous grafts	39 (1.8)%
American College of Cardiology/American Heart Association type	
A or B1	622 (29.4%)
B2	849 (40.1%)
C	506 (24.0%)
Ostial	645 (30.5%)
Eccentric	1350 (63.8%)
Vessel angulation (>45°)	476 (22.5%)
Diffuse disease	1043 (49.3%)
Bifurcation	229 (10.8%)
Trifurcation	6 (0.3%)
Moderate to severe calcification	472 (22.3%)
Chronic total occlusions	288 (13.6%)
In-stent restenosis	213 (10.1%)
Intraluminal thrombus	123 (5.8%)

Values are expressed as mean±standard deviation or n (%).

Table 3. Procedural characteristics.

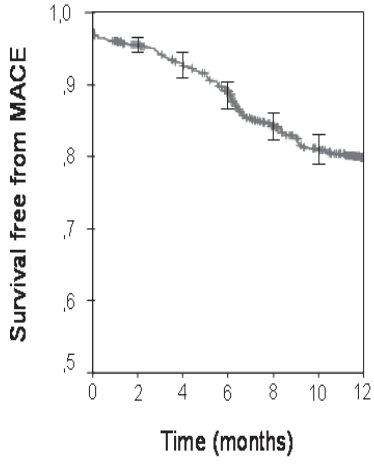
Lesions	N=2116
Taxus stents per patient	2.02±1.16
Taxus stents per lesion	1.55±0.77
Taxus length per patient (mm)	46.37±30.1
Taxus length per lesion (mm)	35.66±21.37
Pre-dilation	1651 (78.0%)
Post-dilation	678 (32.0%)
Intravascular ultrasound	206 (9.7%)
Directional coronary atherectomy	26 (1.2%)
Rotablation	27 (1.2%)
Cutting balloon	150 (7.1%)
Maximum balloon dilation pressure (ATM)	14.4±2.9
Peri-procedural glycoprotein IIbIIIa inhibitors*	388 (36.4%)
Medical therapy at discharge*	
Aspirin	1041 (97.7%)
Beta-blockers	610 (57.3%)
Calcium channel antagonists	267 (25.1%)
Clopidogrel	766 (71.9%)
Nitrates	126 (11.8%)
Statins	813 (76.3%)
Ticlopidine	291 (27.3%)

Values are expressed as mean±standard deviation or n (%); *per patient (n=1065) analysis.

Mid and long-term clinical outcomes.

Clinical follow-up was available at 7 and 12 months in 969 (91.0%) and 883 (82.9%) patients, respectively, and is reported, together with 1-month follow-up, in Table 4. Specifically, median follow-up duration was 12.2 months (1st-3rd quartiles 11.9-13.0). Despite the complex patient and lesion features, major adverse cardiovascular events occurred at 7 months in 198 (20.4%) patients, and most of them (149 [15.4%]) were percutaneous repeat revascularizations, respectively 37 (3.8%) on the target vessel but far from the target lesion, and 106 (10.9%) on the target lesion. Accordingly, CABG was needed in only 12 subjects (1.2%). Figure 1 shows the overall major adverse cardiovascular event-free survival according to the Kaplan-Meier method. In addition, the favorable performance of PES in this complex setting was confirmed by the remarkably low rate of definite or probable stent thrombosis (cumulative 0.8%, acute 0.3%, subacute 0.3%, and late (>1 month) 0.2%. Notably, no case of stent thrombosis between 6 and 12 months was reported. Stent thrombosis defined as definite only was similarly uncommon (cumulative 0.7%, acute 0.3%, subacute 0.2%, and late 0.2%). Figure 2 shows survival free from thrombosis-related events (cardiac death, myocardial infarction, or stent thrombosis) according to the Kaplan-Meier method.

Figure 1.



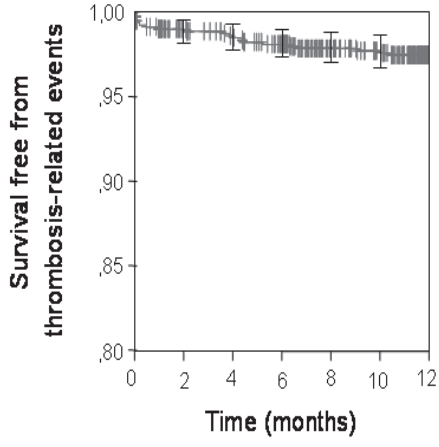
Survival free from major adverse cardiovascular events (MACE, ie cardiac death, non-fatal myocardial infarction, or target vessel revascularization, either surgical or percutaneous), with 95% confidence intervals.

Table 4. Clinical outcomes.

Patients	N=1065
Cumulative 1-month clinical events	
Major adverse cardiovascular events	46 (4.3%)
Cardiac death	4 (0.4%)
Myocardial infarction	35 (3.3%)
CABG	1 (0.1%)
Percutaneous target vessel revascularization	9 (0.8%)
Percutaneous target lesion revascularization	6 (0.5%)
Cumulative 7-month clinical events (N=969)	
Major adverse cardiovascular events	198 (20.4%)
Cardiac death	12 (1.2%)
Myocardial infarction	41 (4.2%)
CABG	12 (1.2%)
Percutaneous target vessel revascularization	149 (15.4%)
Percutaneous target lesion revascularization	106 (10.9%)
Cumulative 12-month clinical events (N=883)	
Major adverse cardiovascular events	205 (23.2%)
Cardiac death	15 (1.7%)
Myocardial infarction	43 (4.9%)
CABG	12 (1.4%)
Percutaneous target vessel revascularization	151 (17.1%)
Percutaneous target lesion revascularization	108 (12.2%)
Definite or probable stent thrombosis	
Acute	3 (0.3%)
Subacute	3 (0.3%)
Late (>1 month and <6 months)	2 (0.3%)
Very late (>6 months)	0
Cumulative	8 (0.8%)

Values are expressed as n (%).

Figure 2.



Survival free from thrombosis-related events (ie cardiac death, myocardial infarction, or probable stent thrombosis), with 95% confidence intervals.

Angiographic follow-up.

Baseline and post-procedural core-lab angiographic analysis was completed on all cases. On the other hand, angiographic follow-up was available for 1071 lesions (64.7% of those treated with PES). Details of such angiographic analysis are available in Table 5. In particular, despite the high-risk characteristics of the lesions treated with PES in this study, late loss and binary restenosis rates appeared similar to those reported in trials employing PES in lower risk patients, with in-stent values of 0.54±0.63 mm and 14.7%, respectively.

Table 5. Quantitative coronary angiographic (QCA) results.

Lesions	Baseline (N=1655)	Post-procedural (N=1655)	Follow-up (N=1071)
In-segment			
Reference vessel diameter (mm)	2.59±0.51	2.82±0.54	2.66±0.64
Minimum lumen diameter (mm)	0.78±0.47	2.12±0.55	1.73±0.71
Lesion length (mm)	17.55±13.24	25.86±15.08	26.31±15.83
Diameter stenosis (%)	70.12±16.15	25.24±11.22	36.94±21.26
Binary restenosis	-	-	222 (20.7%)
Late loss	-	-	0.38±0.62
In-stent			
Reference vessel diameter (mm)	-	2.94±0.48	2.71±0.59
Minimum lumen diameter (mm)	-	2.52±0.46	1.97±0.73
Lesion length (mm)	-	6.13±3.22	7.62±6.37
Diameter stenosis (%)	-	14.48±7.77	29.37±21.79
Binary restenosis	-	-	157 (14.7%)
Late loss	-	-	0.54±0.63
Proximal edge			
Reference vessel diameter (mm)	-	3.18±0.54	2.96±0.65
Minimum lumen diameter (mm)	-	2.78±0.65	2.5±0.82
Lesion length (mm)	-	3.71±1.91	3.75±1.91
Diameter stenosis (%)	-	12.9±11.58	17.11±19.58
Binary restenosis	-	-	73 (6.8%)
Late loss	-	-	0.82±0.78
Distal edge			
Reference vessel diameter (mm)	-	2.61±0.49	2.39±0.64
Minimum lumen diameter (mm)	-	2.1±0.56	1.93±0.69
Lesion length (mm)	-	4.92±0.36	4.85±0.57
Diameter stenosis (%)	-	19.87±13.2	21.75±20.9
Binary restenosis	-	-	77 (7.2%)
Late loss	-	-	0.10±0.71

Values are expressed as mean±standard deviation or n (%)

Exploratory univariate and multivariable analyses.

Univariate analysis identified the following predictors of MACE: number of diseased vessels (p<0.001), peripheral vascular disease (p=0.009), treatment of a bifurcation (p=0.034), a complex (p=0.027), or an ostial lesion (p=0.040), final TIMI flow <3 in any of the treated vessels (p=0.033), number of treated lesions (p<0.001), number of implanted PES (p=0.001), and per-patient PES length (p=0.002). Multivariable analysis including these covariates simultaneously disclosed that the only multivariable predictor of MACE was number of treated lesions (p=0.002). Results of logistic regression analysis were confirmed at Cox proportional hazard analysis (p<0.001 for number of treated lesions at multivariable analysis). Among univariate predictors of death, we identified achievement of complete revascularization (p=0.005), congestive heart failure (p<0.001) or acute coronary syndrome (p=0.002) at admission, diabetes (p=0.016), chronic renal failure (p<0.001), and left ventricular ejection fraction (p=0.026). Among these, only complete revascularization (p=0.015), acute coronary syndrome at admission at admission (p=0.013), and chronic renal failure (p=0.001) remained as significant multivariable predictors of death. Number of diseased vessels (p=0.009), peripheral vascular disease (p=0.010), target vessel (p=0.041), treatment of a chronic total occlusion (p=0.004), bifurcation (p=0.042), use of intravascular ultrasound (p=0.003), number of treated lesions (p=0.001), and final TIMI flow (p<0.001) were univariate predictors of myocardial infarction, while only treatment of a chronic total occlusion (p=0.036), number of treated lesions (p=0.001), and final TIMI flow (p=0.001) remained as multivariable independent predictors. Univariate analysis identified the following predictors of TVR: prior infarction (p=0.036), number of diseased vessels (p=0.002), target vessel (p=0.003), number of treated lesions (p=0.001), per-lesion PES length (p=0.007), and per-patient PES length (p=0.011). Multivariable analysis including these covariates simultaneously disclosed that the only multivariable predictors of TVR were prior infarction (p=0.008) and target vessel (p=0.004), with a higher risk of TVR in lesions located in a left main or in a saphenous vein graft. Finally, univariate analysis disclosed the following predictors of cumulative stent thrombosis: treatment of a bifurcation (p=0.035) or ostial lesion (p=0.050), reference vessel diameter (p=0.027), and maximum balloon dilation pressure (p=0.002). Multivariable analysis including these covariates simultaneously

showed however that only ostial location (p=0.018) and maximum balloon dilation pressure (p=0.003) independently predicted stent thrombosis, with this event being more frequent in ostial lesions or after dilation with lower pressures. Specifically, lesions with stent thrombosis had been dilated at a median of 10 atm (1st-3rd quartiles 8-13), while lesions without thrombosis had been dilated at a median of 14 (12-16).

DISCUSSION

Findings of the present multicenter registry, appraising the safety and effectiveness of PES in high-risk patients and lesions, are three-fold: a) in light of the complex clinical and anatomical setting, the performance of the device was satisfactory, with the vast majority of events due to repeat percutaneous revascularization procedures and only 12 cases CABG at 12-month follow-up; b) optimal antithrombotic regimens, including pre-procedural thienopyridine pretreatment or loading, peri-procedural glycoprotein IIb/IIIa usage at physician's discretion, and long-term (≥8 months) double antiplatelet treatment, yielded low rates of stent thrombosis and other thrombosis-related events, a remarkable achievement given the very complex patient and lesion setting; c) the powerful anti-proliferative effect of PES was confirmed even in these series of complex procedures, as shown by rates of binary restenosis and values of late loss obviously lower than those of historical bare-metal stent controls. Other important findings stemming from the TRUE registry have already been presented, including data on bifurcation lesions and thienopyridine treatment.[15-16]

Current clinical research context

Since their introduction, drug-eluting stents in general and PES in particular have been widely adopted by interventional cardiologists worldwide.[1,3-4] However, as with most medical interventions, evidence of benefit for PES was at first limited to highly selected patients with relatively benign and uncomplex lesions.[3-4] While such proof of effect provided the basis for the diffusion among interventionists together with the results of the first pivotal trial, the TAXUS IV,[5] uncertainty has persisted on the risk-benefit balance of this device in higher risk patients and lesions.

More recent randomized trials enrolling complex patients and lesions have been reported in support of the use of PES, including the TAXUS V and the TAXUS VI trials.[17-18] specifically, the TAXUS V trial reported on 1156 patients undergoing PCI in small, very large, or long lesions with either PES (n=577) or bare-metal stents (n=579) for a mean stent length per patient of 28 mm.[17] At 9 months, compared with bare-metal stents, PES reduced target lesion revascularization from 15.7% to 8.6% and target vessel revascularization from 17.3% to 12.1%. Similar benefits were found concerning binary angiographic restenosis, which was reduced from 33.9% to 18.9% in the entire study cohort, as well as among patients receiving 2.25-mm stents (49.4% vs 31.2%), 4.0-mm stents (14.4% vs 3.5%), and multiple stents (57.8% vs 27.2%). The TAXUS VI similarly enrolled 448 patients with a target coronary lesion length ranging from 18 to 40 mm, treating them with PES (n=219) or bare-metal stents (n=227) for a mean stent length per patient of 33 mm, showing at 9 months a 9.1% rate of target vessel revascularization in the PES group and 19.4% in the BMS group.[19] Despite the novel data on higher-risk patients provided these most recent TAXUS studies, even these trials were limited by strict selection criteria and obvious issues of external validity typical of randomized studies.[19] Notably, chronic total occlusions, bifurcations, and left main interventions were explicitly excluded from these study, while they formed a major part of included cases in the true study.

Beside our current work, other carefully designed prospective observational studies have provided a thorough and as far as possible unbiased appraisal of the risk-benefit balance of PES in true high-risk patients. In this context, precise and complete data are evolving, especially given the fact that PES were introduced into clinical practice only few years ago and thus long-term follow-up is incomplete. Nonetheless, Ong et al reported on unselected patients treated with PES (N=576) or sirolimus-eluting stents (N=508) in the Thoraxcenter, Rotterdam.[7] At 1-year follow-up major adverse cardiovascular events occurred in 13.9% and 10.5% respectively, with an adjusted hazard ratio of 1.20 (0.85 to 1.70), while clinically driven target vessel revascularization was 5.4% versus 3.7%, respectively (hazard ratio 1.38 (0.79 to 2.43). Despite the absence of explicit selection criteria, in this study only 4% of subjects were treated for left main disease and 16% for bifurcation lesions, with a total stent length per patient of 42.9 mm, thus making their patient population at a lower risk than that of the

TRUE study. Similar results have been reported in larger post-marketing surveillance studies, such as the ARRIVE, STENT, and WISDOM registries.

Limitations of the present study

Drawbacks of non-randomized trials are well known,[2] and are also pertinent to the TRUE Registry. Of utmost relevance to the current debate on the safety of drug-eluting stents[20-22] is the length of follow-up, which is mainly limited to the 7-month frame in this work and thus likely underestimates event rates, specifically stent thrombosis. Thus, at this time no definitive conclusions on the risk-benefit balance of PES after 1 year in high-risk patients similar to those enrolled in the TRUE study can be drawn. In addition, angiographic follow-up was recommended on a clinical basis, given the high-risk patient characteristics, but even patients not willing to undergo angiographic follow-up could be enrolled. This thus lead to a relatively low angiographic follow-up rate, at least when compared to randomized trials with systematic angiographic control.[3-4] In addition, PES were implanted at the physician's discretion, thus patient inclusion is representative of current treatment practices at participating centers. Finally, the lack of an clinical event committee for all events should be viewed with caution, even if angiographic analyses and adjudication of target vessel events were performed by an independent core laboratory.

Conclusions

The TRUE multicenter prospective study, enrolling more than 1000 patients with complex clinical or lesion features undergoing PES implantation, supports the favorable mid-term performance of this drug-eluting stent, especially given the profile of enrolled subjects and the limited number of stent thromboses.

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7

Clinical outcome following aleatory implantation of paclitaxel-eluting or sirolimus-eluting stents in complex coronary lesions.

John Cosgrave, Pierfrancesco Agostoni, Lei Ge, Ioannis Iakovou, Alaide Chieffo, Giuseppe GL Biondi-Zoccai, Giuseppe M. Sangiorgi, Matteo Montorfano, Iassen Michev, Flavio Airoldi, Mauro Carlino, Nicola Corvaja, Ermino Bonizzoni, Antonio Colombo.

EMO Centro Cuore Columbus and San Raffaele Hospital, Milan, Italy.

Published in the *American Journal of Cardiology* 2005;96:1663-1668.

ABSTRACT

To compare the clinical efficacy of paclitaxel-eluting stents (PES) and sirolimus-eluting stents (SES) in a contemporary cohort of complex patients. We collected data on 9-month outcomes in 529 patients (281 in the PES group and 248 in the SES group) treated with drug eluting stents in de-novo lesions. The end-point was: per-patient in-hospital and follow-up major adverse cardiac events defined as a composite of death, myocardial infarction and target vessel revascularization, including target lesion revascularization. There were no in-hospital deaths or repeat revascularizations, while 5.7% of the PES and 2% of the SES group developed a myocardial infarction (p=0.04). At a median follow-up of 10.6 months, the major adverse cardiac events rate was similar between the 2 groups (18.1% vs. 21%; adjusted hazard ratio [HR]: 0.85, 95% confidence interval 0.57-1.25), without any difference in the occurrence of death or myocardial infarction. Diabetes and total stent length were independent predictors of major adverse cardiac events. Propensity analysis confirmed the similarity between the two devices (HR: 0.87 [0.62-1.25]). The majority of restenosis was focal and only two patients required surgical revascularization. In summary implantation of DES in complex lesions is associated with favorable results and most of the patients remain free from surgical revascularization at follow-up. Overall both the available stent platforms have similar performance characteristics.

INTRODUCTION

The potential of drug eluting stents (DES) to significantly reduce restenosis has encouraged the increasing treatment of complex lesions which in the bare metal stent era may have been considered prohibitive due to the necessity for repeat interventions.[1-9] Also the technical approach of most interventionalists has changed from focal stenting to one of complete lesion coverage and often stenting from "normal vessel to normal vessel". This has led to a significant increase in the number of stents deployed and to an increase in total stent length.[10] Since March 2003, when the paclitaxel-eluting stent (PES) became available for clinical use in our institution, we undertook a contemporary comparison between both stents in our everyday practice.

METHODS

Between the 1st of March 2003 and the 28th of February 2004 all consecutive patients treated with a single type of drug eluting stent were considered for our analysis. Patients were excluded if they received a mixture of different types of DES, if a bare metal stent was implanted, if the lesion was a restenosis or they had an acute myocardial infarction. During this time period a total of 839 patients were treated with a DES, 179 were treated for restenotic lesions, 91 had a mixture of different types of DES implanted and 40 had a mixture of DES and bare metal stent. The remaining 529 patients (867 lesions) comprise the study cohort.

All patients gave written informed consent prior to the procedure. Antiplatelet therapy and peri-procedural heparin dosing followed standard protocols[11]. Following the procedure all patients were prescribed dual anti-platelet therapy for 1 year. Platelet glycoprotein IIb/IIIa receptor inhibitors, interventional approach and intra-vascular ultrasound usage were all at the operator's discretion. Stent selection while at the operators discretion was carried out in an aleatory fashion.

Clinical follow-up was performed by telephone contact or office visit at 1, 6, 9 and 12 months after the index procedure. Angiographic follow up was encouraged for all

patients; those who did not undergo angiography were asymptomatic with a negative test for inducible ischemia. The clinical endpoints analyzed were in-hospital and post-discharge total death, myocardial infarction, target vessel revascularization and target lesion revascularization during the total follow up period. The follow-up data were combined into a composite endpoint of major adverse cardiac events, defined as a composite of death, myocardial infarction and target vessel revascularization, which was evaluated on a per patient basis and was considered the primary endpoint. Target lesion revascularization was also analyzed separately on a per-lesion basis. All deaths were considered cardiac unless otherwise documented. A non-Q-wave myocardial infarction was defined as a total creatine kinase elevation of greater than 2 times the upper limit of normal in combination with an elevation in the creatine kinase-MB fraction. If this enzyme elevation was associated with the development of a new pathological Q-wave it was considered to be a full thickness or Q wave infarction. Target lesion revascularization was defined as repeat revascularization secondary to a stenosis ≥ 50% within the stent or within the 5 mm borders proximal or distal to the stent edge at the follow-up angiogram. Target vessel revascularization was defined as repeat revascularization of the target vessel. Stent thrombosis was defined as any of the following: i) angiographic documentation of intra-stent filling defect or stent occlusion associated with a clinical event or ii) sudden cardiac death or post-procedural myocardial infarction after successful DES implantation not clearly attributable to any other coronary lesion.[12-14]

Coronary angiograms were analyzed using validated edge detection system (CMS, version 5.2, MEDIS, The Netherlands).[15] Angiographic restenosis was defined as diameter stenosis ≥ 50% by quantitative coronary angiography within a previously stented segment (stent and 5 mm proximal and distal) at the follow-up angiogram. Continuous variables are presented as means ± standard deviation or medians (inter-quartile range [IQR]) and categorical variables as frequencies (%). Continuous variables were compared using independent sample Student's *t* or Mann-Whitney U test. Categorical variables were compared with chi-square statistics. The variables entered into the multivariate model were stent type, diabetes mellitus, reference vessel diameter, stent length, bifurcation, chronic total occlusion, IVUS done and glycoprotein IIb/IIIa inhibitor usage. The Cox proportional-hazards regression

model was used to identify the independent predictors of major adverse cardiac events at follow-up. In order to account for potential differences between the SES and PES cohorts, a propensity analysis was performed on a patient-based setting for major adverse cardiac events and on a lesion-based setting for target lesion revascularization.[16-17] Both were performed using Stratified Cox Regression with DES type as fixed dummy covariate and propensity score quartiles (propensity to be treated with PES estimated by non-parsimonious multivariable logistic regression) as stratification variable. In the lesion-based analysis, as observations recorded in the same patient cannot be considered independent [18], the sandwich estimator of variance-covariance matrix was employed in order to take into account clustered data (more lesions within the same subject). The results are reported as adjusted hazard ratios (HR) with associated 95% confidence interval (CI). A p-value of <0.05 was considered to be statistically significant and all reported p-values are two-sided. Statistical analysis was performed using SPSS 11.5 (SPSS Inc.) and SAS 8.2 (SAS Institute Inc.).

RESULTS

Baseline demographic and procedural data are presented in Table 1. Overall the complexity of this cohort is demonstrated by the high percentage of multi-vessel disease (75%), previous bypass surgery (20%), B2 or C lesions (70%) and the mean stent length per patient (52±37 mm). The two groups were well matched apart from a higher percentage of patients with previous bypass surgery in the PES group. The lesion characteristics were different between the two groups with a higher proportion of B2 and C type lesions and a larger reference vessel diameter in the PES group. During the index procedure cutting balloon pre-dilation and intravascular ultrasound use were more common in the PES group, while more patients in the SES group received glycoprotein IIb/IIIa inhibitors. The mean stent size, final max balloon diameter, post-procedural minimal lumen diameter and reference vessel size were all larger in the PES group. Angiographic success was achieved in 99.8% of the PES group and 99.6% of the SES group.

Table 1. Baseline clinical and procedural characteristics of the patients and the lesions treated in the two groups.

	PES (n=281)	SES (n=248)	P-value
Age (years)	62.3 ± 9.9	62.1 ± 11.5	0.8
Men	86.8%	89.1%	0.5
Ejection Fraction (%)	53.2 ± 10	51.7 ± 9.9	0.09
Prior myocardial infarction	48.4%	49.2%	0.86
Prior coronary angioplasty	31.3%	37.1%	0.17
Prior coronary bypass surgery	24.9%	16.1%	0.014
Risk factors			
Family history	44.1%	45.6%	0.79
Hypertension	65.5%	63.7%	0.71
Hypercholesterolemia	71.9%	66.9%	0.22
Current smoker	19.9%	16.9%	0.67
Diabetes Mellitus	23.8%	24.2%	0.92
Diet controlled	2.8%	2.4%	
Oral hypoglycaemics	13.2%	17.3%	
Insulin	7.8%	4.4%	
Unstable angina pectoris	25.3%	26.2%	0.84
Narrowed coronary arteries			0.9
Single	27%	25.8%	
Double	34.5%	36.3%	
Triple	38.4%	37.9%	
Intra-aortic balloon pump	3.6%	2.4%	0.61
Total IIb/IIIa inhibitors	12%	21.7%	0.002
Bail out IIb/IIIa inhibitors	3.9%	2.8%	0.328
Number of Stents per patient	2.08 ± 1.33	2.17 ± 1.5	0.5
Range	1-8	1-9	
Total stent length (mm)	51.1 ± 36.1	53.2 ± 39.2	0.5
Range	8-232	8-207	
Lesions	**(n=445)**	**(n=422)**	
Vessel involved			0.42
Left main	5.6%	3.1%	
Left anterior descending	40.2%	43.5%	
Circumflex	26.1%	28%	
Right coronary artery	19.9%	18.9%	
Bypass graft	2.4%	2.1%	
Other	5.8%	4.4%	
Bifurcations	21.4%	20.8%	0.86
Chronic total occlusions	13.9%	11.4%	0.26
Calcified lesions	24.3%	24.1%	0.95

AHA/ACC lesion type			<0.001
A	1.8%	1.9%	
B1	23.4%	35.9%	
B2	48.6%	44%	
C	26.3%	18.2%	
Directional atherectomy	1.6%	1.2%	0.77
Rotational atherectomy	1.8%	0.5%	0.11
Cutting Balloon	18.3%	10.6%	0.001
Intra-vascular ultrasound	21.2%	12.3%	0.001
Number of stents per lesion	1.31 ± 0.65	1.27 ± 0.58	0.42
Stent length (mm)	31.9 ± 20.3	31.2 ± 17.1	0.59
Stent diameter (mm)	3.05 ± 0.38	2.92 ± 0.38	<0.001
Max. balloon diameter (mm)	3.09 ± 0.4	2.98 ± 0.41	<0.001
Max inflation pressure (atm)	15.8 ± 3.5	15.7 ± 3.2	0.61

Data are presented as percentages or means ± standard deviation, unless otherwise specified.

PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent.

Serial quantitative coronary angiography data are shown in Table 2. Angiographic follow-up was available in 196 patients in the PES group (69.8%) at a median of 6.6 months post procedure (IQR 5.7-8) and 163 patients (65.7%) in the SES group at a median of 7.1 months post procedure (IQR 5.8-8.75). The percentage of routine and symptom driven follow-up angiography were similar in both groups, the symptom driven angiography was 18% in the PES group and 22% in the SES group (p = 0.175). There was no statistical difference in restenosis rates between the PES and SES groups (17.3% compared with 19.6%, p = 0.48). The late lumen loss which was not normally distributed was higher in the PES group (0.41 [IQR –0.02-0.85] compared with 0.29 [IQR –0.09-0.66] after SES, p = 0.03). The majority of restenosis demonstrated a focal pattern (PES 55.8% compared to SES 66.7% p = 0.44) and 76.5% were intra-stent.

Table 2. Quantitative coronary angiographic data.

	PES	SES	P-value
Pre-procedure			
Number of lesions	(n=445)	(n=422)	
Reference vessel diameter (mm)	2.79 ± 0.64	2.7 ± 0.58	0.028
Minimal luminal diameter (mm)	0.84± 0.53	0.85 ± 0.49	0.947
Diameter stenosis (%)	69.0 ± 17.3	68.0 ± 17.2	0.401
Lesion Length (mm)	13.3 ± 9.5	13.5 ± 9.5	0.775
Post-procedure			
Reference vessel diameter (mm)	3.19 ± 0.55	3.07 ± 0.53	0.001
Minimal luminal diameter (mm)	2.83 ± 0.52	2.70 ± 0.50	<0.001
Diameter stenosis (%)	11.1 ± 7.6	12.3 ± 7.9	0.023
Acute gain (mm)	1.99 ± 0.63	1.85 ± 0.59	0.001
Follow-up			
Number of lesions	(n=296)	(n=267)	
Reference vessel diameter (mm)	2.99 ± 0.54	3.03 ± 0.52	0.39
Minimal luminal diameter (mm)	2.28 ± 0.84	2.27 ± 0.88	0.98
Diameter stenosis (%)	24.9 ± 22.8	26.0 ± 24.8	0.58
Late loss (mm)	0.55 ± 0.76	0.45 ± 0.76	0.15
Median (IQR)	0.41 (-0.02–0.85)	0.29 (-0.09–0.66)	0.03
Angiographic restenosis	17.3%	19.6%	0.48

Data are presented as means ± standard deviation or percentages unless otherwise specified. IQR: interquartile range; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent.

There were no in-hospital deaths or peri-procedural revascularizations. In the SES group 200 patients (80.6%) and in the PES group 240 patients 85.4% had complete CK measurements following PCI. The incidence of in-hospital myocardial infarction was 5.7% in the PES group and 2% in the SES group (p= 0.043) with only one Q-wave myocardial infarction in the PES group. This increase in incidence of peri-procedural myocardial infarction in the PES group was present even in patients treated without glycoprotein IIb/IIIa inhibitors (3.9% vs. 2% p=0.16). Median clinical follow up was 10.6 months (IQR 8.4-12.8) and only 4 patients (all in the SES group) were lost to follow up. The major adverse cardiac events rate was 18.1% in the PES group vs. 21% in the SES group (p = 0.44) and there were no differences between the groups in the rate of follow-up death, myocardial infarction or late stent thrombosis (Table 3). Multivariate Cox regression analysis showed that the stent type was not associated

with any benefit (HR 0.85 [95% confidence intervals: 0.57-1.25]; p=0.4), while the only independent predictors of major adverse cardiac events (all with p<0.001) were diabetes (HR 2.06 [1.37-3.10]), total stent length per patient (HR 1.008 [1.004-1.012] for every mm increase) and IABP use (HR 5.33 [2.66-10.68]). A patient-based analysis using a propensity score confirmed these results (HR for stent type 0.87 [0.62-1.25]; p=0.46).

A lesion-based analysis revealed that there was a 9.6% target lesion revascularization rate in PES compared with 12.1% in the SES group (p = 0.27) and a target vessel revascularization rate of 11.8% compared with 14.2% respectively, p = 0.31 (Table 3). Importantly only two patients required surgical intervention of which only one was a target lesion revascularization, the other being a target vessel revascularization for disease progression. Multivariate analysis also showed no differences between the two devices (HR 0.73 [0.48-1.13]; p=0.16). Independent predictors of target lesion revascularization (both with p<0.001) were diabetes (HR 2.34 [1.50-3.65]) and lesion length (HR 1.03 [1.02-1.05] for every mm increase). Again, in the lesion-based propensity model similar results were obtained (HR for stent type 0.78 [0.49-1.26]; p=0.32).

Table 3. In-hospital and follow-up clinical events in the total cohort, according to stent type.

	PES (n=281)	SES (n=248)	P-value
In-hospital			
Death	0	0	-
Repeat revascularization	0	0	-
Myocardial infarction*	5.7% (16)	2% (5)	0.043
Acute thrombosis*	0.3% (1)	0	-
Follow-up			
Total death	2.5% (7)	2.4% (6)	0.95
Non-cardiac	0.7% (2)	0	-
Myocardial infarction*	2.5% (7)	2.4% (6)	0.95
Late thrombosis*	1.4% (4)	1.6% (4)	1.0
TLR (per-patient)	12.5 % (35)	16.5% (41)	0.2
TVR (per-patient)	14.9% (42)	19.4% (48)	0.2
Major adverse cardiac events	18.1% (51)	21% (52)	0.44
TLR (per-lesion)	9.6% (43)	12.1% (51)	0.27
TVR (per-lesion)	11.8% (53)	14.2% (60)	0.31

Data are presented as percentages and absolute numbers. *

All the cases of stent thrombosis (acute or late) were adjudicated as myocardial infarctions. PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent; TLR: target-lesion revascularization; TVR: target-vessel revascularization.

As diabetes was shown to be an important independent predictor of events at follow-up, we performed a post-hoc analysis. Diabetes was present in 67 patients (23.8%) from the PES and 59 patients (23.7%) from the SES groups. The major adverse cardiac events rates in PES and SES groups were 23.9% and 36.7% respectively (relative increase 65%; adjusted HR 0.63 [0.33-1.20]; p=0.16) and the lesion-based target lesion revascularization rates were 14.7% and 21.4% (adjusted HR 0.66 [0.33-1.32; p=0.24) (Table 4). In the PES diabetic subgroup 51 patients (76.1%) underwent follow-up angiography and the restenosis rate per lesion was 19.3%, in the SES group 44 patients (73.3%) underwent angiographic follow-up and restenosis was found in 28.8% patients (p=0.142). In contrast in non-diabetic patients the major adverse cardiac events rates were 16.4% and 16% respectively (adjusted HR 1.02 [0.62-1.67]) (Table 5), also there was little difference in the rate of target lesion revascularization (PES 7.8% compared with SES 9.1%, p=0.58).

Table 4. In-hospital and follow-up clinical events in the diabetic patients, according to stent type.

	PES (n=67)	SES (n=60)	P-value
In-hospital			
Death	0	0	-
Repeat revascularization	0	0	-
Myocardial infarction	1.5% (1)	1.7% (1)	1.0
Follow-up			
Total death	3% (2)	6.7% (4)	0.42
Myocardial infarction*	4.5% (3)	3.3% (2)	1.0
Late thrombosis*	1.5% (1)	1.7% (1)	1.0
TLR (per-patient)	19.4 % (13)	28.3% (17)	0.3
TVR (per-patient)	19.4% (13)	33.3% (20)	0.1
Major adverse cardiac events	23.9% (16)	36.7% (22)	0.12
TLR (per-lesion)	14.7% (17)	21.4% (22)	0.22
TVR (per-lesion)	16.4% (19)	24.3%(25)	0.17

Data are presented as percentages and absolute numbers. * All the cases of late stent thrombosis were adjudicated as myocardial infarctions. PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent; TLR: target-lesion revascularization; TVR: target-vessel revascularization.

Table 5. In-hospital and follow-up clinical events in non-diabetic patients, according to stent type.

	PES (n=214)	SES (n=188)	P-value
In-hospital			
Death	0	0	-
Repeat revascularization	0	0	-
Myocardial infarction	7% (15)	2.1% (4)	0.03
Follow-up			
Total death	2.3% (5)	1.1% (2)	0.45
Myocardial infarction*	1.9% (4)	2.1% (4)	1.0
Late thrombosis*	1.4% (3)	1.6% (3)	1.0
TLR (per patient)	10.3 % (22)	12.8% (24)	0.44
TVR (per patient)	13.6% (29)	14.9% (28)	0.77
Major adverse cardiac events	16.4% (35)	16% (30)	0.91
TLR (per-lesion)	7.8% (26)	9.1% (29)	0.58
TVR (per-lesion)	10.2% (34)	10.9%(35)	0.8

Data are presented as percentages and absolute numbers. * All the cases of late stent thrombosis were adjudicated as myocardial infarctions. PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent; TLR: target-lesion revascularization; TVR: target-vessel revascularization.

DISCUSSION

The main findings of this report are as follows: (1) Successful DES implantation in complex lesions has not completely abolished the restenotic response (2) Similar to previous data the majority of restenosis demonstrated a more benign pattern and was amenable to percutaneous treatment (3) In the overall population the performance characteristics of the two stent platforms are similar.

Contrary to most randomized studies,[4,5,7,19] our cohort is composed of a complex group of patients including bifurcation lesions, chronic total occlusions, a high percentage B2/C lesions and multi-vessel stenting. Thus our major adverse cardiac events rate of 19.4% in the total population which is predominately driven by revascularization is more representative of the true efficacy of DES in a highly challenging cohort of patients. Indeed it is doubtful that many of these patients would have been treated

percutaneously in the bare metal stent era. Most of the restenotic lesions were focal, in agreement with previous data,[20-21] and only two patients required bypass surgery, while all the others were amenable to percutaneous treatment and indeed were successfully treated.

Due to some differences in the raw outcomes we used a propensity model. This statistical method allows us to make our two groups more comparable compensating for potential confounding variables, such as smaller reference vessel diameter and stent size in the SES group with a higher proportion of complex lesions and intra-vascular ultrasound use in the PES group. The use of this propensity analysis confirmed the similar performance characteristics of both stents.

While the performance of both stents is similar, looking at the raw data there is a suggestion of benefit for PES in our diabetic patients. While these findings are in concordance with some studies and with the proposed mechanism of action of paclitaxel in diabetics, we feel it is inappropriate to further elaborate on these data due to the small sample size and lack of formal randomization.[4,22]

An interesting finding in our study is the apparent contradiction between the degree of late loss compared to angiographic restenosis and target lesion revascularization. While the late loss is significantly lower in the SES group, the restenosis and target lesion revascularization rates are similar between the two stents. It must be remembered that the late loss is a calculated average of non-normally distributed data and many patients have luminal loss that does not cause angiographic restenosis.[23] In this regard there may be a difference between both stents with sirolimus exhibiting an all or nothing response while there may often be some degree of neo-intimal hyperplasia in PES.[24]

The incidence of peri-procedural myocardial infarction in the PES group, while higher than that seen in the SES, is not abnormally high.[25] This difference could potentially be explained by the complexity of the cases or the difference in glycoprotein IIb/IIIa inhibitor use. It is important to point out that this increase in incidence of peri-procedural myocardial infarction in the PES group was present even in patients treated without glycoprotein IIb/IIIa inhibitors (3.9% vs. 2%), because of this, all the peri-procedural myocardial infarction were reviewed independently by two experienced interventional cardiologists. The agreement was that the stent type

was not primarily involved, while small side-branch occlusion and extensive calcified atherosclerotic disease were the most frequent potential causes.

This study has limitations. The lack of true randomization is the most important one. The fact that one stent is considered more deliverable could explain the finding of more complex lesions in the PES group. Despite this hypothesis, we feel that the operators involved in this study were very experienced and only on very few occasions could they have selected “a priori” one type of stent because they felt they could not have delivered the other one. The low rate of angiographic follow up must be considered a limitation however the rate of angiographic follow up was similar in the two groups.

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8

Angiographic analysis of pattern of late luminal loss in sirolimus and paclitaxel eluting stents

Pierfrancesco Agostoni,* John Cosgrave,* Giuseppe GL Biondi-Zoccai, Giuseppe M Sangiorgi, Lei Ge, Gloria Melzi, Simon Corbett, Flavio Airoldi, Matteo Montorfano, Alaide Chieffo, Iassen Michev, Mauro Carlino, Antonio Colombo.

San Raffaele Hospital and EMO Centro Cuore Columbus, Milan, Italy

*Drs. Agostoni and Cosgrave contributed equally to this article.

Published in the *American Journal of Cardiology* 2007;99:593-598.

ABSTRACT

Late loss is becoming an important endpoint to compare drug eluting-stents, however little is known about its pattern of distribution. We sought to analyze the pattern of late loss distribution in sirolimus eluting-stents (SES) and paclitaxel eluting-stents (PES) in a consecutive cohort of patients. From a cohort of 529 patients treated with drug eluting stents in 1 year, we selected all patients who underwent angiographic follow-up. 359 patients with 592 de-novo lesions received either SES (286 lesions) or PES (306 lesions). Late loss and binary angiographic restenosis were analyzed. Binary restenosis occurred in 56 lesions (19.6%) treated with SES, compared to 53 (17.3%) treated with PES (p=0.48). Both late loss distributions were skewed to the right and were not normally distributed (p<0.001 for SES, p=0.003 for PES). Late loss was significantly lower in SES group (p=0.03), with a median value of 0.29 mm (inter-quartile range:-0.09–0.66) versus 0.41 mm (-0.02–0.85) after PES. Analyzing only restenotic lesions, late loss had a normal distribution in SES and PES (respectively, p=0.96 and p=0.44) and was similar in the two groups (1.75±0.51 vs. 1.82±0.62, p=0.48). Evaluating non-restenotic lesions, late loss was also normally distributed in both groups (p=0.75 for SES, p=0.73 for PES), but it was significantly lower (p=0.002) after SES implantation (0.14±0.39) compared to PES (0.27±0.44). In conclusion, both SES and PES have a bimodal pattern of late loss distribution. The observed difference in late loss between SES and PES seems to be partially explained by the reduction in late loss after SES in non-restenotic lesions (where SES approaches “zero-late-loss”). Thus, late loss may not be a reliable marker of the true efficacy of these devices, due to its complex and non-gaussian distribution.

INTRODUCTION

We have recently published a comparison of our experience with sirolimus (SES) and paclitaxel eluting stents (PES).[1] We found a significantly greater degree of late loss following PES implantation but a similar incidence of restenosis and target vessel revascularization for both stent platforms. We therefore decided to analyze the distribution of late loss to better understand this apparent contradiction. Indeed, some studies already assessed late loss distribution in the balloon angioplasty and in the bare metal stent eras and they consistently showed that late loss is not normally distributed. Specifically, a bimodal pattern of distribution has been shown following balloon and bare stent.[2,3] A bimodal distribution is evident when two values occur more frequently than the others. Specifically, after balloon and stent treatment, there seem to be two different lesion populations corresponding to the two peaks (i.e. means) of the two gaussian curves superimposed in the bimodal distribution: one that tends to develop restenosis (with higher late loss) and one that has a lower likelihood to develop restenosis (with lower late loss). Of interest, the gaussian curves describing these two populations tend to have a large overlap for "intermediate" values of late loss.[2,3]

METHODS

Between March 2003 (when PES became available in our institution) and March 2004 all consecutive patients treated with a single type of drug eluting stent (DES) and undergoing angiographic follow-up were considered for our analysis. Patients were excluded if they received a mixture of different types of DES or if they had a bare metal stent implanted during the index procedure. Subjects with stents implanted in restenotic lesions or previously treated with brachytherapy were also excluded. During this time period a total of 839 patients were treated with DES, 179 were treated for restenotic lesions, 91 had a mixture of different types of DES implanted and 40 had a mixture of DES and bare metal stents. The remaining 529 patients (872 lesions) received a single type of DES, either SES or PES. Angiographic

follow-up was encouraged for all the patients 6 to 9 months post-procedure, unless clinically indicated at an earlier time. The cohort of lesions with angiographic follow-up comprised our study population.

Quantitative coronary angiography analysis.

Digital coronary angiograms were analyzed offline by operators blinded to the procedure, using the validated automated edge detection system CMS (version 5.2, MEDIS Medical Imaging Systems, The Netherlands). Matched views were selected for angiograms recorded before and immediately after the intervention and at follow-up. Each angiographic sequence was preceded by an intra-coronary injection of 0.2 mg of nitroglycerin. Angiographic measurements were made in the stented segment (i.e. the stent plus the proximal and distal edges, defined as 5 mm proximal and distal to the stent) during diastole using the contrast-filled guiding catheter for magnification calibration. The parameters obtained were reference vessel diameter (RVD), minimal luminal diameter (MLD), and percent diameter stenosis at baseline, post-procedure and at follow-up.[4] Acute gain was defined as the difference between the MLD at the end of the intervention and the MLD at baseline. In-segment late lumen loss was calculated as the difference in MLD noted between measurements immediately after the procedure and at follow-up. Binary angiographic restenosis was defined as diameter stenosis >50% by quantitative coronary angiography within a previously stented segment, at the follow-up angiogram.[5] Restenosis patterns were qualitatively assessed using the Mehran classification system.[6]

Statistical analysis.

Categorical variables are expressed as frequencies (%) and were compared using the chi-square test or the Fisher's exact test, as appropriate. Continuous variables are presented as means ± standard deviation or medians [interquartile range (IQR)]. The normality of the distribution of the continuous variables was tested by means of the Kolmogorov-Smirnov goodness-of-fit test, and a skewness index was used to assess the measure of the asymmetry of the distribution. A normal distribution has a skewness value of zero, as it is symmetric. A distribution with a significant positive skewness is left-skewed and has a long right tail, while a negative skewed distribution

has a long left tail. Continuous variables were compared using independent sample Student's *t* or Mann-Whitney U test, as appropriate. A p-value of <0.05 was considered to be statistically significant and all reported p-values are two-sided. Statistical analysis was performed using SPSS 11.5 (SPSS Inc.).

RESULTS

Angiographic follow-up was performed in 163 patients (286 lesions) out of 248 patients (449 lesions) in the SES group, and in 196 patients (306 lesions) out of 281 patients (423 lesions) in the PES group. The angiographic follow-up rate was not significantly different between the two groups (66% vs. 69%, respectively, p=0.32). The median time to angiographic follow-up was 7.1 months (IQR: 6–8.8) in the SES group and 6.6 months (IQR 5.7–8.1) in the PES group (p=0.15). Baseline demographic and procedural data of the SES and PES cohorts are presented in Table 1, while the characteristics of the lesions treated with SES and PES are shown in Table 2. The two patient groups were well matched with only minor differences, except for a higher elective usage of glycoprotein IIb/IIIa inhibitors in SES group. Some lesion characteristics were different between the two groups with a higher proportion of C type lesions and a larger mean stent size and final max balloon diameter in the PES group. Angiographic success was achieved in 100% of the procedures.

Table 1. Baseline clinical and procedural characteristics in the two groups of patients.

	SES (N=163)	PES (N=196)	P-value
Age (years)	61.3±11.4	62.1±9.4	0.44
Men	146 (89.6%)	169 (86.2%)	0.34
Ejection Fraction (%)	52±10	54±10	0.07
Prior myocardial infarction	83 (50.9%)	98 (50%)	0.86
Prior percutaneous coronary intervention	58 (35.6%)	60 (30.6%)	0.32
Prior coronary bypass surgery	27 (16.6%)	44 (22.4%)	0.16
Hypertension	102 (62.6%	132 (67.3%)	0.34
Hypercholesterolemia*	115 (70.6%)	150 (76.5%)	0.2
Current smoker	28 (17.2%)	37 (18.9%)	0.89
Diabetes	44 (27%)	51 (26%)	0.83
Unstable angina pectoris	41 (25.2%)	44 (22.4%)	0.55
Double/triple coronary vessel disease	124 (76%)	144 (73.5%)	0.51
Multi-lesion coronary intervention	71 (43.6%)	71 (36.2%)	0.16
Intra-aortic balloon pump	6 (3.7%)	8 (4.1%)	0.84
Elective glycoprotein IIb/IIIa inhibitors	30 (18.4%)	17 (8.7%)	0.006
Intra-vascular ultrasound	16 (9.8%)	32 (16.3%)	0.07

*Defined as total cholesterol level >200 mg/dl or known statin therapy. Data are presented as numbers (percentages) or means ± standard deviation. PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent.

Table 2. Baseline and procedural lesion characteristics in the two groups.

	SES (N=286)	PES (N=306)	P-value
Coronary artery involved			0.51
Left main	12 (4.2%)	20 (6.5%)	
Left anterior descending	129 (45.1%)	128 (41.9%)	
Left circumflex	84 (29.4%)	82 (26.8%)	
Right	49 (17.1%)	64 (20.9%)	
Ramus	12 (4.2%)	12 (3.9%)	
Bifurcations	66 (23.1%)	71 (23.2%)	0.97
Chronic total occlusions	36 (12.6%)	50 (16.3%)	0.19
Calcified lesions	65 (22.7%)	79 (25.8%)	0.38
AHA/ACC lesion type			<0.001
A	5 (1.7%)	5 (1.6%)	
B1	101 (35.3%)	69 (22.5%)	
B2	131 (45.8%)	144 (47.1%)	
C	49 (17.1%)	88 (28.8%)	
Number of stents per lesion	1.3±0.6	1.3±0.6	0.67
Stent length per lesion(mm)	28 (18–33)	24 (20–32)	0.32
Stent diameter (mm)	2.93±0.36	3.04±0.36	<0.001
Max. balloon diameter (mm)	2.98±0.40	3.08±0.38	0.001
Max inflation pressure (atm)	15.5±3.1	15.8±3.5	0.28

Data are presented as numbers (percentages), means ± standard deviation or median (inter-quartile range). ACC/AHA: American College of Cardiology/American Heart Association; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent.

Quantitative coronary angiographic analysis.

Serial quantitative coronary angiography data are shown in Table 3. Baseline RVD was normally distributed in both DES (p=0.51 for SES, p=0.99 for PES by the Kolmogorov-Smirnov goodness-of-fit test) and it was larger in the PES group. Pre-procedural MLD and diameter stenosis were not normally distributed in both groups (p<0.05 for all) and not significantly different between the two devices (p>0.05 for all). After the procedure, all the 3 parameters evaluated, namely RVD, MLD and percent diameter stenosis, were normally distributed after SES implantation (respectively p=0.31, p=0.20 and p=0.24) and after PES deployment (respectively p=0.68, p=0.83 and p=0.10). They were all larger in the PES group. Also acute gain was normally distributed (p=0.47 in SES and p=0.15 in PES) and larger after PES (Table 3). At follow-up, RVD remained normally distributed in both groups (p=0.15 for SES, p=0.64 for PES). MLD was not normally distributed in either group (p=0.005 for SES, p=0.03 for PES) and skewed to the right (skewness: -0.67 for SES and -0.61 for PES). Also, percent diameter stenosis distribution was not normally distributed either in SES or PES (p<0.001 for both), but in this case the curve was skewed to the left (skewness, 1.48 and 1.51 respectively). No significant differences in the three parameters were evident between the two devices using either parametric or non-parametric tests (Table 3). The binary angiographic restenosis rate was similar (p=0.48) between SES (19.6%) and PES (17.3%). The majority of restenosis demonstrated a focal pattern (SES: 62.7% vs. PES: 55.8%, p=0.57) and was intra-stent (SES: 74.5% vs. PES: 76.9%, p=0.55). Late loss analysis revealed a non normal distribution of the values after SES (p<0.001) and PES (p=0.003), and both curves were skewed to the left (SES skewness 1.13, PES skewness 1.14, figure 1). Utilizing the parametric Student's *t*-test, which is largely based on Gaussian assumptions, no significant difference (p=0.15) was found between SES (0.45 mm±0.76) and PES (0.55 mm±0.76). While using the more appropriate non-parametric Mann-Whitney U test, late loss after SES (0.29 mm [IQR: -0.09–0.66]) was significantly lower (p=0.03) than after PES (0.41 mm [IQR: -0.02–0.85]). To further investigate the pattern of late loss distribution after DES implantation, we divided the SES and PES late loss values according to the presence of binary angiographic restenosis, which is currently recognized as the most common and reliable angiographic parameter to evaluate the effectiveness of a coronary

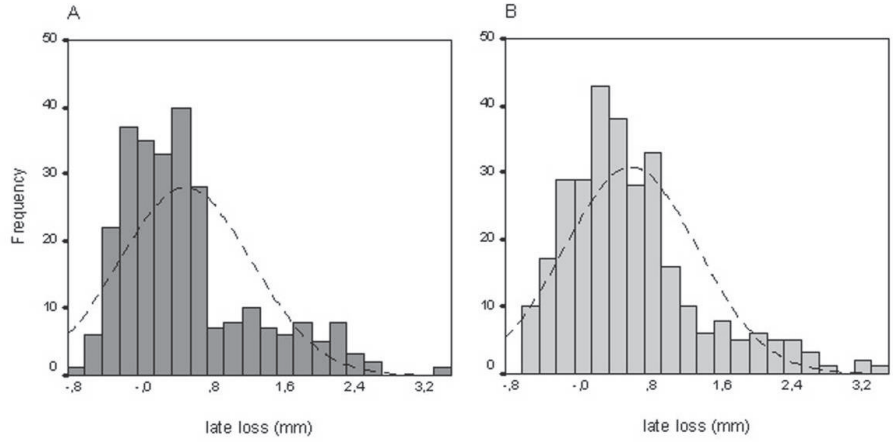
device.[7] Restenotic lesions after SES and PES showed a normal distribution of late loss (respectively p=0.96 for SES and p=0.44 for PES, figure 2) and late loss was similar in the two groups (respectively, 1.75 mm±0.51 vs. 1.82 mm±0.62, p=0.48). Evaluating non-restenotic lesions, late loss was also normally distributed after both devices (p=0.75 for SES, p=0.73 for PES, figure 3), but it was significantly lower (p=0.002) after SES implantation (0.14 mm±0.39) with respect to PES (0.27 mm±0.44).

Table 3. Quantitative coronary angiographic data.

	SES (N=286)	PES (N=306)	P-value
Pre-procedure			
Reference vessel diameter (mm)	2.69±0.57	2.81±0.61	0.01
Minimal luminal diameter (mm)	0.85±0.51	0.82±0.53	0.60
Diameter stenosis (%)	68±18	69±18	0.30
Lesion Length (mm)	13.3±9.5	13.4±9.9	0.83
Post-procedure			
Reference vessel diameter (mm)	3.10±0.55	3.18±0.50	0.05
Minimal luminal diameter (mm)	2.72±0.50	2.83±0.49	0.005
Diameter stenosis (%)	12±8	11±7	0.60
Acute gain (mm)	1.87±0.61	2.01±0.64	0.007
Follow-up			
Reference vessel diameter (mm)	3.03±0.51	2.99±0.54	0.38
Minimal luminal diameter (mm)	2.27±0.88	2.28±0.84	0.98
Median (IQR)	2.41 (1.89–2.85)	2.37 (1.86–2.83)	0.79
Diameter stenosis (%)	26±25	25±23	0.59
Median (IQR)	16 (9–34)	17 (10–31)	0.85
Late loss (mm)	0.45±0.76	0.55±0.76	0.15
Median (IQR)	0.29 (-0.09–0.66)	0.41 (-0.02–0.85)	0.03
Angiographic restenosis	56 (19.6%)	53 (17.3%)	0.48

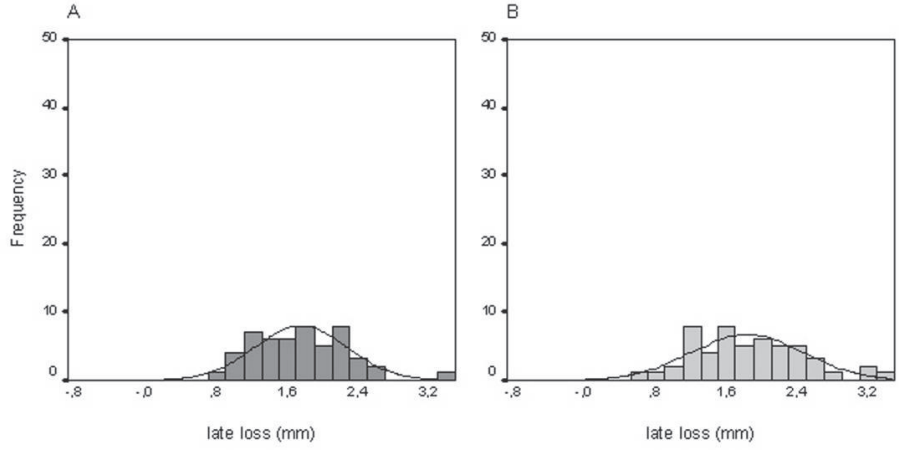
Data are presented as number (percentages) or means ± standard deviation, unless otherwise reported. IQR: inter-quartile range; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent.

Figure 1.



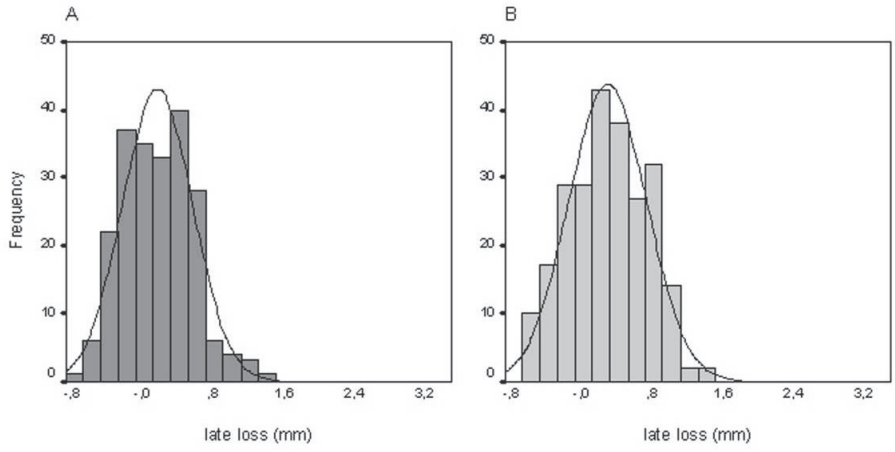
Patterns of late loss distribution in the total SES lesions (**A**) and in the total PES lesions (**B**). A superimposed hypothetical normal curve derived from the values considered is shown in both graphs and it appears clearly inadequate to represent the real distribution of late loss values either after SES or PES, as shown by Kolmogorov-Smirnov test (respectively $p<0.001$ and $p=0.003$).

Figure 2.



Pattern of late loss distribution in the restenotic SES lesions (**A**) and in the restenotic PES lesions (**B**). The superimposed normal curve is in this case adequate to characterize the distribution of late loss in both stents (Kolmogorov-Smirnov test: respectively $p=0.96$ and $p=0.44$).

Figure 3.



Pattern of late loss distribution in the non-restenotic SES lesions (**A**) and in the non-restenotic PES lesions (**B**). Also in this situation the normal curve adequately corresponds to the distribution of late loss values (Kolmogorov-Smirnov test: respectively p=0.75 and p=0.73).

DISCUSSION

The main findings of this report are: (1) late loss following both SES and PES implantation is not normally distributed and seems to follow a bimodal distribution with 2 peak values, one for non-restenotic lesions and one for restenotic lesions; (2) despite similar angiographic restenosis rates late loss following SES implantation is significantly lower than following PES implantation; (3) the significant difference in late loss between the 2 platforms is predominantly accounted for by the difference found in the non restenotic lesions.

We have shown that the distribution of late loss for both platforms is non-normal and that late loss has a significantly skewed distribution with a long right tail. In other words, the lower late loss values are more frequently represented and the higher values are consequently less common in the overall distribution. This finding concurs with previous data and has implications for any analysis of late loss.[8] The more commonly utilized means ± standard deviations analyzed with a parametric

test may not accurately estimate the true differences in late loss as was the case with our data set. In particular, means do not adequately represent the right tail of the distribution. This includes the higher late loss values which best correlate with restenosis. A further finding of our analysis is that not only is the distribution non-gaussian but it demonstrates a bimodal pattern. There are 2 separate gaussian curves for restenotic and non-restenotic lesions, both with their respective mean and standard deviation. This has important implications for any attempts to transform the data into a normal distribution. Indeed, commonly used transformations such as the logarithmic, power or square root, to convert a skewed distribution into a normal one, are not applicable to our distribution. The non-normal distribution of late loss following SES implantation has previously been alluded to;[8] however the bimodal distribution is a new observation following DES implantation. The bimodal nature of the distribution may not have been apparent in previous studies due to the relatively low restenosis rates and hence inadequate power.[8,9] Our population is one of the most complex reported in the literature following DES implantation and consequently our restenosis rates are higher. Thus our analysis is more powerful than the others to assess the presence of a specific distribution of late loss of restenotic lesions. Our data suggest a normal distribution for late loss in restenotic lesions. This gaussian curve is clearly distinguished from the gaussian late loss distribution in non-restenotic lesions. However a partial overlap of the two curves is present for late loss values between 0.5 and 1.5 mm (figures 1,2 and 3), thus suggesting that the relationship between late loss and restenosis is not linear. In other words, a late loss of 1.5 mm can be evident after DES implantation without leading to restenosis, while on the contrary a late loss of 0.5 mm may lead to restenosis.

An intriguing finding in our study is the apparent contradiction between the different degree of late loss in SES vs. PES and the similarity in the incidence of angiographic restenosis. The significant reduction in late loss after SES was driven by the more profound inhibition of neo-intimal proliferation in lesions which did not develop restenosis. Indeed, in non restenotic lesions treated with SES, luminal dimensions were maintained with only 0.14 mm of late loss. This value approximates to the postulated “zero-late-loss” shown in the non-restenotic cohort of lesions of the

RESEARCH registry and in the RAVEL trial and closely resembles that found in the first trial testing SES in humans, the First-in-Man (FIM) study, where it was 0.16 mm.[8,10,11] Also the variability of late loss in all these cohorts of non-restenotic SES lesions (expressed by the standard deviation) was very similar, ranging between 0.3 and 0.39. These values approximate the current variability obtained when performing repeated quantitative angiographic measurements in the same coronary segment in different moments, and may be an expression of the actual limitations in accuracy of the automated edge detection systems used to obtain quantitative coronary angiographic data. In contrast our analysis has shown that the degree of late loss after PES implantation was not-negligible and higher than SES in non-restenotic lesions (0.27 mm), with also a broader standard deviation (0.44 mm). Confirmatory data come from TAXUS I in which no binary restenosis occurred but mean late loss was 0.36 with a standard deviation of 0.48.[12] These data highlight the occurrence of some degree of lumen narrowing even in non-restenotic lesions after PES implantation. Thus, while SES seems to approach an all-or-none response, PES still exhibits some degree of neo-intimal hyperplasia.

Recently Mauri et al. attempted to validate late loss as a reliable predictor for the angiographic and clinical effectiveness first of SES,[13] and then of DES in general.[14] In their first paper, they built a model that monotonically predicted the dichotomous binary restenosis rate from the continuous late loss value.[13] This model was based on a complex power transformation in order to normalize the skewed distribution of late loss in the SIRIUS trial.[15] The power of 0.13 (which is a root) was used after adding late loss to a fixed value in order to avoid negative late loss values, that would not allow this transformation (as the authors explain in the online supplement). This approach is mathematically debatable as the combination of the addition of a constant and a subsequent power transformation alters the relationship between the values of the variable. We have recently applied this methodology to the late loss values observed in the "head-to-head" randomized SES versus PES trials.[16] Our analysis demonstrated that the proposed model has a poor overall ability to predict the real incidence and relative risk of restenosis after the 2 types of DES, and that the difference in late loss after SES vs. PES overestimated the respective real difference

in restenosis. In a second paper, Mauri et al. extended their preliminary finding of a monotonic correlation between late loss and binary restenosis after SES, to several published stent trials.[14] However there were major drawbacks in this correlation. First, their analysis included data from bare metal stent and DES trials. Indeed, much of the statistical weight of the relationship found by Mauri et al, was dependent on bare metal stent trials. Second, they mixed all the different types of DES as a single entity in one group. Thus, the relationship they found might not be present or might have a different shape if analyzed according to each type of DES. In our opinion, the authors incorrectly extrapolated the conclusions obtained from different bare metal stent and DES trials to the direct DES vs. DES comparison.[17] Finally, in both the papers, the authors did not recognize the possible existence of a bimodal pattern of distribution of late loss after stent,[3] considering the distributions used as only left skewed and thus prone to mathematical transformation.

Several limitations should be taken into account. The lack of randomization and the non-complete angiographic follow-up cast a light of caution on the direct comparison of SES vs. PES. In fact, the primary aim of this paper was the analysis of the pattern of late loss distribution in both devices and not their direct comparison.

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Re-examining Minimal Luminal Diameter Relocation and Quantitative Coronary Angiography – Intravascular Ultrasound Correlations in Stented Saphenous Vein Grafts: Methodological Insights from the Randomized RRISC Trial

Oscar Semeraro,* Pierfrancesco Agostoni,* Stefan Verheye, Glenn Van Langenhove, Paul Van den Heuvel, Carl Convens, Frank Van den Branden, Nico Bruining, Paul Vermeersch, for the RRISC (Reduction of Restenosis In Saphenous vein grafts with Cypher stent) trial investigators.

Antwerp Cardiovascular Institute Middelheim, Ziekenhuis Netwerk Antwerpen, Antwerp, Belgium and Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands

* Drs. Agostoni and Semeraro equally contributed to this manuscript.

Published in *EuroIntervention* 2009;4:633-640.

ABSTRACT

Background: Angiographic parameters (such as late luminal loss) are common endpoints in drug-eluting stent trials, but their correlation with the neointimal process and their reliability in predicting restenosis are debated.

Methods and Results: Using quantitative coronary angiography (QCA) data (49 bare metal stent and 44 sirolimus-eluting stent lesions) and intravascular ultrasound (IVUS) data (39 bare metal stent and 34 sirolimus-eluting stent lesions) from the randomized Reduction of Restenosis In Saphenous vein grafts with Cypher stent (RRISC) trial, we analyzed the "relocation phenomenon" of QCA-based in-stent minimal luminal diameter (MLD) between post-procedure and follow-up and we correlated QCA-based and IVUS-based restenotic parameters in stented saphenous vein grafts. We expected the presence of MLD relocation for low late loss values, as MLD can "migrate" along the stent if minimal re-narrowing occurs, while we anticipated follow-up MLD to be located close to post-procedural MLD position for higher late loss.

QCA-based MLD relocation occurred frequently: the site of MLD shifted from post-procedure to follow-up an "absolute" distance of 5.8 mm [2.5-10.2] and a "relative" value of 29% [10-46]. MLD relocation failed to correlate with in-stent late loss (rho=0.14 for "absolute" MLD relocation [p=0.17], and rho=0.03 for "relative" relocation [p=0.81]). Follow-up QCA-based and IVUS-based MLD values well correlated in the overall population (rho=0.76, p<0.001), but QCA underestimated MLD on average 0.55±0.49 mm, and this was mainly evident for lower MLD values. Conversely, the location of QCA-based MLD failed to correlate with the location of IVUS-based MLD (rho=0.01 for "absolute" values - in mm [p=0.91], rho=0.19 for "relative" values - in % [p=0.11]). Overall, the ability of late loss to "predict" IVUS parameters of restenosis (maximum neointimal hyperplasia diameter, neointimal hyperplasia index and maximum neointimal hyperplasia area) was moderate (rho between 0.46 and 0.54 for the 3 IVUS parameters).

Conclusions: These findings suggest the need for a critical re-evaluation of angiographic parameters (such as late loss) as endpoints for drug-eluting stent trials and the use of more precise techniques to describe accurately and properly the restenotic process.

INTRODUCTION

Quantitative coronary angiography (QCA) has become a trustful tool to evaluate the restenotic process and the relative efficacy of percutaneous interventions (1,2), and it has been routinely used to define endpoints in recent trials involving drug-eluting stents (3-7). One of the most commonly used angiographic endpoints is late luminal loss, which is the difference between post-procedure and follow-up minimal luminal diameter (MLD). This parameter has several limitations. The accuracy of the correlation between late loss and the neointimal restenotic process is still debated (8-10), and its reliability in predicting restenosis and repeated revascularization is also questioned (3,11-15). Moreover, as late loss is calculated regardless of the respective axial location of the MLD along the stent between post-procedural and follow-up QCA analysis, MLD relocation can be another important technical limitation affecting the value of late loss (16,17).

All the data presented in the aforementioned referenced publications were analyzed in studies performed in native coronary arteries, but no data are available in diseased saphenous vein grafts (SVG), which can be used as good model for QCA analysis, because of the lack of side branches and the limited probability of overlap with other vessels, (despite the possible presence of surgical clips and wires, which in any case are easily recognizable at QCA).

Using QCA and intravascular ultrasound (IVUS) data from the Reduction of Restenosis In Saphenous vein grafts with Cypher stent (RRISC) trial, which randomly compared sirolimus eluting stent versus bare metal stent in SVG (18), we comprehensively assessed values and drawbacks of late loss. In particular, we analyzed the “relocation phenomenon” of MLD and we focused on its possible correlation with the degree of late loss formation. On one hand, we expected for low values of late loss potentially significant MLD relocation, as MLD can easily “migrate” along the stent maintaining similar absolute post-procedural and follow-up values if minimal in-stent re-narrowing occurs. On the other hand, for high late loss values we anticipated follow-up MLD to be located close to the post-procedural MLD position, as post-procedural MLD is known to be a powerful predictor of restenosis (19). We further correlated QCA-based and IVUS-based restenotic parameters in stented SVG.

METHODS

Population selection. The RRISC is a randomized, double blind, trial. Its design and results have been previously published (18,20). Briefly, 75 patients with a history of previous coronary artery bypass surgery and with 96 “de novo” target lesions localized in 80 diseased SVG with a reference vessel diameter >2.5 and <4.0 mm, were included . Patients were randomly allocated in a 1:1 ratio to treatment with Cypher sirolimus-eluting stent or BX-Velocity bare metal stent (both from Cordis, Johnson & Johnson, Miami Lakes, FL).

Coronary angiography was repeated at 6 months (± 15 days) and IVUS analysis was recommended, only during follow-up angiography, in every SVG treated with a study stent. IVUS was performed after injection of 0.2 mg of nitroglycerin with a 30 MHz ultrasound probe (Ultracross 2.9F, Boston Scientific Corporation, Natik, MA), connected to the Galaxy ultrasound console (Boston Scientific Corporation), and a motorized pullback (speed: 0.5 mm/sec).

QCA analysis.

Digital coronary angiograms were analyzed offline by an independent expert, not performing any of the procedures and blinded to treatment allocation, using a validated automated edge detection system (CAAS II, PIE Medical, Maastricht, The Netherlands). His intra-observer variability for QCA measurements is <5%. Matched views were selected for angiograms recorded before the intervention, immediately after and at 6-month follow-up. A single monoplane view was analyzed per lesion treated, specifically the least foreshortened one was selected. Angiographic measurements were made in the stent during diastole using the contrast-filled guiding catheter for magnification calibration. In case overlapping stents were placed, a single in-stent value was measured. MLD was evaluated at baseline, at the end of the procedure and at 6-month follow-up. Binary angiographic restenosis was defined as a diameter stenosis >50% at follow-up control angiography. Late lumen loss was calculated as the difference in MLD between measurements immediately after the procedure and at follow-up. We defined the position of MLD in the stent as the distance of MLD from the proximal edge of the stent, either post-procedure and

at follow-up. The difference between post-procedural MLD position and follow-up MLD position was the "absolute" relocation of MLD (in mm). In order to overcome partially the possible errors in QCA measurement due to vessel foreshortening, we defined also the "relative" position of MLD in the stent as the ratio, expressed as percentage, between the distance of MLD from the proximal edge of the stent and the total length of the stent, either post-procedure and at follow-up. The difference between post-procedural "relative" MLD position and follow-up "relative" MLD position was the "relative" relocation of MLD, expressed as a percentage.

$$\textit{"relative" MLD location} = \frac{\text{MLD position in stent (mm)} - \text{proximal stent edge position (mm)}}{\text{total length of the stent (mm)}}$$

We decided to analyze only in-stent and not in-segment parameters, because in-stent late loss has been shown to correlate better with binary restenosis than in-segment late loss (3), and it is more indicative of the real restenotic process inside the stent. Furthermore, in bare metal and sirolimus-eluting stent there is no evidence of edge effect as conversely present with radioactive stents (21).

IVUS analysis. Quantitative IVUS analysis was performed by an independent expert not performing any of the procedures and blinded to treatment allocation. The analysis was executed using a validated software (Curad, version 4.32, Wijk bij Duurstede, The Netherlands), allowing semi-automated detection of luminal and stent boundaries in reconstructed longitudinal planes (L-mode views) (22). Due to catheter motion during the cardiac cycle, non-gated IVUS pullbacks result in a saw-tooth-appearance of the coronary segment on the longitudinal views and thus interfere with the contour detection algorithms used in IVUS software packages. In order to obtain a smooth appearance of the vessel wall structures in the longitudinal views, the Intelligate image-based gating method was applied (23,24). This validated technique eliminates catheter-induced artefacts by retrospectively selecting end-diastolic frames, thus resulting in more reliable volumetric measurements. This method has been expanded by introducing the so-called Intelliview, which shows

during the analysis of the end-diastolic L-mode view the corresponding complete cardiac cycle of the IVUS images made at that particular position on a second computer screen. This enhances the capabilities to determine more accurately the blood-intima-stent interfaces. By detecting the borders of the stent struts and the lumen-intima interface, volumetric quantitative coronary ultrasound analysis was obtained for stent and lumen. The intra- and inter-observer variability of this methodology has been reported (25). All the bi-dimensional data were derived from the tri-dimensional reconstruction of the stent-lumen IVUS image, including:

- neointimal hyperplasia index defined as neointimal hyperplasia volume divided by the length of the stent,
- lumen and neointimal hyperplasia cross sectional areas and diameters (minimum, maximum and mean).

As for the QCA analysis, we defined the IVUS position of MLD in the stent as the distance of MLD from the proximal edge of the stent, in this case only at follow-up. In details, we knew from the software the frame numbers where the stent started and where the MLD was along the IVUS pullback, and we knew the frame thickness (in mm). Thus, "absolute" MLD position was calculated as the difference between the frame where the stent started and the frame where the MLD was located, multiplied for the frame thickness. The "relative" MLD position was calculated as the percentage ratio between the "absolute" MLD position and the stent length computed as the difference between the last and the first frame where the stent was visible (meaning the end and the begin of the stent itself) multiplied for the frame thickness.

"absolute"
MLD = (frame where MLD is - frame where stent starts) * frame thickness (mm)
location

"relative" "absolute" MLD location (mm)
MLD = ----------
location (frame where stent ends – frame where stent starts) * frame thickness (mm)

Statistical analysis.

Data are presented as medians [interquartile ranges] if continuous or as frequencies (percentages) if dichotomous. Comparisons were respectively done with the Mann Whitney U test or the chi-square test. Bivariate correlations were graphically represented with scatter plots and the degree of these correlations was tested with the non-parametric Spearman's rho correlation coefficient. In case the same variable was measured with different techniques (as it is the case of MLD, measured with QCA and IVUS), a Bland-Altman graph (plotting on the X axis the mean of the values measured with the different techniques and on the Y axis the difference between the same values) was graphically implemented in order to obtain the degree of agreement between the techniques. A 2-sided p-value <0.05 was considered significant.

RESULTS

The baseline characteristics of the patients and lesions enrolled have been already described (18,20). Overall 93 lesions (49 treated with bare metal stent and 44 with sirolimus-eluting stent), from 72 patients, were included in the present QCA analysis because 3 patients did not undergo angiographic follow-up (Table 1). IVUS was performed in 73 lesions (39 treated with bare metal stent and 34 with sirolimus-eluting stent) from 59 patients at 6-month follow-up and this cohort constituted the IVUS-QCA study population (Table 2).

Table 1. Baseline data of the 93 lesions evaluated in the Quantitative Coronary Angiography (QCA) post-procedural and follow-up cohort.

	Value (mm)
Nominal stent length	23 [18-33]
Nominal stent diameter	3.5 [3-3.5]
Post procedure QCA	
Stent length at QCA	21.3 [17.1-27.7]
Minimal luminal diameter at QCA	2.8 [2.5-3.1]
Follow-up QCA	
Stent length at QCA	21.6 [17.6-27.1]
Minimal luminal diameter at QCA	2.3 [1.7-2.8]

Data are presented as medians [interquartile ranges].

Table 2. Baseline data of the 73 lesions evaluated in the Quantitative Coronary Angiography (QCA) – Intravascular Ultrasound (IVUS) follow-up cohort.

	Value (mm)
Nominal stent length	23 [18-33]
Nominal stent diameter	3.5 [3.25-3.5]
Follow-up QCA	
Stent length at QCA	20.7 [17.5-27]
Minimal luminal diameter at QCA	2.3 [1.7-2.8]
Follow-up IVUS	
Stent length at IVUS	22.2 [18.1-31.2]
Minimal luminal diameter at IVUS	2.9 [2.4-3.2]
Mean stent diameter at IVUS	3.5 [3.1-3.7]
Minimal stent diameter at IVUS	3.2 [2.8-3.4]

Data are presented as medians [interquartile ranges].

QCA relocation of MLD.

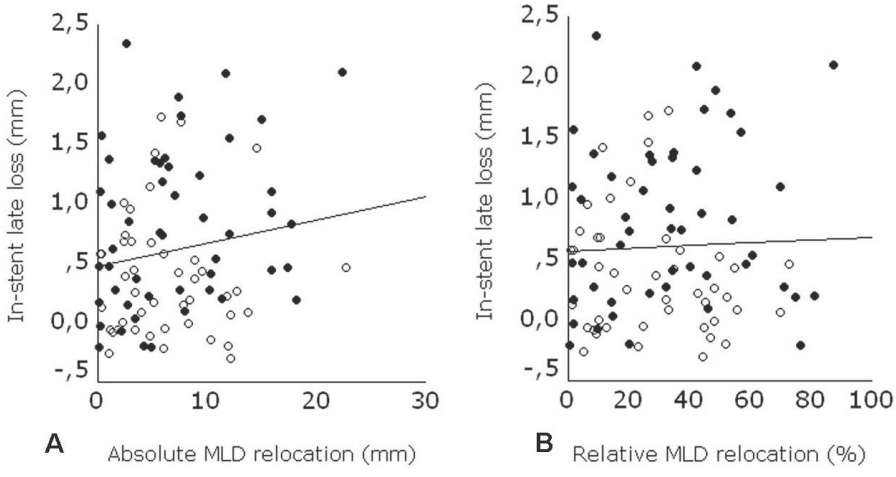
On average, the site of MLD shifted from post-procedure to follow-up an "absolute" distance of 5.8 mm [2.5-10.2] and a "relative" value of 29% [10-46], without difference between bare metal and sirolimus-eluting stent (respectively p=0.65 and p=0.44). The "absolute" and "relative" relocations were respectively 5.9 mm [2.4-11.1] and 33% [12-47] after bare metal stent versus 5.1 mm [2.5-8.9] and 26% [10-45] after sirolimus-eluting stent.

In-stent late loss was not correlated to the "absolute" MLD relocation in the overall population (rho= 0.14, p=0.17), in the bare metal stent group (rho= 0.24, p=0.10) and in the sirolimus-eluting stent group (rho= -0.05, p=0.74) (figure 1A). There was also no correlation for the "relative" MLD relocation in the overall population (rho= 0.03, p=0.81), in the bare metal stent group (rho= 0.16, p=0.26) and in the sirolimus-eluting stent group (rho= -0.18, p=0.23) (figure 1B).

To further assess the potential impact of MLD relocation on late loss, we divided our study lesions in two groups, namely lesions in which minimal versus significant relocation occurred, according to the median value of "absolute" and "relative" MLD relocation. Of interest 8 out of 46 (17.4%) lesions with minimal (< 5.8 mm) "absolute" MLD relocation had significant (> 29%) "relative" MLD relocation, while 9 out of 47 (19.1%) lesions with significant (> 5.8mm) "absolute" MLD relocation had minimal

(< 29%) “relative” MLD relocation. No differences were noted in late loss value between the minimal and the significant relocation groups according to the “absolute” or to the “relative” value, except in the bare metal stent lesions, in which late loss was slightly significantly higher when MLD shifted > 5.8 mm in “absolute” value (Table 3).

We also performed a second sensitivity analysis, assessing the degree of MLD relocation according to presence or absence of binary restenosis (which is an indicator of higher or lower late loss) at the follow-up coronary angiogram. In the whole cohort considered, there were 20 restenoses out of 93 lesions (21.5%): 5 out of 44 in the sirolimus eluting stent group and 15 out of 49 in the bare metal stent group. Also in this case, no differences were noted in the degree of relocation according to the presence or absence of binary restenosis (Table 4).



Scatter plot for in-stent late loss versus the “absolute” (**A**) or the “relative” (**B**) minimal luminal diameter (MLD) relocation, showing in both cases lack of correlation between the parameters considered (black dots: bare metal stents, white dots: sirolimus-eluting stents).

Table 3. Late loss comparisons between minimal and significant minimal lumen diameter (MLD) relocation groups in the "absolute" and "relative" relocation populations.

	In-stent late loss (mm)		P-value
	Minimal MLD relocation group	Significant MLD relocation group	
"Absolute" MLD relocation			
Overall population	0.41 [0-0.87]	0.46 [0.19-1.23]	0.14
Bare metal stent	0.47 [0.03-1.10]	0.89 [0.43-1.41]	0.04
Sirolimus-eluting stent	0.38 [-0.06-0.67]	0.22 [-0.03-0.48]	0.50
"Relative" MLD relocation			
Overall population	0.47 [0-1.06]	0.43 [0.16-0.96]	0.81
Bare metal stent	0.61 [0.15-1.17]	0.79 [0.34-1.41]	0.25
Sirolimus-eluting stent	0.41 [-0.06-0.89]	0.18 [0-0.45]	0.23

Data are presented as medians [interquartile ranges]. MLD: minimal luminal diameter.

Table 4. "Absolute" and "relative" minimal lumen diameter (MLD) relocation according to the presence or absence of binary angiographic restenosis.

	No binary restenosis	Binary restenosis	P-value
Late loss (mm)	0.27 [0.01-0.60]	1.44 [1.18-1.72]	-
"Absolute" MLD relocation (mm)			
Overall population	5.1 [2.4-10.2]	5.8 [4.8-11.1]	0.33
Bare metal stent	5.8 [2-10.9]	7 [2.6-11.7]	0.60
Sirolimus-eluting stent	4.9 [2.4-8.9]	5.8 [5-11]	0.35
"Relative" MLD relocation (%)			
Overall population	29 [10-46]	30 [14-45]	0.79
Bare metal stent	30 [13-48]	35 [9-48]	0.68
Sirolimus-eluting stent	29 [10-47]	26 [16-29]	0.80

Data are presented as medians [interquartile ranges]. MLD: minimal luminal diameter.

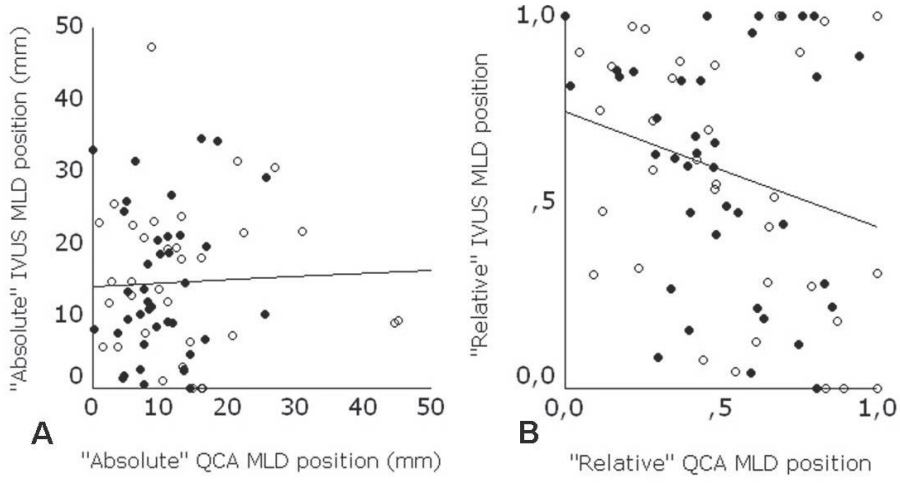
IVUS-QCA correlations.

In the subgroup of patients undergoing IVUS at 6-month follow-up, both the "absolute" and "relative" position of the angiographic MLD along the stent at follow-up failed to correlate respectively with the "absolute" and "relative" position of the IVUS in-stent MLD (absolute value: rho=0.01, p=0.91, relative value: rho=0.19, p=0.11). This

remained true analyzing bare metal or sirolimus-eluting stents separately (figures 2A and 2B). Angiographic and IVUS in-stent MLD values at follow-up well correlated in the overall population (rho=0.76, p<0.001), and in the 2 types of stent separately (rho for bare metal stent=0.81, rho for sirolimus-eluting stent=0.61) (figure 3). However, on average QCA underestimated MLD of 0.55 mm (±0.49 mm) with respect to IVUS and this was more manifest at lower values of MLD as evident from the Bland Altman plot (figure 4).

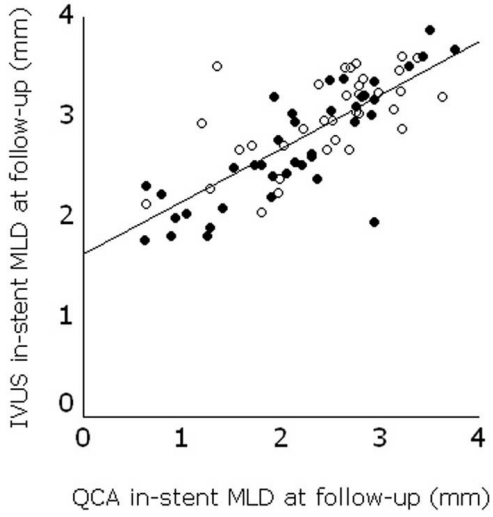
Overall, the ability of angiographic in-stent late luminal loss to "predict" IVUS parameters of restenosis (maximum neointimal hyperplasia diameter, neointimal hyperplasia index and maximum neointimal hyperplasia area) was moderate with a rho ranging between 0.46 and 0.54 (figure 5).

Figure 2.



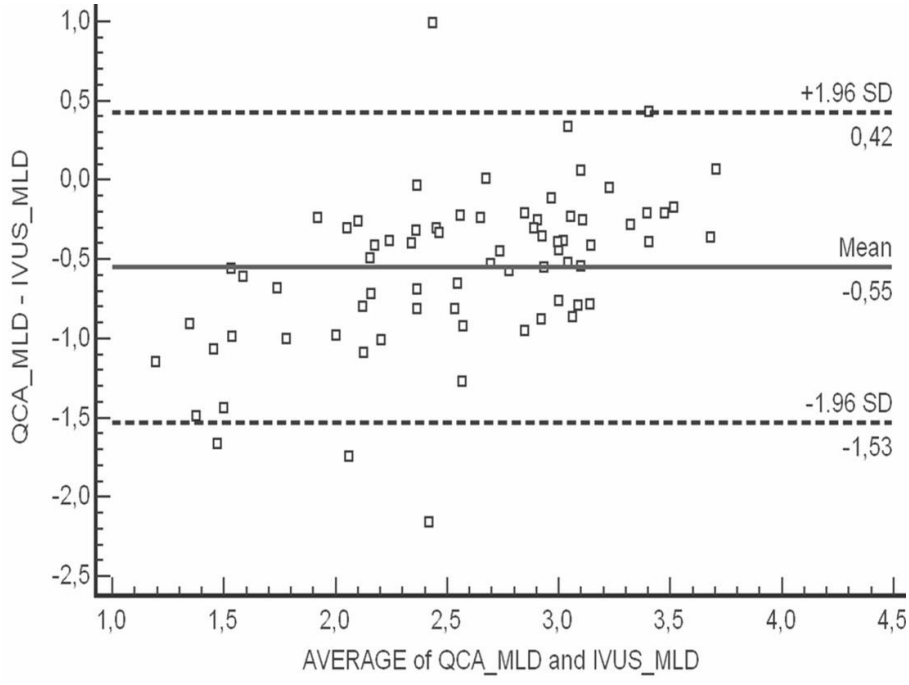
Scatter plot for the "absolute" (**A**) or "relative" (**B**) minimal luminal diameter (MLD) position along the stent at follow-up analyzed by quantitative coronary angiography (QCA) versus the same value analyzed by intravascular ultrasound (IVUS), showing in both cases lack of correlation between the parameters considered (black dots: bare metal stents, white dots: sirolimus-eluting stents).

Figure 3.



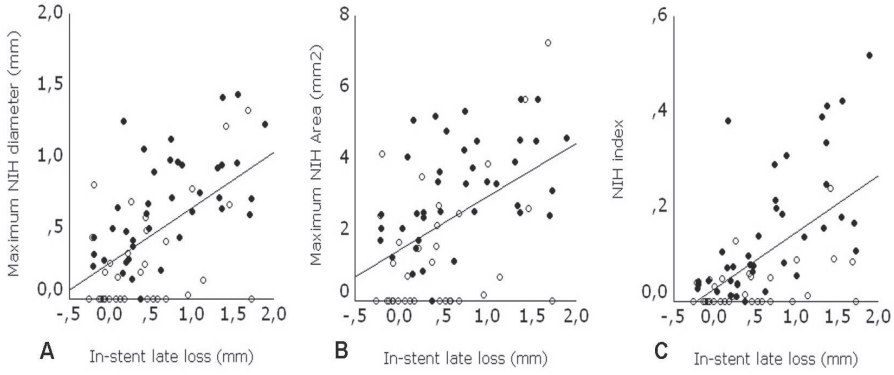
Scatter plot for quantitative coronary angiography (QCA) versus intravascular ultrasound (IVUS) minimal luminal diameter (MLD) values, showing good correlation (rho=0.76, $p<0.001$) (black dots: bare metal stents, white dots: sirolimus-eluting stents).

Figure 4.



Bland Altman plot for the mean of the quantitative coronary angiography (QCA)-based and intravascular ultrasound (IVUS)-based minimal luminal diameter (MLD) values versus the difference between the same values, showing an average 0.55 mm underestimation of QCA MLD with respect to IVUS MLD, more evident for lower values of MLD.

Figure 5.



Scatter plot for in-stent late loss versus maximum neointimal hyperplasia (NIH) diameter (**A**), maximum NIH area (**B**) and NIH index (defined as NIH volume / stent length) (**C**), showing overall moderate correlation between late loss and the intravascular ultrasound parameters of restenosis (rho between 0.46 and 0.54) (black dots: bare metal stents, white dots: sirolimus-eluting stents).

DISCUSSION

Although late luminal loss has been extensively applied to investigate the performance of drug-eluting stents (3-7), this angiographic parameter has already shown several limitations (9-15). Our study offers additional fuel to this debate.

First, also in our analysis of stented SVG, angiographic MLD relocation is a frequent phenomenon, as already shown in previous studies focused in native coronary arteries (16, 17). MLD relocation has the potential to impact adequate calculation of late loss and thus analysis and interpretation of stent trial results. Second, high values of in-stent late loss were measured also when significant in-stent MLD relocation occurred. Conversely to what we anticipated, for elevated values of late loss follow-up MLD was not necessarily located close to the post-procedural MLD position. Indeed, despite post-procedural MLD is a well-established predictor of restenosis (19), our data suggest that the restenotic process described by QCA does not necessarily occur at the site of post-procedural MLD but also somewhere else along the stent. Third,

we found that QCA and IVUS follow-up MLD values have a good correlation, but also that QCA underestimates MLD mainly for lower values. This finding has been already shown in previous reports (10). The novel information of our study is that the MLD position along the stent at follow-up is different when analyzed with QCA or IVUS, despite the acceptable correlation of MLD values between the two techniques. This data further reinforce the limitations of QCA in describing the restenotic process.

Late loss is a bi-dimensional parameter defined as the difference between 2 focal measurements, namely post-procedural and follow-up MLD. These MLD are measured at different time points, thus for 1 late loss value 2 measures are exposed to the inherent 0.2 mm resolution limit of QCA (which barely correspond to the facet of 1 pixel). Moreover, the calibration factor for each MLD measurement is calculated using a different guiding catheter as reference for each time point. All these factors create systematic and random errors, and may explain the poor accuracy and precision of QCA analysis. Of interest, all the aforementioned limitations of QCA appear to remain valid also in SVG, which could potentially constitute a simpler conduit for appropriate QCA analysis, due to the lack of side branches and overlap with other vessels.

The historical value of late loss remains undeniable (1). However, with the present study we offer additional limitations of the reliability of this parameter to those already known. In particular, in the drug-eluting stent era, absolute late loss values became far smaller than values in the bare metal stent era. Thus, while late loss can be relatively reliable when comparing bare metal to drug-eluting stents due to the expected large difference between the devices, its value can become trivial in trials comparing different types of drug-eluting stents. Indeed, little late loss differences detected after deployment of different drug-eluting stents can be still significant (due to the lower power needed by continuous endpoints to find statistical significance), but their real angiographic and clinical implication can be negligible. We thus raise doubts about the consistency of late loss as surrogate for the restenotic process mainly when differences between devices are small (in the order of 0.1-0.4 mm). Indeed as the resolution of QCA is approximately 0.2 mm (i.e. around 1 pixel), late loss, as derived by 2 different QCA measurements, can be even more affected by this resolution limit.

Limitations.

The major limitations affecting this study are related to the overall small sample size of the cohort analyzed and to the lack of IVUS investigation performed immediately after the deployment of the stent but only at 6-month follow-up control. Furthermore, there are also inherent limitations in the techniques used to generate the measurements. In particular, stent length as measured by QCA and by IVUS can be shorter than the real length due respectively to foreshortening in a non-perpendicular angiographic view and to IVUS catheter forward-backward movement inside the stent. Moreover, the MLD in case of eccentric vessel appearance can be underestimated by a single monoplane QCA analysis. In any case, these two techniques, despite these systematic limitations, are nowadays the most commonly used tools to evaluate the performance of intracoronary devices.

Conclusions.

The findings of our study suggest the need for a critical re-evaluation of commonly used QCA endpoints, such as late loss, for upcoming drug-eluting stent trials and the use of more precise techniques to describe with more accuracy the restenotic process.

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10

Randomized, Multi-Center Study of the Pimecrolimus-Eluting and Pimecrolimus/Paclitaxel-Eluting Coronary Stent System in Patients with De Novo Lesions of the Native Coronary Arteries: The GENESIS Trial

Stefan Verheye, Pierfrancesco Agostoni, Keith D Dawkins, Joseph Dens, Wolfgang Rutsch, Didier Carrie, Joachim Schofer, Chaim Lotan, Christophe L Dubois, Sidney A Cohen, Peter J Fitzgerald, Alexandra J Lansky.

Antwerp Cardiovascular Institute Middelheim, Antwerp; Oost-Limburg Hospital, Genk; University Hospital Gasthuisberg, Leuven; all in Belgium. Charité Medical School, Humboldt-Universität, Berlin; Hamburg University Cardiovascular Center, Hamburg; all in Germany. Southampton University Hospital, Southampton, United Kingdom. Rangueil Hospital, Toulouse, France. Hadassah-Hebrew University Medical Centre, Jerusalem, Israel. Clinical Research Cordis Corporation, Warren, NJ; Stanford University Medical Center, Stanford, CA; Columbia University Medical Center and Cardiovascular Research Foundation, New York, NY; all in the USA.

Published in *JACC Cardiovascular Interventions* 2009;2:205-214.

ABSTRACT

Objectives: To compare, in a randomized multi-center trial, paclitaxel-eluting stents (CoStar) versus pimecrolimus-eluting stents (Corio) versus stents with dual elution of both drugs (SymBio) in native coronary arteries.

Background: The CoStar cobalt-chromium reservoir-based stent platform, eluting paclitaxel in a controlled way via a bioresorbable polymer, reduces restenosis versus its respective bare stent. The reservoir system allows the use of other drugs targeted to different mechanisms involved in the process of vascular restenosis, and simultaneous loading of multiple, synergistic drugs.

Methods: Patients with single de novo lesions were asymmetrically randomized to one of the 3 types of stent (1:2:2). Six-month coronary angiography was planned in all. The primary analysis was a non-inferiority test for the primary endpoint of 6-month angiographic in-stent late lumen loss of Corio versus CoStar and SymBio versus CoStar. Secondary endpoints included binary angiographic restenosis and major adverse clinical events (cardiac death, myocardial infarction, target vessel revascularization).

Results: The trial was prematurely suspended after 246 patients were enrolled (planned enrollment: 375 patients): 49 patients received CoStar, 97 SymBio and 100 Corio. In-stent late loss was significantly reduced with CoStar versus either SymBio or Corio (0.58±0.58 versus 0.96±0.73 and 0.58±0.58 versus 1.40±0.67 mm, $p<0.001$ for both comparisons). Binary in-stent restenosis rates were respectively 7.1%, 20% and 40.9% ($p<0.001$ for both comparisons), 6-month major adverse cardiac event rates were respectively 2.0%, 14.4% and 39.0% ($p<0.001$ for both comparisons).

Conclusions: Stents eluting pimecrolimus or the dual combination of pimecrolimus and paclitaxel failed to show angiographic non-inferiority when compared to paclitaxel-eluting stents.

INTRODUCITON

The CoStar stent (Conor Medsystems, Menlo Park, California) is a cobalt chromium alloy stent platform designed to elute paclitaxel without the use of a surface polymer and drug coating, but with a technology consisting of multiple laser-cut reservoirs within the stent struts (Figure 1). These reservoirs are filled with a polymer/drug matrix consisting of a bioresorbable poly-lactic-co-glycolic polymer and paclitaxel. The drug elution occurs with both directional and kinetic control. The CoStar paclitaxel-eluting stent (PES) has been proven superior to the respective bare cobalt chromium stent in reducing angiographic restenosis and repeated revascularizations at 8 months (1).

Figure 1. The CoStar Stent

Photograph of the CoStar stent (**A**). Magnification demonstrates the laser-cut reservoirs and a bridge element (**B**).

While the CoStar PES failed to demonstrate non-inferiority to the first-generation Taxus PES (Boston Scientific, Maple Grove, Minnesota) for the primary endpoint of 8-months major adverse cardiac events (MACE) in the COSTAR II trial (2), the concept of reservoir technology of the stent, associated with the bioresorbable polymer delivery matrix, still offers the potential for alternative dose kinetic and elution profile improvements aimed at developing more effective and safer drug-eluting stents. Indeed, this technology allows loading and independent elution control of drugs targeting various mechanisms involved in the restenotic process. It permits also simultaneous, independent delivery from a single stent of more than one therapeutic agent by placing different polymer/drug combinations in alternate, adjacent reservoirs. This combined delivery can concurrently address multiple physiologic stimuli responsible for the pathological events following stent implantation (3). Once the discharge of the loaded drug(s) is complete, the polymeric delivery matrix is absorbed leaving a bare metal stent implanted.

Pimecrolimus is a compound, currently approved by the U.S. Food and Drug Administration and the European Medicines Agency for the topical treatment of atopic dermatitis. It is an anti-inflammatory agent with immunosuppressant properties, belonging to the class of calcineurin-inhibitors. Pimecrolimus inhibits the activation and proliferation of T-lymphocytes and the release of several growth factors. In addition, it targets mast cell release of pro-inflammatory mediators including histamine, cytokines, tryptase and eicosanoids (4). Even though this agent does not exert any specific anti-proliferative action, it may reduce the response of smooth muscle cell proliferation and neointimal hyperplasia by decreasing the localized inflammatory response and the resultant cascade of physiologic reactions secondary to the arterial injury caused by stent implantation (5,6).

This study was designed to determine the effectiveness of the anti-inflammatory molecule pimecrolimus alone and of the synergistic combination of pimecrolimus with an anti-proliferative agent such as paclitaxel (with the potential of simultaneous inhibition of two different mechanisms of restenosis), loaded in a drug-eluting stent with the Conor reservoir technology, on the neointimal reaction process assessed in humans by angiography.

METHODS

The GENESIS (randomized, multi-center study of the pimecrolimus-eluting and paclitaxel-elutinG coronary stent system in patiENts with de novo lEsionS of the native coronary arterIeS) trial is a prospective, asymmetrically randomized, multicenter, open-label, three-arm trial. The local Ethics Committee of every hospital enrolling patients approved the trial design.

Patient population

Patients were included if they were >18 years-old, with documented stable or unstable angina pectoris and had one de novo target lesion ≤25 mm in length, with a reference vessel diameter (RVD) of 2.5 to 3.5 mm and with visually estimated stenosis of ≥50 and <100%, localized in a native coronary artery. Clinical exclusion criteria were: female of childbearing potential, myocardial infarction (MI) within the previous 72 hours, cardiogenic shock, documented left ventricular ejection fraction <25%, acute or chronic renal dysfunction (creatinine >2.0 mg/dl), cerebrovascular accident within the past 6 months, gastrointestinal bleeding within the past 3 months, thrombocytopenia (platelet count <100000/mm3), contraindications to aspirin, clopidogrel or contrast agents, known sensitivity to pimecrolimus, paclitaxel, cobalt chromium or the poly-lactic-co-glycolic polymer, current assumption of colchicine, chronic systemic steroid or immunosuppressant therapy or systemic paclitaxel assumption within 12 months of the index procedure, life expectancy <24 months, current participation in another investigational drug or device study. Angiographic exclusion criteria were: prior revascularization of the target vessel within the preceding 6 months, left main stenosis, ostial stenosis, bifurcation lesion, severe calcification or presence of thrombus by visual estimation, pre-treatment of the target lesion with any unapproved device or atherectomy or laser or cutting balloon, or prior brachytherapy in the target vessel. All enrolled patients provided written informed consent prior to the index procedure.

Procedural protocol, randomization and follow up

After percutaneous access was obtained, heparin was administered to maintain an activated clotting time >250 seconds (or >200 seconds if Glycoprotein IIb/IIIa inhibitors were given). Glycoprotein IIb/IIIa inhibitors were given at operator's discretion. Randomization was performed after baseline angiography was obtained, using a computerized central randomization service. Randomization was stratified by site and was accomplished at each site using an interactive voice randomization system. Eligible patients were randomized in a ratio of 1:2:2 respectively, to one of three treatment arms: CoStar PES (11 µg nominal dose in a 3.0x16 mm stent) or SymBio pimecrolimus/paclitaxel-eluting stent (162.5 µg pimecrolimus/11 µg paclitaxel nominal dose in a 3.0x16 mm stent) or Corio pimecrolimus-eluting stent (325 µg nominal dose in a 3.0x16 mm stent). Direct stenting was allowed and left at operator's discretion. In case of dissection or incomplete lesion coverage, the use of additional stents of the same type as the assigned stent was mandated. The first 30 patients enrolled into each arm were automatically allocated into an Intravascular Ultrasound (IVUS) sub-study; IVUS was performed at the end of the procedure according to standard protocols after injection of 0.2 mg of nitroglycerin with a 20-40 MHz ultrasound probe and with motorized pullback (speed: 0.5 mm/sec). Aspirin (100-300 mg/day) was given daily and clopidogrel (loading dose of at least 300 mg pre-procedure and 75 mg/day thereafter) was administered for at least 6 months in all patients. Serial blood samples for creatine kinase and creatine kinase–MB were routinely obtained 8-12 and 16-24 hours after the intervention. Patients were evaluated clinically 1 and 6 months after the procedure. Coronary angiography was planned at 6 months (± 30 days) in all patients and IVUS analysis was planned in the cohort of patients receiving IVUS at baseline. Angiography was performed earlier if there were recurrent symptoms, but if restenosis was not found during this repeated angiography, a new angiography was done at 6 months.

Quantitative coronary angiography and IVUS analysis

Digital coronary angiograms were analyzed offline by an independent core laboratory, using a validated automated edge detection system (Medis, Leiden, The Netherlands) (7). Matched views were selected for angiograms recorded before and immediately

after the intervention and at 6-month follow up. Angiographic measurements were made both in the stent and in the stented segment (defined as the stent plus the 5 mm edges proximal and distal to the stent) during diastole using the contrast-filled guiding catheter for magnification calibration. In case overlapping stents were placed, a single in-stent value was measured, and the segment was considered as the entirely stented segment plus the 5 mm proximal to the more proximal stent and the 5 mm distal to the more distal stent implanted. Lesion RVD, minimal luminal diameter (MLD), percent diameter stenosis and length were obtained at baseline. RVD, MLD and diameter stenosis were evaluated at the end of the procedure and at follow up, for the in-stent, proximal edge, distal edge and in-segment sections. Acute gain was defined as the difference between the in-stent MLD at the end of the intervention and the MLD at baseline. Late lumen loss was calculated as the difference in MLD between measurements immediately after the procedure and at follow up. Binary angiographic restenosis was defined as diameter stenosis ≥50% by quantitative coronary angiography (QCA), at the follow up angiogram (8). Restenosis patterns were assessed using the Mehran classification system (9).

Quantitative IVUS analysis was performed offline by an independent core laboratory, using validated software (echoPlaque, Indec Systems, Mountain View, California), allowing semi-automated detection of luminal and stent boundaries in reconstructed longitudinal planes. Volumetric quantitative coronary ultrasound analysis was obtained for vessel, stent and lumen. Neointimal volume was computed as the difference between stent volume and lumen volume. Percent volume obstruction was calculated as the ratio between the neointimal volume and stent volume x 100. Incomplete stent apposition was defined as one or more stent struts clearly separated from the vessel wall with evidence of blood speckles behind the strut in a vessel segment not associated with any side branches (10).

Endpoints and definitions

The primary endpoint of the study was 6-month in-stent late lumen loss (11,12). Secondary angiographic endpoints included in-segment late loss, in-stent and in-segment binary restenosis (≥50% diameter stenosis), and in-stent and in-segment MLD at 6 months post-procedure. Secondary IVUS endpoints were percent volume

obstruction of the stent and incidence of late acquired incomplete stent to vessel apposition at 6 months. Secondary clinical endpoints were 30-day and 6-month MACE rates, defined as an adjudicated composite of cardiac death, new MI not clearly attributable to a non-intervention vessel or clinically driven target vessel revascularization (TVR). In addition, clinically driven target lesion revascularization (TLR) at 6 months post-procedure was evaluated. Death was divided into 2 categories: cardiac and non-cardiac. Cardiac death was defined as death due to acute MI, or to complication of the index procedure (including bleeding, vascular repair, transfusion reaction, or bypass surgery) or any death in which a cardiac cause cannot be excluded. Non-cardiac death was defined as a death not due to cardiac causes. Myocardial infarction was defined in 2 ways: a) Q-wave MI was diagnosed when chest pain or symptoms consistent with myocardial ischemia and new pathological Q-waves in two or more contiguous ECG leads were present; b) non-Q-Wave MI was defined as Creatine Kinase elevated >2 times the upper laboratory normal with the presence of elevated Creatine Kinase-MB in the absence of new pathological Q-waves. Clinically driven TVR and TLR were defined as revascularizations at the target vessel or lesion respectively, associated with positive functional ischemia study or ischemic symptoms and an angiographic diameter stenosis ≥50% by QCA, or revascularization of a target vessel or lesion with diameter stenosis ≥70% by QCA without either angina or a positive functional study. Stent thrombosis was defined according to the Academic Research Consortium criteria (13). Additional secondary endpoints were device, lesion and procedure success. Primary device success was defined as attainment of <50% in-stent residual stenosis of the target lesion using only the assigned device in the absence of device malfunction and device-related complication. Lesion success was defined as attainment of <50% residual stenosis of the target lesion using the assigned device or any percutaneous method. Procedure success was defined as attainment of a final lesion success and no in-hospital MACE. An independent clinical events committee unaware of the patients' treatment assignment adjudicated all the clinical events and an independent data safety monitoring board also reviewed clinical data periodically throughout the trial.

Statistical analysis

The study compared two experimental stents, SymBio and Corio, to the CoStar control stent. The comparisons of interest for the primary outcome of in-stent late loss were SymBio versus CoStar and Corio versus CoStar. The sample size of 375 patients (150:150:75) was based on the non-inferiority hypothesis that the difference between late loss of SymBio or Corio and late loss of CoStar was <0.32 mm with a power of approximately 95% assuming a pooled standard deviation of 0.40 and a significance level of 0.025 for each comparison. All analyses were conducted according to the intention-to-treat principle. For the two primary comparisons, a one-sided p-value of <0.025 was considered significant. Analysis of variance tests and chi-square tests were employed, respectively, for continuous and categorical variables, to compare differences between the three study arms. A two-sided p-value <0.05 was considered significant for all tests. Continuous data are expressed as means ± standard deviations, whereas dichotomous data are summarized as frequencies for all other secondary comparisons. Due to incomplete patient enrollment, statistical analyses were restricted to the primary endpoint of in-stent late loss, and to the predefined QCA, IVUS and clinical secondary endpoints.

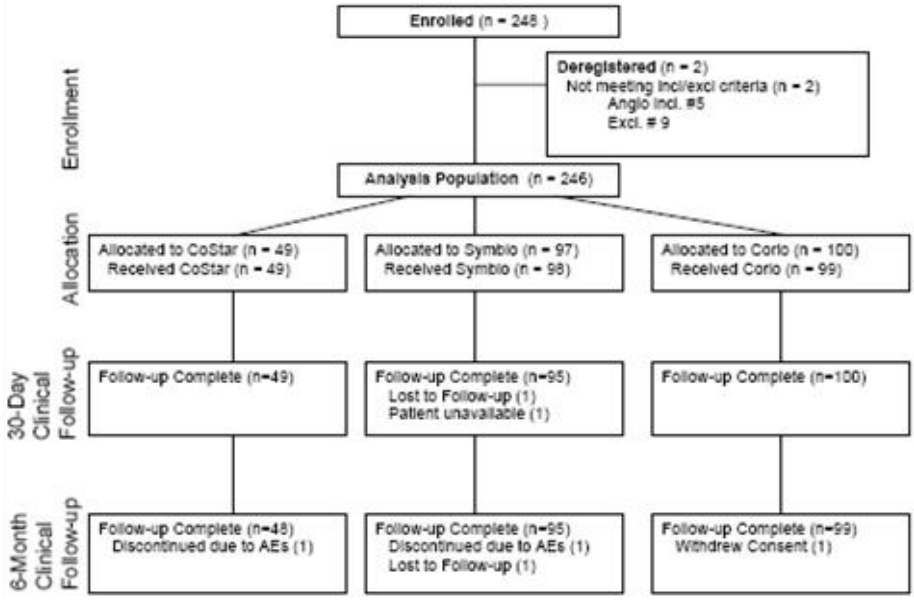
RESULTS

The study was prematurely interrupted in April 2007, after 246 patients had been enrolled. This decision, made by the study principal investigators in consultation with the study sponsor, Conor Medsystems, and with concurrence of the data safety monitoring board, followed notification by the manufacturer of pimecrolimus, Novartis Corporation, of the preliminary results from an Avantec sponsored First-in-Man study evaluating the safety and efficacy of the Avantec pimecrolimus-eluting stent. Subsequently, the COSTAR II trial, also using the CoStar PES, failed to demonstrate non-inferiority for the MACE primary endpoint when compared with the Taxus PES (2). Commercial sale of the CoStar PES was then discontinued in the markets where it was already available. The investigators and the sponsor decided to analyze the data available on all enrolled patients at the time of trial suspension.

Study population, procedural and in-hospital outcomes

Among the 246 patients enrolled, 49 were randomized to CoStar, 97 to SymBio and 100 to Corio (1 patient in the Corio Group received a SymBio stent; Figure 2). Baseline clinical characteristics of the patients, as well as the angiographic and procedural characteristics of the lesions treated are shown in table 1. No deaths occurred during hospitalization. The rate of periprocedural MI was 5% in the Corio group versus 0% in the other 2 groups. Four of the five peri-procedural MIs were CK elevations alone without clinical sequelae, thought to be due to the procedure and not attributed to the stent. The fifth was an unsuccessful direct stenting, followed by pre-dilatation and successful stent placement complicated by a distal dissection that was unsuccessfully treated with 2 additional stents resulting in no flow.

Figure 2. Flow diagram of the Genesis trial



Flow diagram of subject progress through phases of the GENESIS trial.

Table 1. Baseline clinical and procedural characteristics of the patients and the lesions in the 3 groups.

	CoStar (N=49)	SymBio (N=97)	Corio (N=100)	p-value
Age (years)	64.4 ± 9.6	59.9 ± 10.1	64.1 ± 10.0	
Male gender	35 (71.4%)	76 (78.4%)	80 (80%)	
Diabetes Mellitus	18 (36.7%)	17 (17.5%)	32 (32%)	
Insulin Dependent	3/18 (16.7%)	2/17 (11.8%)	15/32 (46.9%)	
Hypertension	36 (73.5%)	65 (67%)	66 (66%)	
Hypercholesterolemia	36 (73.5%)	69 (71.1%)	82 (82%)	
Current smoker	8 (16.3%)	35 (36%)	20 (20%)	
Prior myocardial infarction	11 (22.5%)	29 (29.9%)	26 (26%)	
Prior percutaneous intervention	13 (26.5%)	28 (28.9%)	33 (33%)	
Prior bypass surgery	3 (6.1%)	0	2 (2%)	
Unstable Angina	10 (20.4%)	34 (35%)	25 (25%)	
Ejection Fraction (%)	61.8 ± 8.9	63.7 ± 12.5	63.7 ± 12.1	
Glycoprotein IIB/IIIA inhibitors	1 (2%)	5 (5.2%)	6 (6%)	
Target Vessel				
Left Anterior Descending	20 (40.8%)	50 (51.5%)	49 (49%)	
Circumflex	12 (24.5%)	17 (17.8%)	24 (24%)	
Right Coronary Artery	17 (34.7%)	30 (30.7%)	27 (27%)	
ACC/AHA lesion type				
A	9 (18.4%)	22 (22.7%)	30 (30%)	
B1	14 (28.6%)	31 (31.9%)	31 (31%)	
B2	23 (46.9%)	29 (29.9%)	35 (35%)	
C	3 (6.1%)	15 (15.5%)	4 (4%)	
Direct stenting	29 (59.2%)	55 (56.7%)	53 (53%)	
Post-dilatation	13 (26.5%)	34 (35%)	30 (30%)	
Max inflation pressure (atm)	14.2 ± 2.5	13.6 ± 2.6	13.9 ± 2.5	
Number of stents per lesion	1.04 ± 0.20	1.12 ± 0.41	1.12 ± 0.41	
1	47 (95.9%)	88 (90.7%)	91 (91%)	
2	2 (4.1%)	6 (6.2%)	6 (6%)	
3	0	3 (3.1%)	3 (3)	
Stent diameter used	(n=51)	(n=109)	(n=112)	
2.5 mm	10 (19.6%)	19 (17.4%)	25 (22.3%)	
3.0 mm	24 (47.1%)	47 (43.1%)	62 (55.4%)	
3.5 mm	17 (33.3%)	43 (39.5%)	25 (22.3%)	
Stent length used	(n=51)	(n=109)	(n=112)	
10 mm	9 (17.6%)	17 (15.6%)	15 (13.4%)	
16 mm	24 (47.1%)	57 (52.3%)	64 (57.2%)	
22 mm	12 (23.5%)	25 (22.9%)	24 (21.4%)	
28 mm	6 (11.8%)	10 (9.2%)	9 (8.0%)	
Device success*	48 (98%)	95 (97.9%)	92 (92%)	0.11
Lesion success*	49 (100%)	97 (100%)	98 (98%)	0.68
Procedure success*	49 (100%)	97 (100%)	94 (94%)	0.02

Data are presented as numbers (percentages) or means ± standard deviations, unless otherwise specified.

*Device Success was not achieved when the post procedure residual stenosis was >50% (1), there was a device related AE (4), the device failed or malfunctioned (2), or the treatment of the lesion was not completed with the assigned device only (2), or any combination of the above (2).

Lesion Success was not achieved if the post-procedure residual stenosis was >50% (2).

Procedure Success was not achieved if lesion success was not achieved (1), the patient experienced a peri-procedural MACE (4), or both (1).

QCA and IVUS outcomes

In the SymBio group, one patient was lost to follow up. At 6 months, 7 CoStar patients (14.3%), 2 SymBio patients (2.1%) and 7 Corio patients (7%) did not receive angiographic follow up. Angiographic data are presented in table 2. In-stent late loss was progressively and significantly higher with SymBio (0.96±0.73 mm) and Corio (1.40±0.67 mm) versus CoStar (0.58±0.58 mm). On average, in-stent late loss of SymBio and of Corio was respectively 0.38 ± 0.13 mm and 0.82 ± 0.12 mm higher than CoStar ($p<0.001$ for both). Thus the primary endpoint of the study, non-inferiority of SymBio or Corio in-stent late loss versus CoStar, was not met. In-segment late loss and binary in-stent and in-segment restenosis rates were also progressively higher with SymBio and Corio as compared to CoStar. Among the 4 CoStar in-segment restenoses, 3 were focal (75%) and 1 diffuse (25%). Among the 21 SymBio restenoses, 10 were focal (48%), 7 diffuse (33%), 3 proliferative (14%) and 1 occlusive (5%). Among the 42 Corio restenoses, 11 were focal (26%), 19 diffuse (46%), 9 proliferative (21%) and 3 occlusive (7%). The IVUS results, presented in table 3 and representing a subset of enrolled patients, substantially confirm the QCA data of the complete cohort.

Thirty-day and 6-month clinical outcomes

Clinical events are presented in table 4. Between the end of the hospitalization and the first month after treatment, one additional MI, caused by early stent thrombosis and treated with percutaneous revascularization, was recorded in the Corio group. At 6 months, no cardiac deaths occurred, while 1 MI in the SymBio group (caused by late stent thrombosis, and treated with percutaneous revascularization) and 2 additional MI in the Corio group (both periprocedural during TVR) were recorded. According to the angiographic results, also the rates of TLR and TVR were progressively reduced by CoStar versus SymBio versus Corio, as was the cumulative MACE rate.

Table 2. Quantitative coronary angiography analysis of the lesions treated in the 3 groups.

	CoStar	SymBio	Corio	p-value
Pre-procedure	*(n=49)*	*(n=97)*	*(n=100)*	
Reference vessel diameter (mm)	2.81 ± 0.47	2.87 ± 0.50	2.79 ± 0.45	
Minimal luminal diameter (mm)	0.72 ± 0.31	0.78 ± 0.37	0.76 ± 0.38	
Diameter stenosis (%)	74 ± 11	72 ± 13	73 ± 12	
Lesion Length (mm)	14.4 ± 6	13.8 ± 5.4	14.9 ± 5.5	
Post-procedure	*(n=49)*	*(n=97)*	*(n=100)*	
In-segment				
Minimal luminal diameter (mm)	2.41 ± 0.49	2.41 ± 0.45	2.33 ± 0.47	
Diameter stenosis (%)	16 ± 7	17 ± 8	18 ± 12	
Acute gain (mm)	1.69 ± 0.52	1.63 ± 0.46	1.57 ± 0.50	
Proximal edge				
Minimal luminal diameter (mm)	2.76 ± 0.53	2.83 ± 0.50	2.82 ± 0.52	
Diameter stenosis (%)	12 ± 8	12 ± 9	11 ± 8	
In-stent				
Minimal luminal diameter (mm)	2.82 ± 0.42	2.83 ± 0.39	2.81 ± 0.38	
Diameter stenosis (%)	5 ± 6	7 ± 6	6 ± 5	
Acute gain (mm)	2.10 ± 0.49	2.05 ± 0.46	2.04 ± 0.43	
Distal edge				
Minimal luminal diameter (mm)	2.53 ± 0.57	2.54 ± 0.53	2.47 ± 0.50	
Diameter stenosis (%)	10 ± 7	11 ± 9	12 ± 7	
Follow up	*(n=42)*	*(n=95)*	*(n=93)*	
In-segment				
Minimal luminal diameter (mm)	2.01 ± 0.61	1.71 ± 0.68	1.30 ± 0.68	<0.001
Diameter stenosis (%)	29 ± 16	40 ± 21	54 ± 22	
Proximal edge				
Minimal luminal diameter (mm)	2.59 ± 0.56	2.51 ± 0.71	2.39 ± 0.74	
Diameter stenosis (%)	11 ± 12	14 ± 18	15 ± 21	
In-stent				
Minimal luminal diameter (mm)	2.27 ± 0.64	1.89 ± 0.81	1.41 ± 0.75	<0.001
Diameter stenosis (%)	19 ± 19	33 ± 25	47 ± 25	
Distal edge				
Minimal luminal diameter (mm)	2.34 ± 0.60	2.29 ± 0.61	2.03 ± 0.75	
Diameter stenosis (%)	13 ± 10	13 ± 16	19 ± 23	
Late loss (mm)				
In-segment	0.42 ± 0.48	0.69 ± 0.58	1.07 ± 0.59	<0.001
In-stent	0.58 ± 0.58	0.96 ± 0.73	1.40 ± 0.67	<0.001
Binary angiographic restenosis				
In-stent	3 (7.1%)	19 (20%)	38 (40.9%)	<0.001
In-segment	4 (9.5%)	21 (22.1%)	42 (45.2%)	<0.001

Data are presented as means ± standard deviations, or numbers (percentages).

Table 3. Intravascular Ultrasound analysis of the lesions treated in the 3 IVUS sub-groups.

	CoStar	SymBio	Corio	p-value
Post-procedure	(n=29 analyzed=14)	(n=36 analyzed=24)	(n=32 analyzed=17)	
Target segment length (mm)	20.1 ± 4.8	21.3 ± 8.7	20.4 ± 9.3	
Vessel volume (mm^3)	252.1±109.4	281.6±93.9	320.4±139.1	
Stent volume (mm^3)	126.8±42.9	145.5±57.6	150.7±77.8	
Lumen volume (mm^3)	125.6 ± 41.9	144.7 ± 57.6	149.9 ± 77.5	
Incomplete stent apposition	4/24 (16.7%)	8/27 (29.6%)	6/26 (23.1%)	
Follow up	(n=29 analyzed=16)	(n=36 analyzed=26)	(n=32 analyzed=16)	
Target segment length (mm)	20.8 ± 5.4	21.0 ± 8.3	22.1 ± 9.3	
Vessel volume (mm^3)	319.3±144.7	293.6±100.8	330.3±150.3	
Stent volume (mm^3)	149.6 ± 66.5	139.5 ± 55.6	161.4 ± 85.4	
Lumen volume (mm^3)	122.0 ± 50.5	100 ± 39.9	98.8 ±62.3	
Neointimal volume (mm^3)	27.6 ± 26.6	39.5 ± 24.7	62.6 ± 29.4	
Percent volume obstruction (%)	16.6 ± 12	27.1 ± 12.4	41.2 ± 11.5	<0.001
Incomplete stent apposition	3/20 (15%)	5/28 (17.8%)	2/20 (10%)	0.91
Late acquired	0	0	0	
Persistent	3/20 (15.0%)	5/28 (17.8%)	2/20 (10.0%)	

Data are presented as means ± standard deviations, or numbers (percentages).

Table 4. Thirty-day and 6-month clinical events in the 3 groups.

	CoStar (N=49)	SymBio (N=97)	Corio (N=100)	p-value
30-day				
Death	0	0	0	
Myocardial infarction	0	0	6 (6%)	
Target vessel revascularization	0	0	1 (1%)	
Major adverse cardiac events	0	0	6 (6%)	0.02
Stent thrombosis	0	0	1 (1%)	
6-month				
Death	1 (2%)	0	0	
Cardiac death	0	0	0	
Myocardial infarction	0	1 (1%)	8 (8%)	
Target lesion revascularization	1 (2%)	14 (14.4%)	32 (32%)	<0.001
Target vessel revascularization	1 (2%)	14 (14.4%)	35 (35%)	
Major adverse cardiac events	1 (2%)	14 (14.4%)	39 (39%)	<0.001
Stent thrombosis	0	1 (1%)	1 (1%)	

Data are presented as numbers (percentages).

DISCUSSION

Given the negative outcome of the CoStar II trial in which the CoStar pactlitaxel-eluting stent was shown to be inferior to the Taxus-Liberte stent, one might question whether failure of the Conor reservoir technology is an explanation for the results in this trial. The data in this trial do not support this explanation, as the angiographic and clinical outcomes in the CoStar arm in this study are similar to those reported in the trials that led to CE Mark approval and are markedly better than historical data on bare metal stent outcomes in a similar cohort of patients. In fact, outcomes on the CoStar II trial were attributed to elution of paclitaxel, a drug with a narrow therapeutic index, at the lower end of the release kinetic specification in the CoStar stents used in this trial vs. previous trials that, while within allowable specifications, were inadequate for the more complex 2 vessel disease patients studied in that trial. This conclusion was supported by a post-hoc analysis demonstrating that non-inferiority was met in patients with only single lesions in this trial (22). Additional evidence that the reservoir technology successfully delivered drug is the observation of clinical outcomes in the pimecrolimus arm that were worse than expected compared to historical bare metal stent data. Thus, there appear to be three main findings of this study comparing different drugs as eluted from the Conor reservoir-based stent: a) pimecrolimus is not effective as an anti-restenotic agent; b) paclitaxel demonstrates activity as an anti-restenotic agent; and c) dual drug delivery with independent release kinetic and profile, utilizing the Conor reservoir-based stent, is feasible.

The unexpected outcome of this study was that the GENESIS trial failed to show a significant angiographic or clinical benefit of pimecrolimus. While underpowered and not designed to assess clinical endpoints, the GENESIS trial outcomes suggest that in humans the drug may exacerbate the restenotic response, thus leading to results worse than those observed with bare metal stents. Indeed in the GENESIS trial, stents eluting only pimecrolimus showed the worst late loss, which compares unfavorably with the late loss reported in the literature for bare metal stents in similar lesions and patients.

Pimecrolimus has been approved as topical treatment for inflammatory dermatologic diseases. Despite its “limus” name, it is not a rapamycin analogue. It is best classified

as a tacrolimus analogue that exerts multiple anti-inflammatory effects, including inhibition of interleukin-2 synthesis via calcineurin inhibition, and inhibition of interleukin-4, interferon-γ and release of inflammatory cytokines from mast cells. In contrast to other "limus" drugs, such as sirolimus, it does not bind to the mammalian target of rapamycin. Thus, it does not specifically exert anti-proliferative actions, having no direct effect on cell cycle regulation. However, it has been assumed that it may do so indirectly by interleukin-2 inhibition. Several animal studies strongly suggested that it would be clinically effective in humans as an anti-restenotic molecule when applied locally to atherosclerotic plaques treated with stent implantation (14,15). However, the suggestions of clinical efficacy from the animal data were not confirmed by this current human study. The reasons for this failure are currently unknown. However, several explanations can be hypothesized. First, discrepancies in results between animal experiments and human trials are well known. The porcine model for the pathologic reaction to stent implantation is best suited for determination of safety. Relative human efficacy is less predictable in this model and can only be definitely ascertained in clinical trials (16). Moreover, it is possible that, while inflammation can play an important role in neointimal proliferation in porcine stent models, the inflammatory response to stent implantation as affected by this drug may play a minor, if not insignificant, role as determinant of the restenotic process in humans. Since pimecrolimus has no anti-proliferative properties but mainly anti-inflammatory and immunosuppressant actions, its lack of efficacy would tend to undermine the role of inflammation as central in the restenotic process in humans. Indeed, other drug-eluting stents aimed at inhibiting the inflammatory and immune reaction to stent implantation, such as stents eluting dexamethasone, failed to show benefits when compared with traditional bare metal stents (17-19).

Despite market withdrawal, the CoStar PES provided encouraging results in this study, confirming the positive outcomes of previous trials, where this stent showed the lowest late loss among currently available PES (20,21) and superiority to the respective bare stent (1). The outcomes of patients treated with CoStar in the GENESIS trial are similar to those reported in the COSTAR II trial, where examination of the outcomes suggested that the release of paclitaxel, a drug with a narrow therapeutic index, was insufficient for the more complex lesions and patients enrolled in the

COSTAR II study (22). The CoStar PES differs from other available drug-eluting stents as it has the drug, mixed with a bioresorbable polymer, loaded in reservoirs cut into the stent, rather than having the drug and the polymer on the surface of the stent. This property reduces the exposure of the vessel wall to the polymer and results in an inert bare stent, following the elution of the drug and the dissolution of the polymer. Moreover, these technological advancements of the Conor stent platform, with its laser cut reservoirs and its bioresorbable polymer, which allow also controlled release of drugs, open the road to further investigations with different drugs loaded in the reservoirs and with specific release patterns, tailored to the different mechanisms involved in the patho-physiologic reaction to stent implantation. The GENESIS trial is the first trial to use the Conor reservoir technology to enable dual drug delivery for the treatment of coronary lesions. This trial has indeed demonstrated the ability to deliver two drugs independently with each drug having a different effect on the tissue response to coronary intervention. The theoretical advantages of the delivery of more than one drug include the ability to release multiple agents that synergistically work on different mechanistic pathways to inhibit neointimal growth or produce other biologic effects. Other drugs of interest include also anti-thrombotic agents or pharmacological therapies that can inhibit reperfusion injury during acute MI.

Limitations

The major limitation of this study was the early termination of enrollment. Thus, the study is underpowered for its primary angiographic endpoint. All analyses are post-hoc in nature: descriptive statistics only are presented for the primary and secondary endpoints, and no statistical analysis on differences in clinical endpoints (which the trial was not originally powered for) can be made. Moreover, the external validity of the trial is limited by the specific inclusion and exclusion criteria, thus limiting the applicability of the findings to the enrolled cohort of patients with selected lesions.

Conclusions

In native coronary artery lesions, stents eluting pimecrolimus or the dual combination of pimecrolimus and paclitaxel failed to show angiographic non-inferiority when compared to paclitaxel-eluting stents.

APPENDIX

Steering Committee: Dr. Stefan Verheye (principal investigator); Dr. Keith Dawkins (co-principal investigator).

Clinical Events Committee: Cardiovascular Research Foundation (Dr. G. Dangas).

Data and Safety Monitoring Board: Cardiovascular Research Foundation (Dr. J. Ambrose).

Angiographic Core Laboratory: Cardiovascular Research Foundation (Dr. A. Lansky).

Intravascular ultrasound Core Laboratory: Stanford University Medical Center (Dr. P.J. Fitzgerald).

Data Monitoring: ConorMed Systems, Clinical Research, Cordis Corporation (Louise Gambone).

Statistical Analysis: Biostatistics and Data Management, Cordis Corporation (Steve Ullery).

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Nine-month Clinical, Angiographic and Intravascular Ultrasound Results of a Prospective Evaluation of the AXXESS Self-Expanding Biolimus A9-Eluting Stent in Coronary Bifurcation Lesions: The DIVERGE (Drug Eluting Stent Intervention for Treating Side Branches Effectively) Study

Stefan Verheye, Pierfrancesco Agostoni, Christophe L. Dubois, Joseph Dens, John Ormiston, Stephen Worthley, Brett Trauthen, Takao Hasegawa, Bon-Kwon Koo, Peter J. Fitzgerald, Roxana Mehran, Alexandra J. Lansky.

Antwerp Cardiovascular Institute Middelheim, Ziekenhuis Netwerk Antwerpen, Antwerp, University Hospital Gasthuisberg, Leuven, Oost-Limburg Hospital, Genk, all Belgium; Auckland City Hospital, Auckland, New Zealand; Royal Adelaide Hospital, Adelaide, Australia; Devax, Inc., Lake Forest, CA, Stanford University Medical Center, Stanford, CA, Columbia University Medical Center and Cardiovascular Research Foundation, New York, NY, all in the USA.

Published in the *Journal of the American College of Cardiology* 2009;53:1031-1039.

ABSTRACT

Objectives: To assess safety and performance of the AXXESS self-expanding drug-eluting stent in coronary bifurcation lesions. Percutaneous treatment of coronary bifurcations is a predictor of adverse late outcomes, in part due to the lack of dedicated devices.

Methods: Patients with de novo bifurcation lesions were prospectively enrolled in a multicenter study. The AXXESS stent was deployed at the level of the carina followed by additional sirolimus-eluting stents in the distal parent vessel (PV) and/or side branch (SB). All patients underwent clinical follow up at 9 months; 150 were to receive control angiography and 76 intravascular ultrasound. The primary endpoint was the rate of major adverse cardiac events (MACE): a composite of death, myocardial infarction (MI), and target lesion revascularization (TLR). Secondary endpoints included in-segment restenosis, late loss and % neointimal volume obstruction.

Results: Overall, 302 patients were treated with 299 AXXESS stents (99%). Additional stenting of one branch was performed in 21.7% of patients (17.7% PV, 4% SB), and of both branches in 64.7%. At 9 months, 99.3% of patients returned for clinical follow up; from the angiographic and IVUS sub-studies, 93.3 and 89.4% returned. The cumulative 9-month MACE rate was 7.7% (0.7% death, 3.3% non-Q-wave MI, 1.0% Q-wave MI, 4.3% TLR). Subacute and late stent thrombosis occurred in 0.7% and 0.3% of patients. Total restenosis was 6.4% (3.6% PV, 4.3% SB), late loss was 0.20±0.41 mm in the PV and 0.17±0.34mm in the SB. In the AXXESS stent segment, % neointimal volume obstruction was 4.3±5.2%.

Conclusions: This prospective multicenter study confirms the safety and performance of the AXXESS stent in bifurcation lesions.

INTRODUCTION

Coronary bifurcation lesions are defined as stenoses involving one of the 3 primary epicardial coronary vessels and a branching vessel with a reference vessel diameter (RVD) of at least 2.2 mm (1). The percutaneous treatment of these lesions with stent implantation is associated with increased adverse clinical events and inferior angiographic outcomes, when compared to mid-vessel lesions (2,3). This is mainly due to suboptimal results in the side branch (SB). Despite the implementation of numerous techniques (T-stenting, V-stenting, "kissing" stenting, "crush" stenting, "culotte" stenting) to stent both branches, none of them, even in the drug-eluting stent era, has shown clinical and angiographic superiority to the single parent vessel (PV) stent technique with provisional T stenting of the SB in case of dissection or residual severe disease (4-6).

Novel dedicated stents have recently been developed to provide easier access to the SB and to scaffold more effectively its ostium, matching the stent configuration more closely to the anatomy of the bifurcation. However, clinical data on these devices are still sparse (7). The AXXESS stent (Devax Inc., Lake Forest, California) belongs to this category of dedicated bifurcation lesion stents (8). It is a self-expanding drug-eluting stent, deployed at the level of the carina which provides easy access to the distal branches that subsequently can be provisionally treated with percutaneous coronary intervention (PCI), depending on the disease status of these branches. The rationale behind this stent is to provide an anatomically tailored treatment of the bifurcation with maximum drug coverage and minimum overlap or deformation of the stent struts. The AXXESS stent has been previously tested in clinical practice in the prospective multicenter AXXESS PLUS registry enrolling 139 patients, in whom, together with the AXXESS stent, sirolimus- or paclitaxel-eluting stents were used as additional stents to optimize the procedure. The SB treatment was left at operator discretion and stenting of the SB was performed in approximately half of the lesions. *Post hoc* analysis of lesions treated with stent deployment in the SB provided better procedural outcomes and better late results with <10% restenosis of the SB, as compared to >20% SB restenosis after balloon-only angioplasty (9). The current study was planned to expand these results in a broader population, keeping stricter

protocol obligations for lesion treatment, such as the mandated use of sirolimus-eluting stents as additional stents for the PV and the SB if the residual diameter stenosis exceeded 30%.

METHODS

The DIVERGE (Drug Eluting Stent Intervention for Treating Side Branches Effectively) study is a prospective, multicenter registry. The local Ethics Committee of every hospital participating in the study approved the study design. All enrolled patients provided written informed consent prior to the index procedure.

Patient population

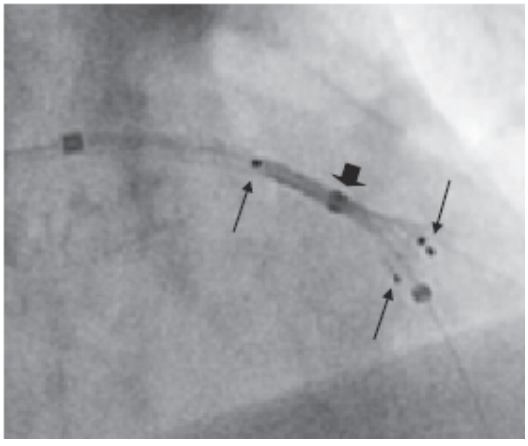
The study population consisted of male and female patients, 18-80 years of age, with documented stable or unstable angina or positive functional study, identified for elective PCI of a *de novo* native coronary artery bifurcation lesion in a major coronary artery where either the PV or the SB had at least a 50% diameter stenosis. The RVD by visual estimate had to be 2.75-3.75 mm in the PV and ≥ 2.25 mm in the SB. The lesion length had to be ≤25 mm in the PV, with ≤10 mm proximal to the carina. The SB ostium needed to be located >12 mm from the left main coronary artery. The angle between the distal PV and the SB had to be <70°. The protocol allowed concurrent treatment of one additional lesion, provided it was located in a different primary epicardial vessel and was successfully treated prior to the bifurcation lesion. Clinical exclusion criteria were: pregnant female; myocardial infarction (MI) within the previous 72 hours; cardiogenic shock; creatine kinase level above the upper limit of normality at the time of the procedure; documented left ventricular ejection fraction <30%; cerebrovascular accident or gastrointestinal/genitourinary bleeding within the past 6 months; renal insufficiency (creatinine >2.0 mg/dl); thrombocytopenia (platelet count <105/mm3); anemia (hemoglobin <10 g/dL); current or planned use of oral anticoagulant agents; contraindications to aspirin, clopidogrel, heparin or contrast agents; known sensitivity to sirolimus, stainless steel, titanium, nickel; life expectancy <2 years; current participation in another investigational drug or device

study. Angiographic exclusion criteria were: previous PCI in the target vessel <9 months from the index procedure; left main stenosis; severe calcification, excessive tortuosity or presence of intraluminal thrombus by visual estimation; pre-treatment of the target lesion with any unapproved device or atherectomy or laser (cutting balloon was allowed).

Study device

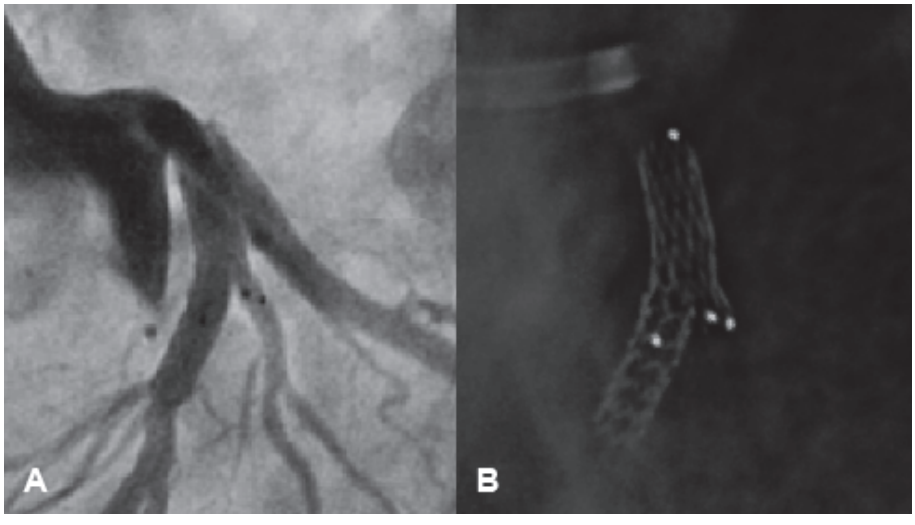
The AXXESS stent is made from a nickel-titanium alloy (nitinol) in the austenitic (super-elastic) phase. The stent elutes Biolimus A9® (Biosensors International, Ltd), a derivative of sirolimus, with similar anti-proliferative properties (10). Drug release is mediated by a bio-absorbable polylactic acid-based polymer (which is metabolized over time into carbon dioxide and water). This drug-polymer coating is applied to the abluminal surface of the stent. The nominal drug loading is 22 µg/mm of stent length for all sizes. The procedure for stent placement typically requires wiring of both branches of the lesion, followed by successful pre-dilation of the PV and the SB in order to provide space for the self expanding stent. The stent is kept in place on the delivery system by a covering sheath, which is clearly visible under fluoroscopy. The stent is deployed by gently retracting the sheath once the stent is in place at the level of the carina. The stent has 1 radiopaque marker at the proximal edge and 3 markers at the distal edge to assist in accurate positioning and deployment at the target site (Figure 1). The AXXESS stent's conical shape and self-expanding property allow it to cover the irregular anatomy of a bifurcation at the level of the carina up to bifurcation angles of 70°. The stent is unique in that it spans both the PV and SB without obstructing access to either, and allows easy passage of additional stents in both branches. If needed, additional stents are implanted to complete lesion coverage. Accurate distal stent position is aided by the presence of the distal markers on the Axxess stent. In this study a small amount (1-2 mm) of overlap was targeted. Post dilation focus is on the distal branch stents, with attention to ensure full deployment at the overlap segments. Because the branch vessel stents are implanted distal to the carina, flow to the side branch is unobstructed, and no strut deformation is induced by post dilation (Figure 2).

Figure 1. Fluoroscopic image showing partially deployed stent position within bifurcation lesion.



Stent (arrows) and cover sheath (block arrow) markers are clearly visible.

Figure 2. Final placement angiogram.



(**A**) Contrast-filled angiogram shows the AXXESS stent in the proximal Left Anterior Descending (LAD) coronary artery (Left Anterior Oblique-view with one marker at the level of the mid-LAD and two markers in the diagonal branch) and an additional Cypher in the mid-LAD, (**B**) Stent boost image shows an enhanced contrast-negative, stent visualization.

Procedural protocol and follow up

After percutaneous access was obtained, heparin was administered to maintain an activated clotting time >250 seconds (or >200 seconds if Glycoprotein IIb/IIIa inhibitors were given). Eligible patients underwent mandatory pre-dilatation of the PV and, at operator's discretion, of the SB. At this point, placement of the AXXESS self-expanding stent at the site of the bifurcation was performed. The stent diameters available for the study were 3.0 mm and 3.5 mm, with lengths of 11 or 14 mm. All patients who had the study stent introduced into the vasculature were considered enrolled in the DIVERGE study. Depending on the disease status of the distal PV and distal SB, adjunctive stenting, in overlap of the distal edge of the AXXESS stent and extending into the branch vessels, was permitted. An "optimal angiographic outcome" was strongly recommended in order to obtain no residual stenosis at the end of the procedure. Thus, additional stents were implanted if there was a residual stenosis of >30% in any segment of the bifurcation. The protocol mandated the use of Cypher sirolimus-eluting stents (Cordis, Johnson & Johnson, Warren, NJ) for this purpose. Bail-out stenting with additional Cypher stents was allowed in case of dissection or incomplete lesion coverage. The first 150 patients enrolled were allocated into an angiographic sub-study, while the first 76 patients at selected sites were allocated into an intravascular ultrasound (IVUS) sub-study. The IVUS examination was performed at the end of the procedure according to standard protocols using a 20-40 MHz ultrasound probe with motorized pullback (speed: 0.5 mm/sec). Aspirin (≥80 mg/day) was given daily and clopidogrel (loading dose of at least 300 mg prior to or immediately after the procedure and 75 mg/day thereafter) was administered for at least 6 months in all patients. A protocol amendment of October 2007 mandated clopidogrel for 12 months post-procedure according to the updated American Heart Association/American College of Cardiology/Society for Cardiovascular Angiography and Interventions recommendations (11). Serial blood samples for creatine kinase and creatine kinase–MB were routinely obtained 8 and 16 hours after the intervention. Patients were evaluated clinically at 1, 6 and 9 months after the procedure. Control angiography and IVUS were performed after the 9 month visit, or earlier if there were recurrent symptoms. If restenosis was not found in an angiography performed <4 months post procedure, a second angiography was done at 9 months.

Quantitative coronary angiography and IVUS analysis

Digital coronary angiograms were analyzed offline by an independent core laboratory, using a validated automated edge detection system (QAngioXA version 7.1.14.0, Medis, Leiden, The Netherlands). Matched views were selected for angiograms recorded before and immediately after the intervention and at follow up. Bifurcation lesions were classified according to the Medina classification (12). Angiographic measurements were made both in the stent and in the stented segment (defined as the whole stented tract plus the 5 mm edges proximal and distal to the stent) during diastole using the contrast-filled guiding catheter for magnification calibration. Lesion RVD, minimal luminal diameter (MLD), percent diameter stenosis and length were obtained at baseline for both the PV and the SB. MLD and diameter stenosis were evaluated at the end of the procedure and at follow up, for the in-segment and in-stent sections in both the PV and the SB, and specifically only for the AXXESS stent. Acute gain was defined as the difference between the MLD at the end of the intervention and the MLD at baseline. Late lumen loss was calculated as the difference in MLD between measurements immediately after the procedure and at follow up. Binary angiographic restenosis was defined as diameter stenosis ≥50% by quantitative coronary angiography, at the follow up angiogram.

Quantitative and qualitative IVUS analyses were performed offline by an independent core laboratory, using validated software (echoPlaque, INDEC Medical Systems, Santa Clara, California), allowing semi-automated detection of luminal and stent boundaries in reconstructed longitudinal planes. Volumetric quantitative IVUS analysis was obtained for vessel, stent and lumen. Serial volumetric measurements were done if baseline and follow-up runs were matched and of adequate quality. Neointimal volume index was computed as the difference between stent volume and lumen volume per mm of stent. Percent volume obstruction was calculated as the ratio between the neointimal volume and stent volume x 100. Incomplete stent apposition was defined as one or more stent struts clearly separated from the vessel wall with evidence of a void behind the strut in a vessel segment not associated with any side branches.

Endpoints and definitions

The primary endpoint of the study was the rate of major adverse cardiac events (MACE) at 9 months; MACE were defined as any of the following: cardiac or non-cardiac death, Q- or non-Q-wave MI, and ischemia driven target lesion revascularization (TLR). Secondary angiographic endpoints included binary restenosis and late lumen loss, evaluated in-segment, in the stented area, and in the AXXESS stent only. Secondary IVUS endpoints were neointimal tissue volume, percent volume obstruction within the study device and the incidence of late-acquired stent incomplete apposition and strut tissue coverage at 9 months. Cardiac death was defined as death due to acute MI, congestive heart failure, cardiac perforation, arrhythmia, cerebrovascular accident within 30 days of the index procedure or complication of the index procedure (including bleeding, vascular repair, transfusion reaction, or bypass surgery) or any death in which a cardiac cause could not be excluded. Non-cardiac death was defined as a death not due to cardiac causes. Myocardial infarction was defined as: a) Q-wave MI when chest pain or symptoms consistent with myocardial ischemia and new pathological Q-waves in two or more contiguous ECG leads were present; b) non-Q-wave MI if Creatine Kinase elevated >2 times the upper laboratory normal with the presence of elevated Creatine Kinase-MB in the absence of new pathological Q-waves. TLR was considered ischemic, defined as repeat revascularization (PCI or bypass surgery) in the presence of a positive functional study for ischemia due to restenosis of any portion of the target lesion, or TLR of a 70% diameter stenosis anywhere within the target lesion. In this study, the target lesion was defined as any treated segment of the bifurcation - PV or SB - plus a border of 5 mm. Stent thrombosis was defined according to the Academic Research Consortium criteria (13). An independent clinical events committee adjudicated all the clinical events and an independent data safety monitoring board reviewed clinical data periodically throughout the study. In addition, several procedure parameters were assessed. Primary device success was defined as deployment of the AXXESS stent without system failure or device related complication. Lesion success was defined as attainment of <50% residual stenosis of the target lesion using the assigned device or any percutaneous method. Procedure success was defined as attainment of a final lesion (angiographic) success in the absence of any in-hospital MACE. Finally,

AXXESS stent placement was evaluated independently by the core laboratory. It was considered accurate if ≥1 of the 3 distal markers of the stent was clearly in each of the PV and SB respectively, or if ≥2 markers were in the triangle formed by the carina and the ostia of the branch vessels.

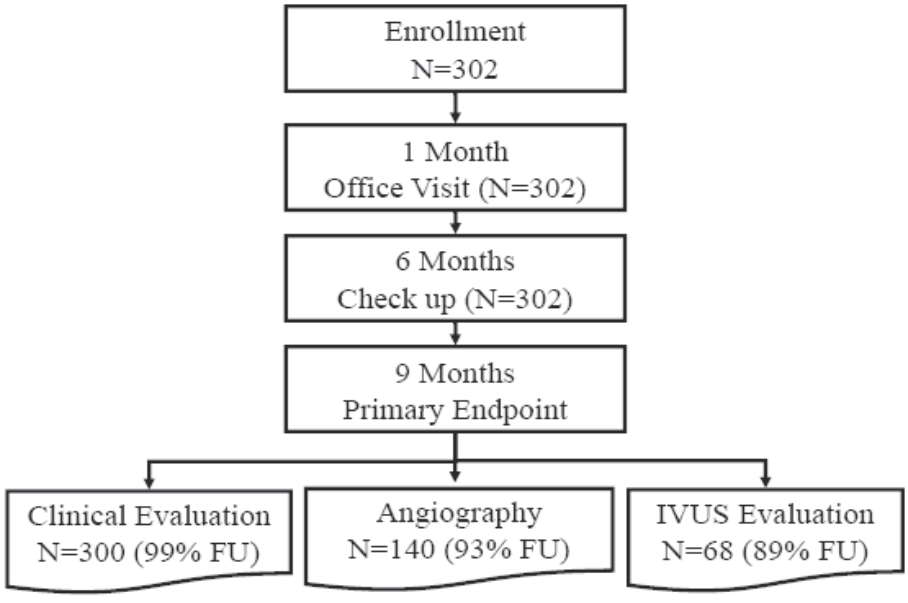
Statistical analysis

All analyses were conducted according to the intention-to-treat principle. Continuous data are expressed as means ± standard deviations or as medians [interquartile ranges], as appropriate, whereas dichotomous data are summarized as frequencies.

RESULTS

Between June 2006 and October 2007, 302 patients were enrolled in the DIVERGE study (Figure 3).

Figure 3: Flow diagram of subject progress through phases of the DIVERGE trial.



Study population, procedural and in-hospital outcomes

Baseline clinical characteristics of the patients are shown in Table 1, while the angiographic and procedural characteristics of the lesions treated are presented in Tables 2 and 3. A majority of the lesions were categorized as 'true' bifurcations (77.4%) and had presence of disease in the side branch (78.1%) according to the Medina classification system. At baseline, mean lesion length and RVD by quantitative coronary angiography were respectively 14.6 mm and 2.93 mm in the PV, and 6.9 mm and 2.3 mm in the SB. The AXXESS stent was placed in 299 out of 302 patients (99.0%). The placement was scored as optimal by the angiographic core lab in 93% of cases. In 3 patients, the AXXESS stent was withdrawn due to anatomical configurations outside of the study inclusion criteria. In two additional cases, the AXXESS stent was not placed at the bifurcation, thus primary device success was obtained in 297 out of 302 patients (98.3%). These lesions were successfully treated with other techniques. Additional stent were placed in the distal branch vessels depending on disease distribution, resulting in the patterns shown in Figure 4. In keeping with the prevalence of diseased side branches in this study, the most frequent treatment pattern was for both branch vessels to be stented (64.7%), but in several cases single distal stents were placed in the PV (17.7%) or the SB (4.0%). Post dilation was performed in 85.8% of cases to a mean inflation pressure of 12.5±3.2 ATM. Lesion (angiographic) success was obtained in 300 out of 302 of patients (99.3%). No deaths, TLR or stent thrombosis occurred during hospitalization. The rate of periprocedural non-Q-wave MI was 3.0%, accounting for all in-hospital MACE. One of these was caused by periprocedural occlusion of the non-stented SB, due to untreatable dissection. Thus, the procedure success rate was 96.7%.

Table 1. Baseline characteristics of the patients enrolled.

	Patients (n=302)
Age (years)	62.8 ± 10.6
Male gender	224 (74.2%)
Body mass index (kg/m^2)	27.5 ± 4.1
Diabetes Mellitus	55 (18.2%)
Insulin Dependent	17/ (5.6%)
Hypertension	171 (56.6%)
Hypercholesterolemia	236 (78.1%)
Current smoker	71 (23.5%)
Prior myocardial infarction	88 (29.1%)
Prior percutaneous intervention	96 (31.8%)
Prior bypass surgery	7 (2.3%)
Unstable Angina	71 (23.5%)
Ejection Fraction (%)	68.4 ± 11.1
Glycoprotein IIB/IIIA inhibitors	36 (11.9%)

Data are presented as numbers (percentages) or means ± standard deviations, unless otherwise specified.

Table 2. Baseline characteristics of the lesions enrolled.

	Lesions (n=302)
Target Vessel	
Left Anterior Descending / Diagonal	244 (80.8%)
Circumflex / Obtuse Marginal	44 (14.6%)
Right Coronary Artery /Posterior Descending	14 (4.6%)
Medina classification of the bifurcation	
1,0,0	20 (6.6%)
1,1,0	36 (12%)
1,0,1	20 (6.6%)
1,1,1	194 (64.5%)
0,1,1	19 (6.3%)
0,1,0	10 (3.3%)
0,0,1	2 (0.7%)
"True" bifurcation lesion (1,0,1 or 1,1,1 or 0,1,1)	234 (77.4%)
Angle between branches (°)	54.2 ± 24.9
Post-dilatation	259 (85.8%)
Mean inflation pressure (atm)	12.5 ± 3.2
Mean balloon size (mm)	2.70 ± 0.29
Proximal main branch	2.78 ± 0.37
Distal main branch	2.55 ± 0.32
Side branch	2.76 ± 0.37
Total number of stents implanted	804
Total stent length (mm)	37.8 ± 14.7
Axxess stent without distal stents	37 (12.3%)
Axxess and distal main branch stents	53 (17.7%)
Axxess and distal side branch stents	12 (4.0%)
Axxess and stent in both branches	194 (64.7%)
Axxess stent/imaging not assessable	6 (2.0%)
Axxess stents placed	299 (99%)
Device success	297 (98.3%)
Lesion success	300 (99.3%)*
Procedure success	292 (96.7%)
Optimal Axxess placement	278/299 (93%)

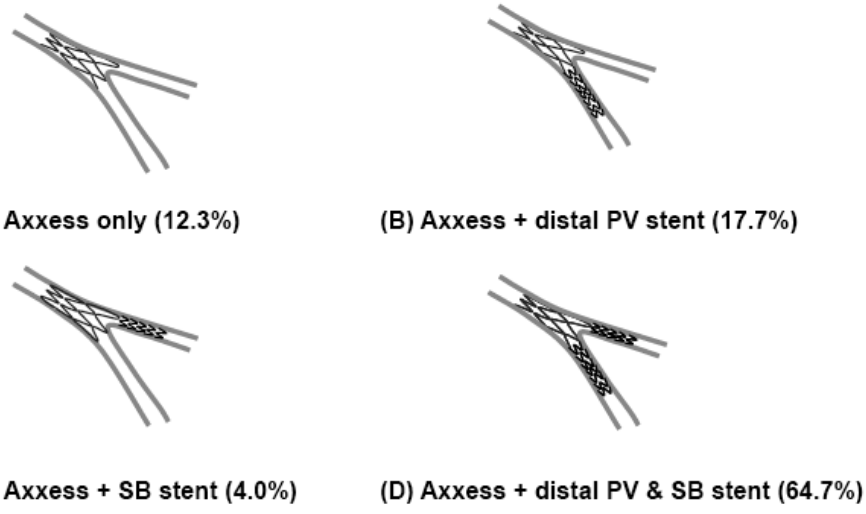
In one patient there was a total occlusion of the side branch, due to untreatable dissection. In a second patient (in whom the Axxess stent was not implanted), there was a residual stenosis at the ostium of the side branch >50% after balloon angioplasty (the vessel was not stented).

Table 3. Quantitative coronary angiography analysis of the lesions treated in the total cohort and in the angiographic sub-group.

	All patients		Angiographic sub-group	
	Parent Vessel	Side Branch	Parent Vessel	Side Branch
Pre-procedure				
Reference vessel diameter (mm)	2.93 ± 0.37	2.30 ± 0.35	2.90 ± 0.32	2.29 ± 0.34
Minimal luminal diameter (mm)	0.87 ± 0.38	1.02 ± 0.58	0.80 ± 0.29	0.97 ± 0.59
Diameter stenosis (%)	70.6 ± 11.8	55.8 ± 22.8	72.4 ± 9.0	57.8 ± 23.5
Lesion Length (mm)	14.6 ± 6.3	6.9 ± 3.1	14.3 ± 6.1	6.9 ± 3.6
Post-procedure				
In-segment				
Minimal luminal diameter (mm)	2.33 ± 0.37	2.01 ± 0.39	2.29 ± 0.33	1.99 ± 0.38
Diameter stenosis (%)	22.2 ± 7.9	18.0 ± 9.3	22.6 ± 8.2	18.8 ± 9.6
Acute gain (mm)	1.47 ± 0.46	0.98 ± 0.60	1.49 ± 0.39	1.01 ± 0.63
In-stent				*(n=112)*
Minimal luminal diameter (mm)	2.69 ± 0.35	2.44 ± 0.33	2.68 ± 0.31	2.41 ± 0.34
Diameter stenosis (%)	9.6 ± 9.1	2.1 ± 6.7	9.2 ± 9.2	2.5 ± 6.9
Acute gain (mm)	1.88 ± 0.41	1.60 ± 0.44	1.89 ± 0.39	1.64 ± 0.44
Axxess only				
Minimal luminal diameter (mm)	3.10 ± 0.41	-	3.08 ± 0.40	-
Diameter stenosis (%)	5.7 ± 5.5	-	6.7 ± 5.4	-
Follow up				
In-segment				
Minimal luminal diameter (mm)	-	-	2.10 ± 0.49	1.82 ± 0.46
Diameter stenosis (%)	-	-	27.5 ± 13.8	22.7 ± 14.9
In-stent				
Minimal luminal diameter (mm)	-	-	2.41 ± 0.56	2.14 ± 0.54
Diameter stenosis (%)	-	-	17.0 ± 16.6	10.5 ± 19.0
Axxess only				
Minimal luminal diameter (mm)	-	-	2.91 ± 0.60	-
Diameter stenosis (%)	-	-	-0.8 ± 18.4	-
Late loss (mm)				
In-segment	-	-	0.20 ± 0.41	0.17 ± 0.34
In-stent	-	-	0.29 ± 0.50	0.29 ± 0.45
Axxess only	-	-	0.18 ± 0.49	-
Binary angiographic restenosis				
In-segment	-	-	5 (3.6%)	6/140 (4.3%)
In-stent	-	-	3 (2.3%)	5/105 (4.8%)
Axxess only	-	-	1 (0.7%)	-
In-segment bifurcation restenosis	-	-	9/140 (6.4%)	
In-stent bifurcation restenosis	-	-	7/140 (5%)	

Data are presented as means ± standard deviations, or numbers (percentages).

Figure 4. Deployment patterns observed in DIVERGE study



Thirty-day and 9-month clinical outcomes

Clinical events are presented in table 4. Between the end of the hospitalization and the first month after treatment, sub-acute stent thromboses resulted in 2 Q-wave MIs (both occurring on day 4 after the index procedure and under double antiplatelet therapy). Both patients underwent urgent percutaneous revascularization, but one event was fatal. There was one ischemia-driven TLR, so that the overall rate of 1-month MACE was 4.0%. At 9 months, clinical follow up was available in 300 patients (99.3%). Two patients withdrew consent for further follow up at 6 months: one was event-free, while the other experienced a TLR after 3 months. The cumulative 9 month MACE rate was 7.7%, including 0.7% death, 4.3% MI and 4.3% TLR. Between 1 and 9 months, one cardiac death was recorded at 8 months in a patient who underwent elective bypass surgery (with proven in-stent restenosis of both the PV and the SB and additional de novo coronary lesions). One Q-wave MI, caused by late stent thrombosis, occurred in a patient 7 months after the index procedure, one month after clopidogrel discontinuation. An additional non-Q-wave MI was caused by iatrogenic total occlusion of the distal target vessel during the planned 9-month control angiography and IVUS (which showed good result of the index PCI), due to

embolization of thrombotic material from the guiding catheter. Both patients were successfully treated with PCI. Finally, there were 8 additional percutaneous TLR, all with proven restenosis (one occurred in a patient who did not receive the AXXESS stent, but a bare metal stent). Of interest, among the total 13 cases of TLR, 6 (46.1%) were PV restenoses (with or without involvement of the SB), 4 (30.8%) were driven exclusively by SB restenosis, and 3 (23.1%) were stent thromboses.

Table 4. In-hospital, cumulative 30-day and cumulative 9-month clinical events.

	All Patients	**Angiographic sub-group**
In-hospital	*(n=302)*	*(n=150)*
Major adverse cardiac events	9 (3%)	5 (3.3%)
Myocardial infarction (all non-Q-wave periprocedural)	9 (3%)	5 (3.3%)
30-day	*(n=302)*	*(n=150)*
Major adverse cardiac events	12 (4%)	7 (4.7%)
Death (cardiac)	1 (0.3%)	1 (0.7%)
Myocardial infarction	11 (3.6%)	6 (4%)
Q wave	2 (0.7%)	1 (0.7%)
non-Q wave	9 (3%)	5 (3.3%)
Target lesion revascularization (percutaneous)	3 (1%)	2 (1.3%)
Early stent thrombosis	2 (0.7%)	1 (0.7%)
9-month	*(n=300)*	*(n=149)*
Major adverse cardiac events	23 (7.7%)	14 (9.4%)
Death	2 (0.7%)	1 (0.7%)
Cardiac death	2 (0.7%)	1 (0.7%)
Myocardial infarction	13 (4.3%)	8 (5.4%)
Q wave	3 (1%)	2 (1.3%)
non-Q wave	10 (3.3%)	6 (4%)
Target lesion revascularization	13 (4.3%)	8 (5.4%)
Percutaneous	12 (4%)	8 (5.4%)
Bypass surgery	1 (0.3%)	0
Stent thrombosis ARC	3 (1%)	2 (1.3%)
Early (probable/possible)	0	0
Early (definite)	2 (0.7%)	1 (0.7%)
Late (probable/possible)	0	0
Late (definite)	1 (0.3%)	1 (0.7%)
Remote target vessel revascularization	19 (6.3%)	11 (7.4%)
Target vessel failure	29 (9.7%)	17 (11.4%)

Data are presented as numbers (percentages).

Quantitative Coronary Angiography and IVUS outcomes

Out of the 150 patients included in the angiographic sub-study, 140 (93.3%) received the planned control angiogram. Angiographic data are presented in table 3. In-bifurcation restenosis occurred in 9 patients (6.4%): 2 patient had restenosis in both the PV and the SB (1 total occlusion starting just before the AXXESS stent and 1 multifocal restenosis in 2 sites, 1 proximal to the AXXESS stent and 1 in the SB stent), 3 patients had PV restenosis (1 proximal to the AXXESS stent, and 2 in the PV stent after the bifurcation), 4 patients had SB restenosis (including also the patient with the total occlusion of the non-stented SB causing a periprocedural MI at baseline).

Out of the 76 patients included in the IVUS sub-study, 68 (89.4%) received the planned control IVUS. Baseline and follow up 3-dimensional volumetric analyses were available for the AXXESS stent in 54 patients and 56 patients, respectively. Of the 68 follow up patients, serial 3-dimensional analysis for the AXXESS stent was available in 51 patients, and serial qualitative analysis for incomplete stent apposition was possible in 62 AXXESS stents. The IVUS data are presented in table 5. Follow-up neointimal hyperplasia obstruction within the AXXESS stent in terms of percent of stent volume was 4.3±5.2%. The self expanding AXXESS stent increased in mean volume index from the procedure to follow-up from 7.4±2.0 to 9.6±2.6 mm3/mm of stent, leading to a net increase in lumen volume index from 7.3±2.0 to 9.2±2.5 mm3/mm.

Table 5. Intravascular Ultrasound serial analysis of lesions treated in the IVUS sub-group.

	Post procedure	Follow-up
Vessel volume index (mm^3/mm)	17.0 ± 3.6	18.9 ± 3.7
AXXESS volume index (mm^3/mm)	7.4 ± 2.0	9.6 ± 2.6
Lumen volume index (mm^3/mm)	7.3 ± 2.0	9.2 ± 2.5
Neointimal volume index (mm^3/mm)	-	0.4 ± 0.6
Total neointimal volume (mm^3)	-	2.1 [1.0-6.2]
Percent volume obstruction (%)	-	4.3 ± 5.2
Incomplete stent apposition (AXXESS stent)	22 (35.5%)	17 (27.4%)
Persistent	-	16 (25.8%)
Late acquired	-	1 (1.6%)

Data are presented as means ± standard deviations, medians [interquartile ranges] or numbers (percentages).

DISCUSSION

The use of the AXXESS Biolimus-eluting stent for the treatment of complex bifurcation lesions resulted in: a high procedure success rate (96.7%), a low all-cause cumulative 9-month MACE rate (7.7%, including 3.0% peri-procedural non-Q wave MI), and a low 9-month TLR rate (4.3%). Systematic angiographic follow up of 140 patients revealed an overall in-segment restenosis rate of 6.4% inclusive of both PV and SB. IVUS analysis showed marked suppression of neointimal hyperplasia within the stent and a significant increase in lumen volume over time within the AXXESS stent. In addition, there are several methodological strengths in this study that reinforce the validity of the results obtained: prospective enrollment, multicenter setting, total and independent monitoring of data acquisition, independent evaluation of the events, enrollment of one of the largest published cohorts of patients with bifurcation lesions, and focus on a drug-eluting stent specifically dedicated for bifurcations. The design of the AXXESS stent allows conformability of the stent to the vessel wall, without deformation of the struts and with easy access to both branches for additional PCI. The placement technique is novel, and requires thorough pre-dilation and careful attention to marker position within the bifurcation for optimal positioning. In this study, optimal placement was obtained in 93% of patients. Of the suboptimal placements, a successful angiographic outcome was obtained in all cases. The advantage of this technique is that additional stents can be placed in either or both distal segments provisionally, depending on angiographic appearance, without distortion from their cylindrical shape. This allows the length and diameter of distal stents to be selected for a precise fit to the lesion. Since the AXXESS covers the ostium of the branch vessels, distal stents are placed at or slightly distal to the carina, thus eliminating ostial stent strut obstruction and minimizing stent strut overlap. Thus, techniques used to compress or distort obstructing stent struts in other bifurcation techniques, such as kissing-balloon dilation, are eliminated.

Comparison with the current evidence

Despite the fact that there is no firm agreement on the standard treatment of bifurcation lesions, there is some consensus that a strategy based on single stenting

of the PV with provisional stenting of the SB is recommended; however, neither an advantage nor a disadvantage of stenting both branches has ever been shown. There are a few studies comparing simple to complex strategies for bifurcation lesions. The NORDIC trial compared a single PV sirolimus-eluting stent strategy (with kissing balloon angioplasty of the SB only if the flow was impaired, but not if there was a residual angiographically severe lesion) to a strategy of stenting both the PV and the SB with sirolimus-eluting stents (in this case different techniques were allowed). This trial showed good clinical results, with low 6-month TLR rates in both arms (1.9% in the PV stent arm and 1% in the PV+SB stent arm), not influenced by the angiographic follow up, performed on purpose at 8 months. However, the overall MACE rates evaluated at 6 months (2.9% in the PV stent arm and 3.4% in the PV+SB stent arm) did not include the periprocedural MI, which were as high as 8% in the PV stent group and 18% in the PV+SB stent group. Moreover, post-procedural blood samples for myocardial enzymes were not available in the whole cohort, but only in around 68% of the patients, thus a risk of underestimation of the event rate should also be considered. Furthermore, the angiographic restenosis rate, evaluated at 8 months, remained elevated in both groups (22.5% in the PV stent group and 16% in the PV+SB stent group), mainly driven by the SB restenosis (4). Another single center trial compared the single PV sirolimus-eluting stent technique (with mandated kissing balloon in all patients) and the routine T-stenting technique also with sirolimus-eluting stents, still showing 1-year MACE rates of 12.9% and 11.9% respectively, and 9-month restenosis rates of 12.5% and 13.5% respectively (6). In general, according to these trials, no major differences were noted if balloon-only angioplasty or stenting were performed in the SB and the angiographic restenosis rate still remained above 10% with all the techniques used. A general weakness of these studies is that a specific strategy for the SB treatment was mandated by the protocol, rather than by vessel diameter or presence of disease. On the contrary, the first-in-man AXXESS PLUS study, despite its non-randomized design, suggested improved angiographic outcomes in the SB if it was treated with a drug-eluting stent (with a restenosis rate of 7.9%) as compared to balloon angioplasty (with a restenosis rate of 25%) (9). However stenting of the SB in the AXXESS PLUS study occurred only in half of the cohort enrolled. In the DIVERGE study, stents were used

to obtain an optimal angiographic result in the bifurcation in the same way as would be done for a mid-vessel lesion. Using this approach, a single AXXESS stent was used in 12% of lesions, an additional stent was added in 21.5% of lesions, and a stent was added to both branches is 65% of lesions. The rationale behind this approach was to cover any diseased part of the bifurcation with both stent and drug and to obtain an angiographically "optimal" outcome at the end of the procedure. This strategy resulted in a TLR rate of 4.3%, a total bifurcation restenosis rate of 6.4%, and a SB restenosis rate of 4.3%. Despite the use of multiple stents to obtain complete coverage of the lesion in the bifurcation (seen up to now as possible risk factor for stent thrombosis (5)), the AXXESS strategy may offer beneficial effects in terms of low stent thrombosis rate as was seen in this study: subacute and late stent thrombosis rates according to Academic Research Consortium definitions were 0.7% and 0.3%, respectively (13). One mechanistic explanation could be the combination of the self-expanding properties of the study device with local drug delivery resulting in a large proximal PV lumen, coupled with lack of strut deformation, minimization of stent overlap, and undisturbed flow into the distal branch vessels. Thus, it appears that dedicated stenting technology for bifurcation lesions in combination with site-specific drug delivery offers an excellent outcome in terms of clinical, angiographic and intravascular ultrasound endpoints. Based on these findings, there seems to be no penalty for stenting the side branch, but it remains to be seen in a randomized manner whether this strategy is superior to provisional stenting. Limitations of the technique are the angulation (>70° angulation should be avoided) and the use of multiple stents (which may also be advantageous given the results), yet angiographic analysis did not demonstrate any increase of restenosis at overlapping stent segments.

Limitations

The major limitation of this study is the single arm, non-randomized setting. Despite the encouraging results shown in the DIVERGE study, a randomized trial is warranted to prove the angiographic and clinical superiority of the AXXESS stent versus current bifurcation stenting techniques.

APPENDIX

Participating DIVERGE Investigators:

Belgium: ZNA Middelheim Antwerp – Stefan Verheye; OLV Aalst - William Wijns; Ziekenhuizen Oost Limburg St. Jan - Jo Dens; UZ Gasthuisberg Leuven - Christophe Dubois.

Great-Britain: King's College Hospital - Phillip MacCarthy; University of Leicester Glenfield Hospital - Anthony Gershlick; Royal Infirmary Edinburgh - Neal Uren.

The Netherlands: Amphia Ziekenhuis Molengracht - Peter den Heijer; St. Antonius Ziekenhuis - Benno Rensing; Zwolle Hospital - J.P. Ottervanger.

New-Zealand: Christchurch Hospital - Dougal McClean; Auckland City Hospital - John Ormiston.

Australia: St. Vincent's Hospital Sydney - David Muller; Monash Medical Center - Ian Meredith; St. Vincent's Hospital Melbourne - Rob Whitbourn; Royal Adelaide Hospital - Stephen Worthley.

Steering Committee: Dr. Stefan Verheye (principal investigator).

Data Coordinating Center: Cardiovascular Research Foundation (Dr. R. Mehran).

Clinical Events Committee: Dr. S. Chiu Wong (chairman).

Data and Safety Monitoring Board: Dr. B. Gersh (chairman).

Angiographic Core Laboratory: Cardiovascular Research Foundation (Dr. A. Lansky).

Intravascular ultrasound Core Laboratory: Stanford University Medical Center (Dr. P.J. Fitzgerald, Dr. B. Kwon Koo).

Data Monitoring: Marion Hughes at European Source (Belgium, United Kingdom and The Netherlands), and Precision Clinical Research Group, Inc. (Australia and New Zealand).

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12

Step-by-step StentBoost-guided Small Vessel Stenting Using the Self-Expandable Sparrow Stent-in-Wire

Pierfrancesco Agostoni, Stefan Verheye.

Antwerp Cardiovascular Institute Middelheim, Ziekenhuis Netwerk Antwerpen, Antwerp, Belgium.

Published in *Catheterization and Cardiovascular Interventions* 2009;73:78-83

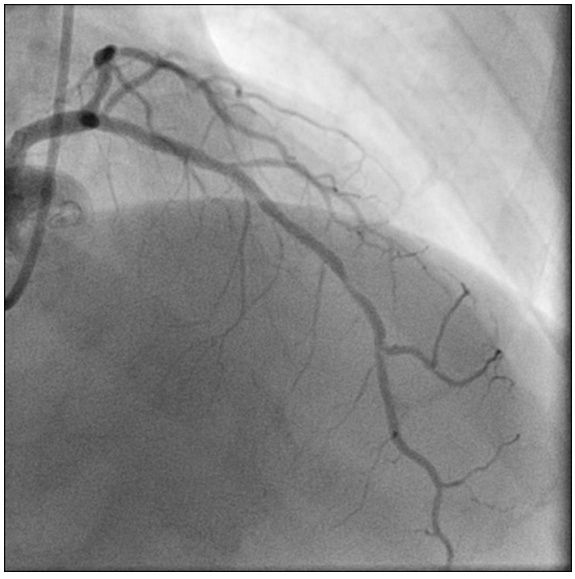
ABSTRACT

A 56 year-old woman underwent percutaneous coronary intervention for a lesion in a small mid-left anterior descending coronary artery (reference vessel diameter by quantitative coronary angiography: 2.11 mm) with a novel drug-eluting stent specifically designed for small vessels, the CardioMind Sparrow stent delivery system. This is a self-expandable sirolimus-eluting nitinol stent directly mounted into a 0.014-inch coronary guidewire. The stent has a very thin strut thickness (67 micron), limiting its radiopacity. A specific X-ray stent-enhancing visualization technique, “StentBoost”, allowed clear visualization and understanding of the steps needed for an appropriate release and deployment of the aforementioned stent.

CASE REPORT

A 56 year-old hypercholesterolemic and hypertensive woman underwent a diagnostic coronary angiogram because of recent onset effort angina with positive stress test. She had a previous history of an inferior myocardial infarction effectively treated with bare metal stent implantation of the mid-right coronary artery, and a successful elective bare metal stenting procedure of the proximal left anterior descending (LAD). The current angiogram revealed good patency of the two previously implanted stents and a single de novo lesion in the mid-LAD (**Figure 1**). As the reference vessel diameter (RVD) of the LAD at the level of the lesion was 2.11 mm by quantitative coronary angiography, the patient met inclusion criteria and was enrolled in the CARE II study (1,2).

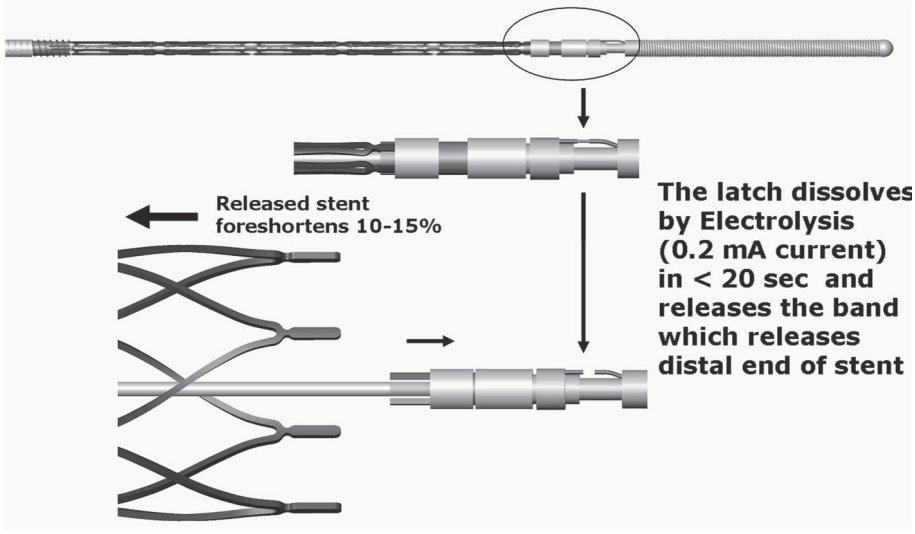
Figure 1.



Normal angiography (right anterior oblique cranial view) of the left coronary artery showing good patency of the stent in the proximal left anterior descending (LAD) artery and a severe stenosis in the mid-LAD. By quantitative coronary angiography, this lesion has a reference vessel diameter of 2.11 mm, a minimal luminal diameter of 0.83 mm, a diameter stenosis of 61% and a length of 7.6 mm.

The CARE II trial is an ongoing study assessing the effectiveness of a novel self-expandable nitinol stent directly mounted into a 0.014-inch coronary guidewire, the Sparrow stent (CardioMind Inc., Sunnyvale, California). The trial plans to enroll 220 patients randomized to 3 arms: the sirolimus-eluting Sparrow stent, the bare Sparrow stent and a conventional balloon-expandable bare metal stent (MicroDriver, Medronic Inc., Minneapolis, Minnesota) in a 4:4:3 respective allocation. The major inclusion criterion is a single de novo lesion in a vessel with RVD between 1.9 and 2.8 mm. The stent used in this trial is a next generation of a previously used stent (3). As mentioned, the stent is directly folded inside a 0.014-inch guidewire. The guidewire, in the segment where the stent is located, has a diameter of 0.006 inches. The Sparrow guidewire is compatible with commercially available over-the-wire or rapid exchange balloon and stent catheters. The Sparrow stent has an extremely thin strut thickness (0.024 inches - 67 micron). This feature has been claimed as a potential drawback due to the suboptimal radiopacity of the device (4). The previous version of the stent was mechanically released at the level of the lesion to treat by means of a covering sheath that was retracted during stent implantation (3). The new version, used in the CARE II trial, operates in a different way. The stent is kept in place by two cylindrical bands (one distal and one proximal) that entrap the edges of the stent inside the wire. Each band is held in place by a metallic latch. Once the stent (which has radiopaque markers at both stent edges) is positioned in the vessel at the level of the lesion to treat, the proximal part of the wire is connected to a sterile adaptor, which in turn is attached, via a sterile pouch, to a non-sterile hand-held power supply that provides electrical current to release the stent. This power supply has two buttons. Button number 1, when pushed, generates a 0.2 mA current that allows electrolytic dissolution of the distal metallic latch, so the distal band and the distal stent edge move away from each other. This mechanism releases the distal portion of the self-expandable stent. During this operation, the stent undergoes a foreshortening of around 10-15% (**Figure 2**). The activation of button number 2 releases the proximal portion of the stent without foreshortening as all the “tension” has been discharged after the first release step. Before release of the proximal stent a gentle counterclockwise rotation of the whole wire is needed in order to “unwind” the unexpanded stent from the wire itself.

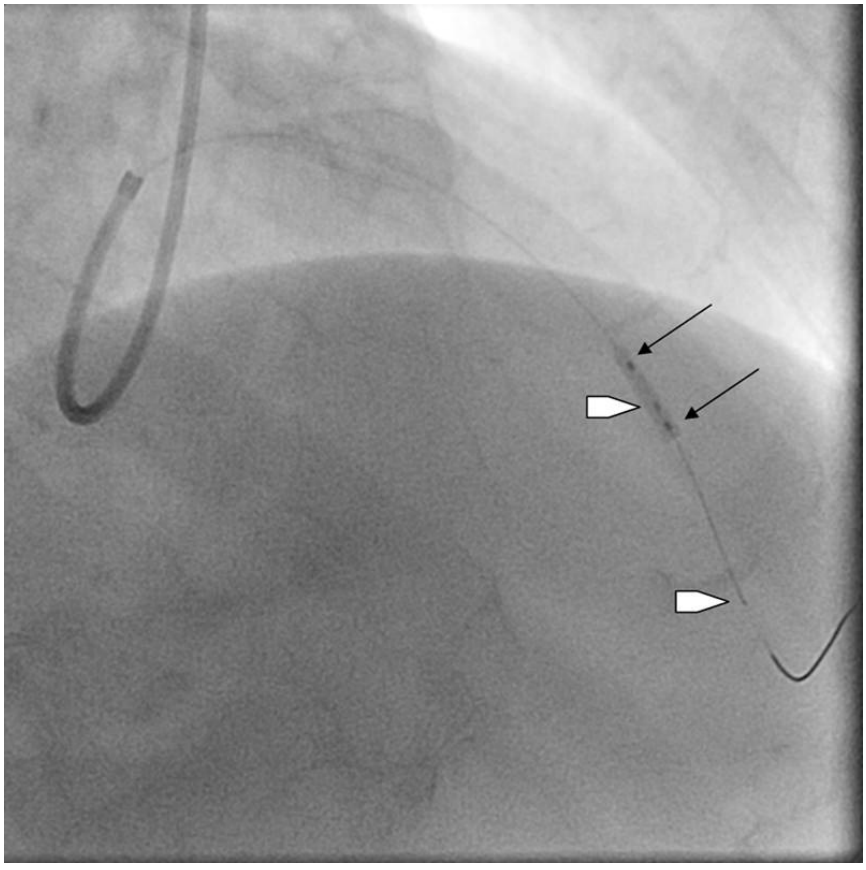
Figure 2.



Graphic representation of the mechanism of release of the Sparrow stent from the guidewire.

After informed consent and randomization, the patient was allocated to the sirolimus-eluting Sparrow stent arm. After pretreatment with a loading dose of clopidogrel (300 mg) and 160 mg of acetylsalicylic acid and full anticoagulation with weight-adjusted unfractionated heparin, the LAD was wired with the Sparrow wire in which a 2.75x17 mm stent was mounted. Balloon pre-dilatation was performed using this wire. Of interest, the 2.5x10 mm diameter balloon could be advanced over the segment of the wire where the stent was located (**Figure 3**).

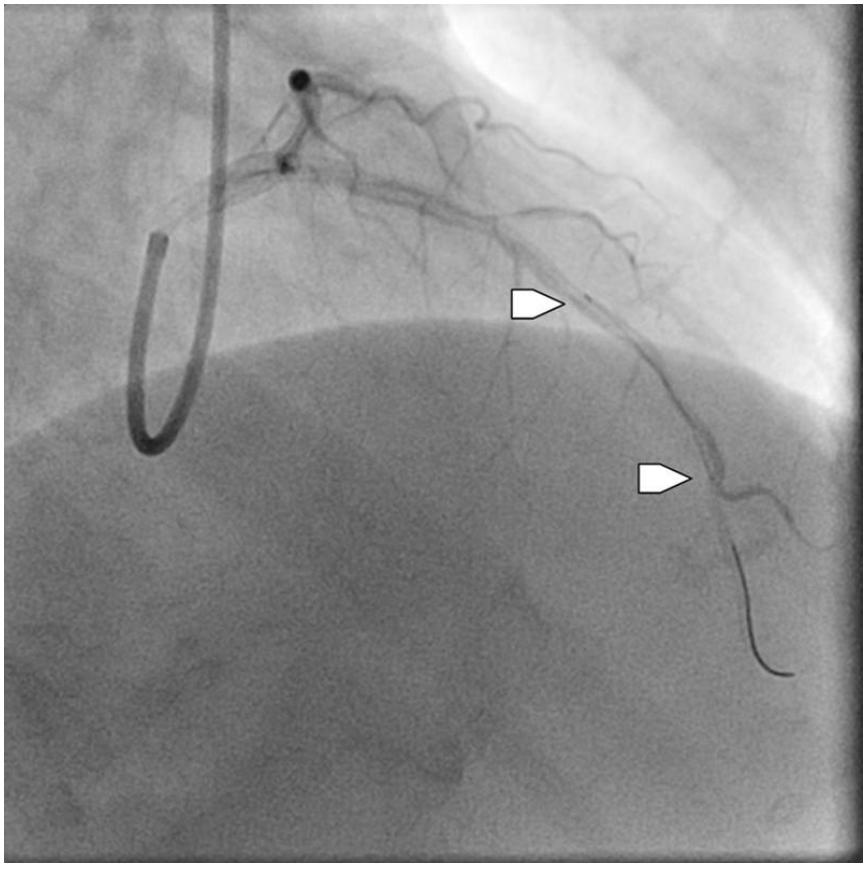
Figure 3.



Pre-dilatation of the LAD lesion with a 2.5x10 mm balloon. The black arrows indicate the balloon markers; the white arrowheads indicate the markers of the Sparrow 2.75x17 mm stent inside the coronary guidewire. Notice the overlap between the distal portion of the balloon and the proximal portion of the stent.

After satisfactory pre-dilatation, the stent was adequately repositioned at the level of the lesion (**Figure 4**) and was ready for release. The first step was the release of the distal portion of the stent from the wire by electrolysis of the distal latch.

Figure 4.

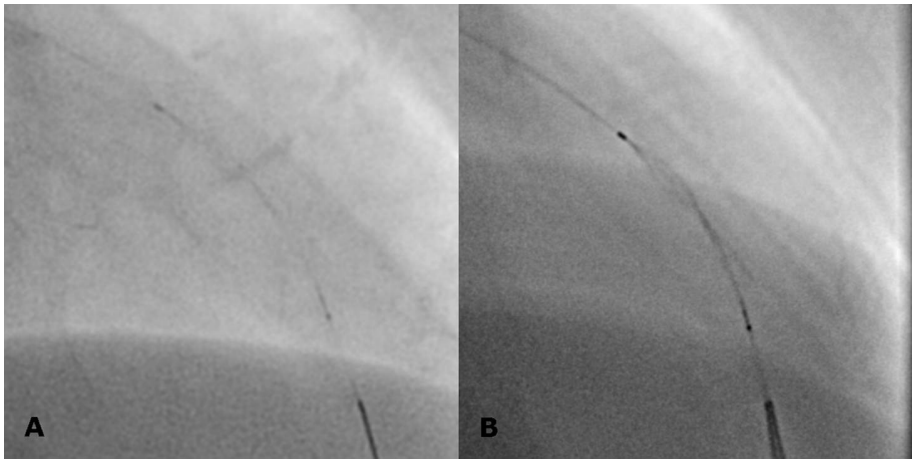


Stent positioning at the level of the lesion. The white arrowheads indicate the markers of the Sparrow stent inside the guidewire.

Visualization of the partial release of the Sparrow stent was not optimal with standard angiography (**Figure 5a**). However, application of StentBoost (Philips Medical Systems Nederland BV, Best, The Netherlands) largely improved the visibility of the device. StentBoost is a recently developed technique that allows an improved angiographic visualization of the stent by enhancing the focus of the X-rays around 2 radiopaque markers (5-8). In this case, the two markers were the distal and proximal markers of the stent in the wire. StentBoost allowed visualization of the distal portion of the

Sparrow stent released from the wire and the “folding” (like a candy wrapper) of the rest of the stent around the wire (**Figure 5b**).

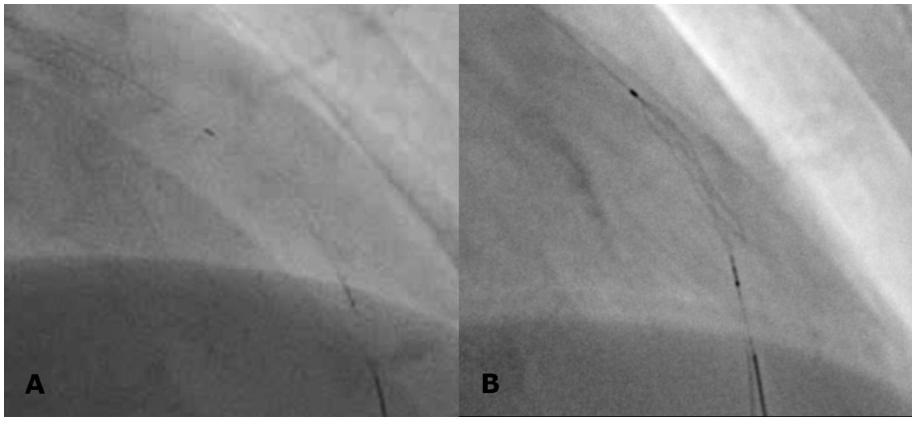
Figure 5.



Release of the distal portion of the Sparrow stent. Visualization by normal angiography (**a**) and by StentBoost (**b**). With StentBoost it is possible to see the stent still “folded” (like a candy wrapper) around the wire.

The second step was the completion of the “unwinding” of the stent from the wire by means of a gentle counterclockwise rotation of the wire itself. After this maneuver, while the normal angiogram did not show the exact deployment of the stent (**Figure 6a**), the stent was clearly visible and appeared expanded, apart from the proximal edge still unreleased, using StentBoost (**Figure 6b**). The third step was the release of the proximal portion of the stent, again by electrolysis. Once in place, post-dilation was required per protocol to ensure optimal expansion of the stent to avoid incomplete vessel wall apposition.

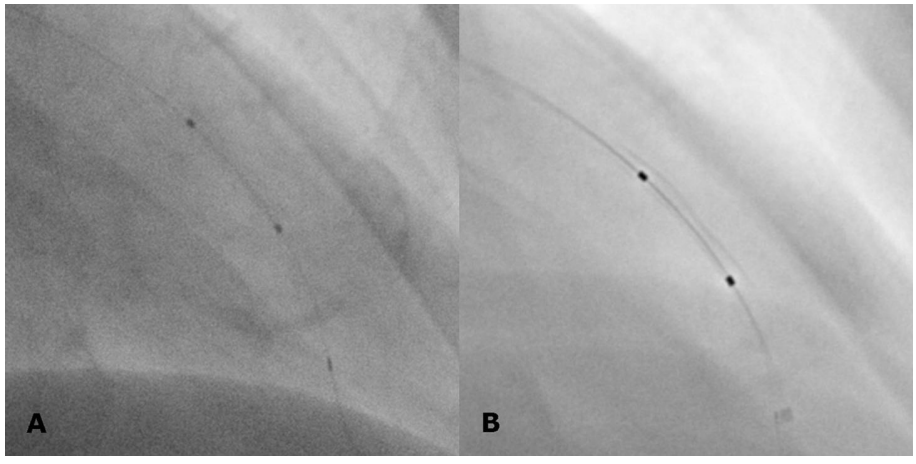
Figure 6.



"Unwinding" of the Sparrow stent from the wire by gentle counterclockwise rotation. Visualization of the result of this maneuver by normal angiography (**a**) and by StentBoost (**b**).

A non-compliant 2.75x15 mm balloon was tracked at the level of the stent. While with normal angiography the exact location of the post-dilatation balloon inside the boundaries of the stent was not completely accurate (**Figure 7a**), StentBoost simplified this process, as the stent was more clearly visible (**Figure 7b**).

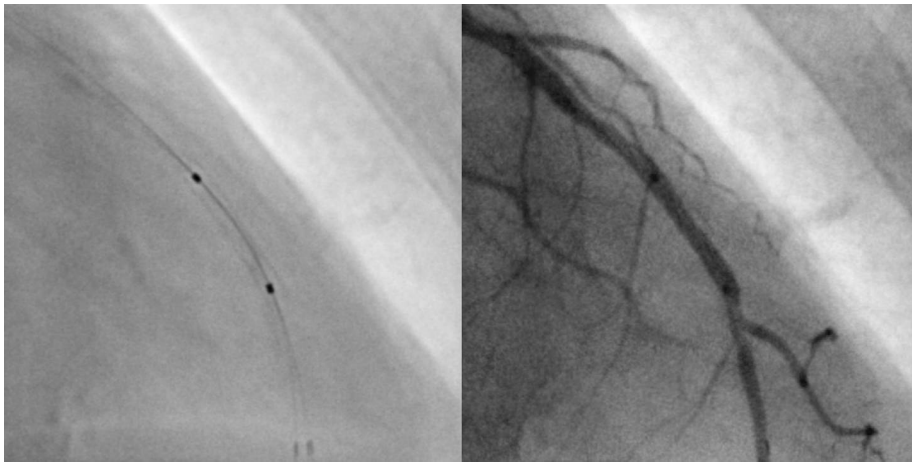
Figure 7.



Positioning of the non-compliant 2.75x15 balloon inside the boundaries of the Sparrow stent. Visualization by normal angiography (**a**) and by StentBoost (**b**). With StentBoost a slight under-expansion of the Sparrow stent in its mid-portion is clearly visible.

StentBoost also allowed the visualization of a region of under-expansion of the stent in the mid-portion. An additional StentBoost image after post-dilatation showed that the stent was well expanded (**Figure 8**).

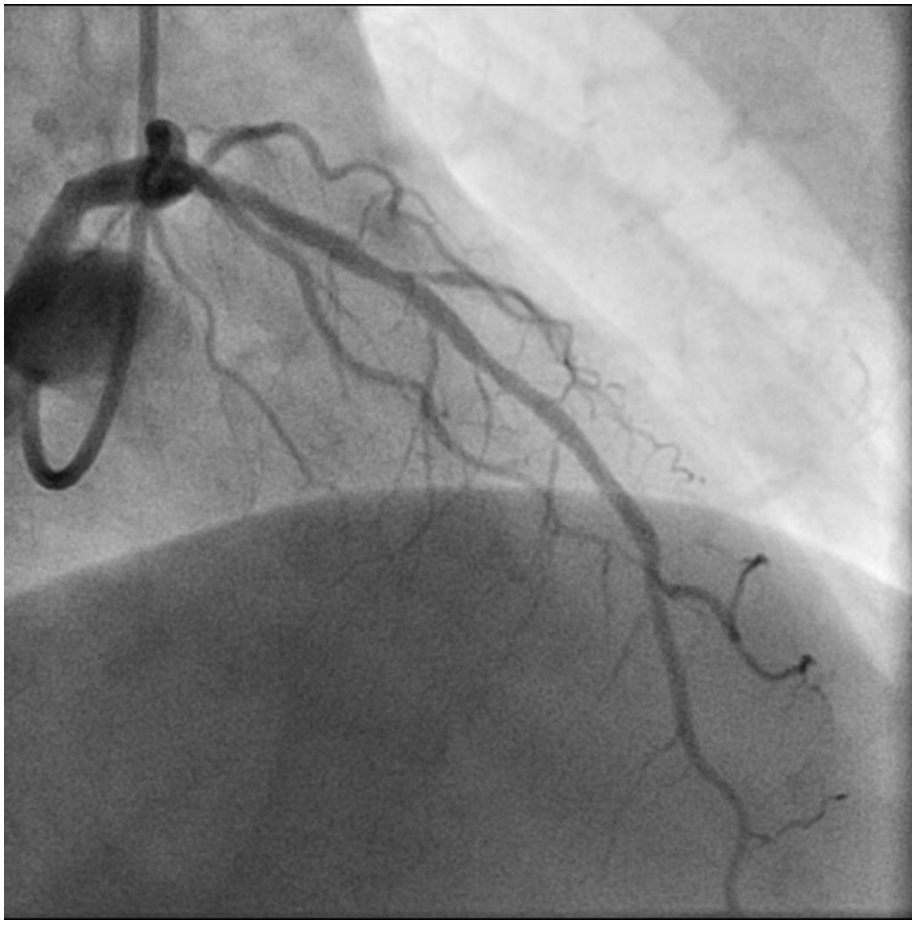
Figure 8.



StentBoost image of the stent and of the vessel after post-dilatation with a 2.75x15 non-compliant balloon.

The final angiogram showed an optimal result (**Figure 9**), confirmed also by intravascular ultrasound. The patient did not suffer any major adverse cardiovascular event during the hospitalization and she was discharged the day after. At one month, she was in good condition and free of angina.

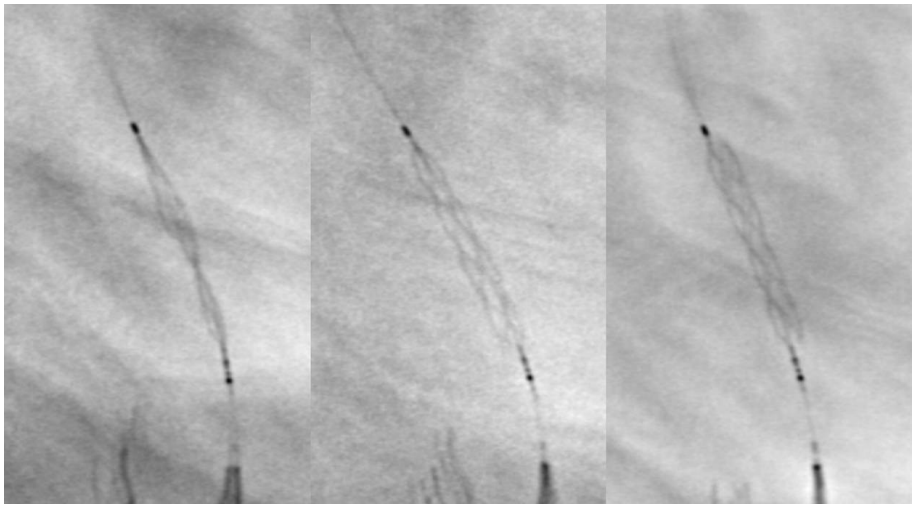
Figure 9.



Final angiographic result.

The progress in the development of new devices tailored for specific anatomies, as this novel stent particularly designed for small vessels with potentially improved crossing profile, flexibility and trackability, can lead to improved results, even more if paralleled by the concurrent progress in imaging techniques, as the angiography-based StentBoost (**Figure 10**). In the current case, the integration of the two technologies allowed a clear understanding of the behavior of the device itself during deployment and consequently to the optimization of the treatment.

Figure 10.



Another example, in another patient enrolled in the CARE II study, of the StentBoost-guided three-step release of the Sparrow stent in a coronary artery.

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D

Discussion

Discussion

Percutaneous coronary interventions are widely recognized techniques to treat coronary artery disease. Indeed these procedures are among the most commonly performed in the hospitals of the western world, reflecting the fact that the disease is the most common in these countries.

However, despite the fast progress in the development of materials and techniques used, several limitations affect the acute and long-term performance of these procedures. In particular, there are three mayor drawbacks: restenosis, thrombosis and technical feasibility to perform the procedure.

Restenosis has been recognized immediately as the major limitation of balloon only angioplasty. A reduction in its frequency was achieved by placing metallic stents in the coronary artery to be treated. However, also stents showed a still significant rate of restenosis. Moreover, thrombosis of the stent rose as another ominous, albeit uncommon, complication.

Simultaneously, technical improvements in the quality of the materials to perform percutaneous coronary interventions allowed a progressive miniaturization and increased performance of all the devices used, from the catheters to the wires, from the balloons to the stents. This led to the possibility for interventional cardiologists to challenge always more complex coronary anatomies, such as tortuous vessels, calcifications, bifurcation lesions, diffusely diseased vessels.

The recent introduction of drug-eluting stents has been a major step forward in further reducing restenosis. The first randomized trials versus bare metal stents, performed in relatively selected patients and lesions showed a dramatic reduction in restenosis rate with extremely low rates in the drug-eluting stent group. However, a potential issue related to the possibly increased incidence of stent thrombosis with these new devices appeared.

Our thesis had two major aims: 1) to assess the values and drawbacks of first-generation drug-eluting stents when used in patients and lesions not included in the aforementioned pivotal trials, and 2) to assess new drug-eluting stents and drug-eluting stents specifically dedicated for selected anatomies.

To achieve these aims, we performed several clinical studies with different design, ranging from retrospective single center single-arm drug-eluting stent registries, to prospective multicenter single-arm drug-eluting stent registries with independent data monitoring and event adjudication, from retrospective single center non randomized contemporary comparisons of different drug-eluting stents, to single center or multicenter randomized clinical trials comparing bare metal and drug-eluting stents or different drug-eluting stents, from case reports to meta-analyses.

Concerning the first aim, we showed in different subsets of patients and lesions that first-generation drug eluting stents achieve good results also in off-label indications, such as in left main coronary artery disease, in saphenous vein graft disease, and in real-life daily practice unselected patients. However, restenosis appeared still to be an issue specifically in the treatment of distal left main disease involving the bifurcation between the left anterior descendens and the circumflex artery, but also in diabetic patients, and in patients in whom multiple lesions or long stents were placed. Moreover, in the treatment of saphenous vein graft disease, we showed an alarming increase in mortality at long term follow up with drug-eluting stents as compared to bare metal stents and this finding seemed mainly driven by potential thrombotic events occurring after placement of these new devices. We specifically undertook a meta-analysis of all studies (including randomized trials and historical or contemporary registries) comparing bare metal to drug-eluting stents in order to observe if our findings could be confirmed or confuted by the other studies. We concluded that the trend we observed in our study was not confirmed when pooling all studies together, however due to the poor design of the majority of the studies included in our meta-analysis, our conclusions could be only seen as a drive to perform new larger randomized trials in saphenous vein graft disease to achieve a final answer about the safety and efficacy of drug-eluting stents in this setting.

The studies we performed allowed us to use the databases to assess also the possible drawbacks and advantages of several angiographic continuous endpoints, such as late lumen loss, commonly used in randomized clinical trials as surrogate for clinical binary events. According to our analyses, these endpoints in the drug-eluting stent era appear inadequate to assess superiority of one device over another. Indeed, we showed that while two different first-generation drug-eluting stents performed

similarly from the clinical point of view in a cohort of "real-life" all comers, significant differences were noted in the amount of late loss between the two stents.

Concerning our second aim, we focused specifically on new potentially promising drug-eluting stents and on stents designed for selected anatomies. As we showed in the first part of the thesis that first-generation drug eluting stents were not free from complications, the search for new drugs and new stent designs appeared crucial in order to improve outcomes of patients treated with percutaneous coronary interventions.

We focused our research first on a new anti-restenotic drug, pimecrolimus, that provided promising results in further reducing restenosis in animal models. We tested by means of a properly designed randomized controlled multicenter international trial a new drug loaded onto a stent (pimecrolimus) with peculiar anti-inflammatory properties, different form the cytostatic properties of the drugs used in the first-generation drug eluting stents (sirolimus and paclitaxel). The trial had a 3-arm configuration, comparing the same stent design (a novel reservoir-based platform) with different drugs loaded onto it: one arm was the already commercialized paclitaxel-eluting stent, the second arm was the pimecrolimus-eluting stent, and the third arm was a stent loaded with a combination of the two drugs. The trial turned out to be negative for the new drug (challenging also the concept that in humans an inflammatory response to the stent plays a major role in the restenotic process), thus pimecrolimus failed to fulfill in humans its preclinical promises as anti-restenotic drug. However, a major step forward of this trial was that it showed the feasibility of loading simultaneously two different drugs on the same stent. This has the potential to open the way for further developments, showing that it is possible to target different biochemical pathways by different drugs on the same stent.

Concerning the development of new stents designed for selected anatomies, we focused on two novel self-expanding drug-eluting nitinol stents, one eluting biolimus and designed for bifurcation lesions, the other eluting sirolimus, designed for small vessels and directly loaded into a 0.014 inches coronary guidewire. The first stent showed, in a multicenter international prospective registry, to be highly deployable and provided very interesting results with angiographic and clinical restenosis rates below 10%. This result is extremely promising as for the first time a one-digit

restenosis rate has been reached with a drug-eluting stent in bifurcation lesions up to now. Moreover, it opens the way for future randomized trials to further confirm and expand the outcomes achieved.

We then described the case of a patient with a lesion in a small vessel, successfully treated with the stent directly loaded into the coronary guidewire. This stent with its extremely low-profile (the same as a routine coronary wire) has the potential to become a major step forward in tackling complex anatomies with extremely tortuous vessels and lesions located in the distal vasculature, where other "traditional" stents would not be able to be tracked. However, clinical data are still missing to confirm it, therefore new studies have been initiated.

To summarize our findings and to project them into the short-term future, this thesis proves that important steps have been made in percutaneous coronary interventions in the last years. The introduction of drug-eluting stents has been a major step forward in this direction, with remarkable benefits in terms of restenosis reduction as compared to bare metal stents. Although some concerns recently arose about their long-term safety, the last data appear to confute these fears. A major issue related to drug eluting stent was to move from the "clinical trials" world to the daily "real life" arena. The fist part of thesis attempts to answer this issue, showing the feasibility and reasonable results of first-generation drug-eluting stents in unselected patients and off-label indications. However, as these devices do not eliminate all the "classical" stent related complications (restenosis, thrombosis and technical feasibility of the procedure), there is definitely room for improvement. Several new drug-eluting stents have recently entered the market and randomized trials are currently underway to show superior efficacy and/or safety profile versus first-generation drug-eluting stents. Some of these second-generation stents appear indeed to outperform the old ones (like everolimus-eluting stents or biolimus-eluting stents), but some others have failed to show additional benefits (like zotarolimus-eluting stents or reservoir-based paclitaxel-eluting stents). As randomized clinical trials and properly designed prospective registries have become pivotal in the decision making process to select the optimal stent in order to obtain evidence-based responses to our clinical problems, we added our work that is presented in the second part of the thesis.

On one hand, we showed the feasibility of loading two different drugs on the same stent. In the near future, new stents loaded simultaneously with more than one drug, such as novel antithrombotic drugs to reduce the thrombosis risk and novel anti-restenotic drugs to control the neointimal response, appear realistic new solutions to minimize all the stent related complications.

On the other hand, we also showed that new stents have been and are being developed, with specific structural characteristics in order to adapt to specific anatomical situations. In particular, we focused on two self-expanding drug eluting nitinol stents, one for bifurcation lesions one for small vessels and extremely tortuous anatomy. Self-expanding stents were already introduced in the early phase of stent evolution, but their results were worse that those of balloon expandable stents. The addition of drugs loaded on these stents allowed a return of these stents in the clinical field, with the potential for more tailored adaptation of the stent itself to the anatomy to be treated. For example, the bifurcation stent we tested in a large prospective controlled international single-arm registry allows for an anatomically adequate reconstruction of the coronary anatomy at the level of the bifurcation without distortion of the stent struts, finding that often happens with non-dedicated stents and routine techniques (such as provisional T-stenting, V-stenting, culotte stenting, crush stenting). Of interest, several dedicated bifurcation stents have been recently developed and are under clinical evaluation, however the bifurcation stent we tested is definitely the one with most clinical data and, seen the promising results of our registry, randomized trials comparing this stents with common stents and techniques in bifurcation lesions are currently in the pipeline. Also the other self-expanding stent we present has the potential to be a major step forward in the evolution of the technology applied to drug-eluting stents. As this stent is loaded directly into a coronary guidewire, the total profile of the device reaches extremely low values, never achieved before. Once the efficacy of this device is proven, its use will definitely expand the indications for percutaneous treatment of lesions that up to now were considered impossible to treat because of their location, such as extremely tortuous or very distal vessels, where conventional stent could not be tracked. Moreover, its self-expanding design and extremely low-strut thickness (the lowest among the stents nowadays available) make this stent extremely flexible and

easily adaptable to the complex tortuous anatomy to be treated. This guidewire-loaded stent helps in avoiding major vessel deformation and distortion, a problem that commonly happens when conventional stents are used. This benefit of the guidewire-loaded stent, based on the adaptability of the self-expanding stent to the original coronary anatomy, applies also to the previously discussed bifurcation stent. This advantage will play a central role in the future to optimize the results of percutaneous interventions.

To conclude, further improvements in stent technology rely on the good combination of adequate engineering work to ameliorate the design of the devices, accurate pharmacological work to find more powerful and safer drugs and polymers, proper preclinical work to test these new devices in animals, and mainly, appropriate clinical work with adequately designed randomized trials to confirm in humans the superiority of these devices to the ones currently available.

S

Summary / Samenvatting

Summary

As detailed in the **introduction**, in this thesis we focused specifically on two parts. The **first part** (from **chapter 1** to **chapter 9**) addressed the expansion of the use of "first-generation" drug-eluting stents (DES) in settings considered off-label according to the instructions for use of these devices (with specific focus on left main coronary artery, saphenous vein grafts and complex "real-life" anatomies). The **second part** (from **chapter 10** to **chapter 12**) investigated the introduction of new stents eluting drugs different from the ones in "first-generation" DES (with focus on the drug pimecrolimus), and the introduction of DES with mechanical characteristics specifically designed for selected anatomies, such as bifurcations and small vessels.

In **chapter 1**, we focused on the percutaneous treatment of left main coronary artery disease. We assessed the short- and mid-term clinical impact of intra-vascular ultrasound guidance in 58 patients, referred for elective percutaneous treatment of unprotected left main coronary artery disease with DES. The use of intravascular ultrasound, employed in 41% of the procedures, was not associated to additional clinical benefit with respect to angiography-assisted stent deployment. However, a major prognostically negative determinant of mid-term major adverse events was the involvement of the left main bifurcation in the percutaneous treatment.

From **chapter 2** to **chapter 5** we focused on the percutaneous treatment of saphenous vein graft disease. In **chapter 2**, we presented the 6-month data of the randomized RRISC trial, a comparison of sirolimus eluting stents (SES) versus bare metal stents (BMS) in patients with diseased saphenous vein grafts (SVG). Overall, 38 patients received 60 SES for 47 lesions, while 37 patients received 54 BMS for 49 lesions. SES was proven to significantly reduce in-stent late loss (primary end point of the study) versus BMS at 6-month follow up. This was associated with a reduction in binary in-stent and in-segment restenosis rate and repeated target lesion and vessel revascularization procedures, without differences in death and myocardial infarction.

In **chapter 3**, we presented the intravascular ultrasound (IVUS) data of the RRISC trial presented in chapter 2. Intravascular ultrasound was performed during 6-month follow-up angiography. We compared the vascular effects of the SES and BMS in SVG. Sirolimus-eluting stent effectively inhibited the neointimal hyperplasia reaction vs.

BMS in diseased vein grafts, without evidence of increased incomplete apposition risk. Minimal incomplete stent apposition was detected only at 3 stent edges (2 BMS, 1 SES) next to ectatic regions of the SVG. However, the neointimal response to overlapping SES layers seemed higher than to a single SES layer. Overlapping SES showed significant increase of the neointimal reaction, and this phenomenon was mainly localized in overlapping SES segments.

In **chapter 4**, we presented the long-term follow-up of the RRISC trial. All the 75 patients randomized to SES versus BMS underwent follow-up up to 3 years. At a median time of 32 months, 29% deaths occurred after SES versus 0%after BMS ($p<0.001$). Moreover the aforementioned difference in the rate of target vessel revascularization, shown at 6 months, was no more statistically significant at longer-term follow up. In this secondary post-hoc analysis, BMS were associated with lower long-term mortality than SES for SVG disease, also without a clear maintenance of the benefits in terms of revascularization procedures.

In **chapter 5**, our aim was to assess, by means of meta-analytic approach, the risk/benefit profile of DES versus BMS in the treatment of SVG disease. Three randomised controlled trials and 15 registry studies were appraised, totaling 3294 patients. At a mean follow up of 19.8 months, no significant differences were found in the risk of death and myocardial infarction. Drug-eluting stents showed superiority in terms of target vessel revascularization. However, according to pre-specified subgroup analyses, this effect seemed less evident at longer-term follow up. In this meta-analysis the use DES in SVG did not seem to be associated to an increased risk of mortality.

In **chapters 6** and **7** we focused on “daily-life” all-comer patients. In **chapter 6**, we evaluated the performance of paclitaxel-eluting stents (PES) in real-world patients at higher risk for major adverse cardiovascular events or restenosis. We conducted a multicenter registry enrolling 1065 very high-risk subjects treated with PES. The inclusion criteria for high-risk definition were: unprotected left main, true bifurcation, chronic total occlusion, long lesion (lesion length >28 mm), small vessel (reference vessel diameter <2.75 mm), or the presence of diabetes mellitus. We found an 18.6% rate of MACE at 7 months, with definite stent thrombosis occurring in only 0.8% of the patients up to 12 months. This work confirmed the satisfactory performance of

PES, especially given the overall profile of enrolled subjects and the limited number of stent thromboses.

In **chapter 7**, we compared the clinical efficacy of PES and SES in a contemporary cohort of complex patients. We collected data on mid-term outcomes in 529 patients (281 in the PES group and 248 in the SES group) treated with drug eluting stents in de-novo lesions. The end-point was major adverse cardiac events defined as a composite of death, myocardial infarction and target vessel revascularization, including target lesion revascularization. At a median follow-up of 10.6 months, the major adverse cardiac events rate was similar between the 2 groups, without any difference in the occurrence of death or myocardial infarction. Diabetes and total stent length were independent predictors of major adverse cardiac events. Propensity analysis confirmed the similarity between the two devices. The majority of restenosis was focal and only two patients required surgical revascularization. Implantation of DES in complex lesions was associated with favorable results and most of the patients remained free from surgical revascularization at follow-up. Overall both the available stent platforms had similar performance characteristics.

In **chapters 8** and **9**, using the databases of some of the previously reported studies, we focused our attention on the methodological significance of specific angiographic parameters, such as late luminal loss. Late luminal loss is defined as the difference between post-procedural minimal luminal diameter (MLD) and follow up MLD and its unit of measure is millimeters. In particular, we investigated its potential values and drawbacks when used as end point for randomized comparisons of DES trials.

In **chapter 8**, using the database of the study presented in chapter 7, we sought to analyze the pattern of late loss distribution in SES and PES. From the cohort of 529 patients treated with DES, we selected all patients who underwent angiographic follow-up: 359 patients with 592 de-novo lesions received either SES (286 lesions) or PES (306 lesions). Late loss and binary angiographic restenosis were analyzed. Binary restenosis occurred in 56 lesions (19.6%) treated with SES, compared to 53 (17.3%) treated with PES. Both late loss distributions were skewed to the right and were not normally distributed. Late loss was significantly lower in SES group. Analyzing only restenotic lesions, late loss had a normal distribution in SES and PES and was similar in the two groups. Evaluating non-restenotic lesions, late loss was also normally

distributed in both groups, but it was significantly lower after SES implantation compared to PES. In conclusion, both SES and PES showed a bimodal pattern of late loss distribution. The observed difference in late loss between SES and PES seemed to be partially explained by the reduction in late loss after SES in non-restenotic lesions (where SES approaches "zero-late-loss"). Thus, late loss appeared not to be a reliable marker of the true efficacy of these devices, due to its complex and non-gaussian distribution.

In **chapter 9**, using quantitative coronary angiography (QCA) and IVUS data from the RRISC trial (presented in chapters 2 and 3), we analyzed the "relocation phenomenon" of QCA-based in-stent MLD between post-procedure and follow-up and we correlated QCA-based and IVUS-based restenotic parameters in stented SVG. We expected the presence of MLD relocation for low late loss values, as MLD can "migrate" along the stent if minimal re-narrowing occurs, while we anticipated follow-up MLD to be located close to post-procedural MLD position for higher late loss. QCA-based MLD relocation occurred frequently and, conversely to our expectations, MLD relocation failed to correlate with in-stent late loss. Follow-up QCA-based and IVUS-based MLD values well correlated in the overall population, but QCA underestimated MLD on average 0.55±0.49 mm, and this was mainly evident for lower MLD values. Conversely, the location of QCA-based MLD failed to correlate with the location of IVUS-based MLD. Overall, the ability of late loss to "predict" IVUS parameters of restenosis (maximum neointimal hyperplasia diameter, neointimal hyperplasia index and maximum neointimal hyperplasia area) was moderate. These findings suggested the need for a critical re-evaluation of angiographic parameters such as late loss as endpoints for DES trials and the use of more precise techniques to describe accurately and properly the restenotic process.

In **chapter 10**, we presented the results of the randomized, international multi-center GENESIS trial, a comparison of newly designed reservoir-based stent platforms eluting paclitaxel (CoStar) versus pimecrolimus (Corio) versus both drugs simultaneously (SymBio) in single native coronary lesions. Overall 49 patients received CoStar, 97 SymBio and 100 Corio. Late loss (the primary end point of the study) was significantly and progressively reduced with CoStar versus SymBio versus Corio. Six-month restenosis and major adverse cardiac events were also progressively lower with

CoStar versus SymBio versus Corio. Thus, stents eluting pimecrolimus or the dual combination of pimecrolimus and paclitaxel failed to show angiographic and clinical benefits versus paclitaxel-eluting stents.

In **chapter 11**, we presented the results of the prospective, single-arm multinational DIVERGE trial, designed to assess safety and performance of a new self-expanding biolimus-eluting nitinol stent, specifically designed for bifurcation lesions, the AXXESS stent. The trial enrolled 302 patients with complex de novo bifurcation lesions. The primary endpoint of cumulative major adverse cardiac events (a composite of death, myocardial infarction and target lesion revascularization) at 9 months was 7.7%. In an angiographic cohort of 150 patients, the overall in-bifurcation restenosis rate at 9 months was 6.4%, with a very low average late loss both in the parent vessel and in the side branch. These results confirmed the safety and performance of the AXXESS stent in complex bifurcation lesions.

In **chapter 12**, we described the case of a 56 year-old woman who underwent percutaneous coronary intervention for a lesion in a small mid-left anterior descending coronary artery (reference vessel diameter by QCA: 2.11 mm) with a novel DES specifically designed for small vessels, the Sparrow stent. This is a self-expanding sirolimus-eluting nitinol stent directly mounted into a 0.014-inch coronary guidewire, with very thin strut thickness (67 micron). We described in details all the technical steps needed for an appropriate release and deployment of the aforementioned stent. All these steps were also facilitated and clarified by “StentBoost”, a specific X-ray-based stent-enhancing visualization technique.

Finally, in the **discussion**, the most important findings of the different studies presented in the various chapters have been discussed and put in perspective.

Samenvatting

Zoals besproken in de introductie**,** is het onderzoek in dit proefschrift gericht op twee delen; ten eerste is aandacht besteed aan de expansie van het oneigenlijk gebruik van de eerste generatie drug-eluting stents (DES), in met name hoofdstam, veneuze bypass grafts en complexe coronaire leasies.(**Hoofdstuk 1 t/m 9**). Ten tweede wordt de introductie van een nieuwe generatie DES beschreven (met focus op de pimecrolimus eluting stent) en de ontwikkeling van nieuwe DES met specifieke mechanische eigenschappen aangepast aan de anatomie zoals bifurcaties en kleine vaten (**Hoofdstuk 10 t/m 12**).

In **hoofdstuk 1**, is de percutane behandeling van hoofdstam afwijkingen besproken. Korte en middellange termijnresultaten van de klinische impact naar het gebruik van intravasculaire echogeleide PCI bij 58 patiënten met onbeschermde hoofdstam letsels, behandeld met een DES. Het gebruik van IVUS, in 41% van de procedures, bleek geen klinische meerwaarde te hebben dan stentplaatsing alleen op geleide van fluoroscopie. Wel blijkt de noodzaak tot behandeling van een bifurcatie stenose in de hoofdstam een belangrijke negatieve voorspeller voor klinische uitkomsten op middellange termijn.

In **hoofdstuk 2 tot en met 5** is aandacht besteed aan de percutane behandeling van veneuze bypass grafts. In **hoofdstuk 2**, worden 6 maands data van de RRISC trial beschreven, waarbij wordt vergeleken tussen sirolimus eluting stents (SES) versus bare metal stents (BMS) in patiënten met afwijkingen in veneuze bypass grafts (SVG). Overall, werden 38 patiënten behandeld met 60 SES voor 47 laesies, terwijl 37 patiënten werden behandeld met 54 BMS voor 49 laesies. SES bleek het het optreden van in-stent late loss (primair eindpunt van de studie) versus BMS bij 6-maands follow-up belangrijk te reduceren. Daarnaast was er een reductie in optreden van binary in-stent en in-segment restenosis ratio en opnieuw noodzakelijke target lesion en vessel revascularisatie-procedures, zonder verschil in optreden van dood en myocard infarcten.

In **hoofdstuk 3**, worden de resultaten van de intravasculaire echo (IVUS) data van de RRISC trial gepresenteerd. Intravasculaire echo werd gedaan tijdens de 6-maands follow-up angiografie. Sirolimus-eluting stents bleken vs. BMS zeer effectief de

neointima hyperplasie te verminderen in SVG, zonder aanwijzingen voor verhoogd risico op malappositie. Minimale stent malappositie werd slechts gevonden in 3 stent edges (2 BMS, 1 SES) naast ectatische afwijkingen in de SVG. Echter, bij overlappende SES lijkt de neointima-reactie hoger dan bij een single SES; in deze regio werd meer neointima hyperplasie gevonden bij IVUS.

In **hoofdstuk 4**, worden de lange termijnresultaten van de RRISC trial beschreven. Alle 75 patiënten gerandomiseerd naar SES versus BMS werden gedurende drie jaren gevolgd. Bij een gemiddelde follow-up van 32 maanden werd overlijden bij 29% van de patiënten behandeld met SES versus 0% na BMS ($p<0.001$) geconstateerd. Daarnaast was het eerderbeschreven verschil in revascularisatie zoals eerder beschreven bij 6 maands follow-up niet meer aanwezig bij lange termijns follow-up. In deze secundaire post-hoc analyse, blijken BMS geassocieerd met een lagere lange termijn-mortaliteit dan SES bij SVG-afwijkingen, zonder bevestiging van de voordelen van SES-gebruik op korte termijn in de zin van revascularisatie-procedures.

In **hoofdstuk 5**, wordt door middel van een meta-analyse, het voor- vs. nadeel van het gebruik van DES versus BMS in de percutane behandeling van SVG beschreven. Drie gerandomiseerde studies en 15 registry's werden geïncludeerd met een totaal van 3294 patiënten. Bij een gemiddelde follow-up van 19,8 maanden, werd geen significant verschil in optreden van dood en myocard infarct gevonden. Drug-eluting stents bleken superieur in de zin van lagere target vessel revascularisatie, hoewel dit effect bij bepaalde subgroep-analyses minder duidelijk aanwezig was bij lange termijn follow-up. In deze meta-analyse blijkt het gebruik van DES in SVG niet geassocieerd met een verhoogde kans op overlijden.

In **hoofdstukken 6** en **7** is de dagelijkse werkelijkheid beschreven. In **hoofdstuk 6**, wordt het gebruik van Paclitaxel Eluting Stents (PES) bij patiënten met een verhoogd risico op restenose of cardiovasculaire events beschreven middels een multicenter registry waarbij 1065 hoog-risico patiënten werden behandeld d.m.v. een PES. De criteria voor hoog-risico indeling waren: onbeschermde hoofdstam, ware bifurcatie stenose, chronic total occlusion, lange laesie (laesie lengte >28 mm), kleine diameter (reference diameter <2,75 mm), of de aanwezigheid van diabetes mellitus. Bij follow-up van 7 maanden wordt een MACE ratio van 18,6% en een stent trombose ratio (definite) van slechts 0,8% gevonden. Deze studie bevestigt de goede klinische

resultaten van PES met een laag percentage stent trombose, zeker gezien de risicostratificatie van de bestudeerde patiëntenpopulatie.

In **hoofdstuk 7**, worden de klinische effectiviteit van PES en SES in een hedendaagse cohort beschreven. Middellange termijndata van 529 patiënten (281 in de PES-groep en 248 in de SES-groep) behandeld met een DES voor de-novo laesies werden verzameld. Het eindpunt werd gedefinieerd als een gezamenlijk optreden van mortaliteit, hartinfarct en target vessel revascularisatie, inclusief target lesion revascularisatie. Bij een gemiddelde follow-up van 10,6 maanden, was het optreden van major adverse cardiac events gelijkwaardig tussen beide groepen, zonder verschil in optreden van dood of infarct. Diabetes en totale stentlengte waren onafhankelijke voorspellers van optreden van major adverse cardiac events. Een propensity analyse bevestigt de overeenkomsten tussen beide devices. De meerderheid van gevonden restenose was focaal en slechts twee patiënten werden behandeld d.m.v. chirurgische revascularisatie. Het gebruik van DES in complexe laesies is geassocieerd met gunstige klinische uitkomst maten. Overall werd geen significant verschil in uitkomst tussen beide devices gevonden.

In **hoofdstuk 8** en **9**, wordt –gebaseerd op de database van enkele voorheen beschreven studies – het methodologische belang van enkele specifieke angiografische parameters zoals late luminal loss (LLL) beschreven. Late luminal loss wordt gedefinieerd als het verschil in minimale lumendiameter (MLD) direct na de procedure en bij angiografisch follow-up, uitgedrukt in millimeters. In het bijzonder worden de potentiële voor- en nadelen van de LLL beschreven, indien gebruikt als onderling vergelijkend naar uitkomst bij DES-trials.

In **hoofdstuk 8**, wordt op basis van de studie zoals beschreven in hoofdstuk 7, een analyse gedaan naar het voorkomen van LLL in SES en PES. Uit de totale populatie van 529 patiënten werden alle patiënten (n=359) met angiografisch follow-up geselecteerd en geëvalueerd op angiografische restenose en LLL in zowel PES- (306) als SES- (286) groep. Binary restenosis trad op in 56 laesies (19,6%) uit de PES groep en in 53 (17,3%) in de SES-groep. LLL was lager in de SES-groep, hoewel de distributie in beide groepen niet normaal verdeeld was. Indien alleen naar de regio van restenose werd gekeken was er wel sprake van een normale verdeling in beide groepen en werd geen onderling verschil tussen SES- en PES-gevonden. Bij

evaluatie van de niet restenotische regio was het voorkomen van LLL lager in de SES- dan PES-groep. In conclusie, blijken zowel SES als PES een in homogeen patroon van LLL distributie te vertonen. Het gevonden verschil in LLL tussen SES en PES wordt gedeeltelijk verklaard door het minder voorkomen van LLL in de niet-restenotische gebieden van de stents ten gunste van SES. Dus LLL lijkt hiermee geen betrouwbare maat voor klinische effectiviteit van deze devices door een inhomogene verdeling.

In **hoofdstuk 9**, worden op basis van quantitative coronary angiography (QCA) en IVUS-data uit de RRISC trial (beschreven in hoofdstuk 2 en 3), het "relocation phenomenon" van op QCA-gebaseerde in-stent MLD tussen post-procedureel en follow-up beschreven. Bovendien wordt een correlatie tussen QCA en IVUS gebaseerde restenose parameters in SVG geanalyseerd. QCA-gebaseerde MLD relocation kwam vaak voor zonder dat er een correlatie werd gevonden met in-stent LLL. Bij follow-up kwamen QCA- en IVUS-waarden in de overall populatie goed overeen, echter gemiddeld onderschatte QCA de MLD met 0,55±0,49 mm bij met name lagere MLD-waarden. Andersom werd geen correlatie gevonden tussen QCA-MLD en de gevonden MLD-waarde met IVUS. Overall, bleek de voorspellende waarde van LLL naar het voorkomen van IVUS parameters van restenose (maximum neointima hyperplasia diameter, neointima hyperplasia index and maximum neointima hyperplasia oppervlak) matig. Deze uitkomsten suggereren een kritische houding ten aanzien van angiografische parameters zoals LLL als uitkomst maat voor DES-studies.

In **hoofdstuk 10**, worden de resultaten van de gerandomiseerde internationale multi-center GENESIS studie gepresenteerd. Het betreft een vergelijk naar nieuwe stent-designs met drug eluting reservoirs waarbij Pacitaxel (CoStar, n=49) versus Picrolimus (Corio, n=97) versus beide drugs samen (SymBio, n=100) in simpele laesies in natieve vaten werd onderzocht. Late loss (primair studie eindpunt) was significant en progressief lager in de CoStar groep versus Symbio en Corio, evenals de restenose en MACE bij follow-up. In conclusie bleken de picrolimus en combinatie paclitaxel/picrolimus eluting stents minder effectief dan de paclitaxel eluting stent tijdens angiografische follow-up en klinische resultaten.

In **hoofdstuk 11**, worden de resultaten van de DIVERGE-trial gepresenteerd. Een prospectieve internationale single arm studie, opgezet om de veiligheid en toepasbaarheid van een nieuwe self-expanding biolimus-eluting nitinol stent (AXXESS) voor bifurcatie laesies te onderzoeken. In totaal werden 302 patiënten met de novo bifurcatie laesies geïncludeerd. Het primaire eindpunt van cumulatieve MACE (overlijden, myocard infarct en TLR) 7,7% bij 9 maands follow-up. Bij een subanalyse van 150 patiënten met angiografische follow-up was de overall restenose ratio 6,4 % met een lage gemiddelde waarde voor LLL in zowel hoofd- als zijtak. Deze resultaten bevestigen de veiligheid en effectiviteit van de AXXESS-stent in complexe bifurcatie letsels.

In **hoofdstuk 12**, wordt een casus beschreven van een 56-jarige vrouw met een stenose in een klein diametervat (QCA 2.11mm) behandeld met een nieuwe DES, specifiek ontworpen voor kleine vaten; de Sparrow-stent. Het betreft een self-expanding sirolimus-eluting nitinol stent gemonteerd op een 0,014-inch coronaire guidewire, met dunne stent struts (67 micron). In detail worden alle technische handelingen en plaatsingsdetails besproken, waarbij eveneens gebruik wordt gemaakt van “StentBoost” voor optimale visualisatie van het device.

Ten slotte worden in de **discussie**, alle voorgaande conclusies nog eens besproken en in perspectief geplaatst.

A

Acknowledgments

Acknowledgments

First of all, please let me thank all the members of the commission, my promotor and my co-promotor, to dedicate their precious time to review my work and to attend the day of the discussion. Dear Prof. Bots, Prof. Colombo, Prof. Moll, Prof. Van Belle, Prof. Van Herwerden, Prof. Grobbee, Prof. Pasterkamp, Prof. Sangiorgi, Dr. Verheye, Prof. Doevendans and Dr. Stella it is a great pleasure and honor for me to divide this very important day with all of you. I am really looking forward for further short- and long-term collaborations with all of you.

This thesis was possible only thanks to all the friends, colleagues and teachers I met on my way till here… So I would like to thank them all simply by following a chronological way, as this is probably the best way for me to avoid missing someone… Moreover, this thesis is a collection of papers and studies performed in different institutions around Europe (in The Netherlands, Italy and Belgium), and it represent a kind of "summa" of all my activities in the last 5 years since I got my degree of cardiologist…

I would like to start from my 6-year university time, in Milan… Giuseppe Biondi-Zoccai, one of my two paranimphs. We studied at the university together, we "fell in love" with cardiology almost together (I was the first but you followed me soon…), we studied cardiology in different cities in Italy, but our continuous contacts led us to join our forces to work together on several projects… And Metcardio began… Beppe, I just want to thank you for all what you gave me in terms of friendship, knowledge, support, suggestions, teaching… And I am sure this is only the beginning of our adventure in the field of interventional cardiology!
Again in Milan, during my clinical rounds as medical student in S. Raffaele Hospital, the "temple of medicine"… Prof. Sergio Chierchia and Alessandra Mailhac, thanks to you I began to love cardiology, firstly in its clinical aspects, I have to admit! And thanks to the thesis for my medical degree, performed under your supervision, I also began to love research and statistics!

Then the 4-year period of Verona arrived, where I was resident in cardiology… Prof. Piero Zardini and later Prof. Corrado Vassanelli, then my first interventional cardiology teachers: Maurizio Anselmi Giorgio Morando and Marco Turri (vi devo così tanto! Grazie per la fiducia e l'amicizia che mi avete dato! E grazie per avermi fatto capire che la mia strada all'interno della cardiologia era solo e soltanto l'interventistica! E ancora grazie per avermi insegnato le basi di questa stupenda disciplina, porto ancora con me oggi molti dei vostri insegnamenti!), all my fantastic mates during our years of residency: Chiara, Luisa, Mara (un grandissimo e speciale bacio a te… tu sai perchè!), Sabrina, Silvia, Davide, Gabriele, Max, Paolo; and all the nurses and technicians in the cath lab, where I started my "career" as invasive cardiologist (I could not define myself interventionalists at that period, as I was "only" performing diagnostic angiograms): Gilda, Grazia, Mari, Monica, Nazi, Albertino, Aleardo, Dario, Enrico, Ermanno, Michelangelo, Paolo… great team, great fun!

In 2004 I moved for 4 months to the Thoraxcenter in Rotterdam… a relatively short period of time but a major step in my growth, mainly thanks to all the wonderful people I met there. Prof. Patrick Serruys, considered the most influential man in interventional cardiology in the last 20 years, what could I say more?? Then all the other fellows, the "real" Thoraxcenter fellows, those spending a couple of years in Rotterdam and not only 4 months like me… Marco Valgimigli (Marchino, quanta strada hai fatto da allora, chapeau! E spero presto si possa iniziare a lavorar insieme seriamente!), Gaston Rodriguez-Granillo (great times in Argentina with you! Looking forward for another "meeting" there!) and Hector Garcia-Garcia (still in Rotterdam… how could you manage for so long? Joking he!), you all accepted me as "first class" fellow there and not only as someone who quickly passed by… thank you all for that!

Back to Italy, again in Milan, this time in Centro Cuore Columbus, with the world-known Prof. Antonio Colombo… I am really delighted you are part of the commission today and I am also honored to be considered one of your fellows. Despite I remained in your institution only for 6 months, that period was very productive for me and allowed me to grow a lot! In the same place I also met Max Sangiorgi, one of the major determinants of my future career, although I did not know it yet… Max,

thanks for being here today, and thanks for being always so honest, open and clear! Last but not least, John Cosgrave, first of all a very good friend and secondly a great physician and researcher; John, I am glad you started liking statistics following my (and Beppe's) suggestions… I think we wrote great manuscripts in that period! And our trip to South Africa was also great!

In March 2005, Max proposed me to move for a couple of years to Antwerp, where he knew a group of guys willing to teach me "real-life" interventional cardiology (indeed, that is what I was mainly missing till that point: the clinical experience in the cath lab!)… Nobody knew at that moment that this would have probably been the most important choice in my life up to now…
Well, in May 2005 I went to Antwerp and started working with these guys in the Middelheim hospital and this is a decision I am sure I will never regret in my life. There I had the opportunity to learn how to perform (and sometimes how not to perform!) percutaneous coronary interventions, and I could exploit my small statistical knowledge to publish several nice papers and to grow in my scientific knowledge, but most of all I met a fantastic group of people! Frank Van den Branden, the head of the department, one of the most amazing bosses I met in my life, balanced, open, honest, clear, what should I add more? Glenn Van Langenhove, my other paranimph and the first one to believe in my potentials as interventional cardiologist (actually the first one who let me work routinely in the cath lab alone… I still remember august 2005, I was in Antwerp for a couple of months –so almost without experience– and we were the two of us to cover the two cath labs during the summer as everybody else was gone for holiday… I was forced to do PCIs as you were busy in the other cath lab and nobody else could help me! And you pushed me to go for it! Let's skip the "disasters" I made…); Glenn, I will be in debt with you for life! Stefan Verheye, member of the commission and my guide in the world of science applied to interventional cardiology and my instructor in how to manage public relations with the industries; Stefan, I learned so much from you and every time I ask you something you always give me the right suggestion, looking forward for new collaborations soon! Paul Vermeersch, the workhorse of the cath lab, the man of 7-800 PCI per year; Paul, how many did you let me do in my period in Antwerp?! And

working with you together at the catheterization table was so much fun all the times! Good luck with your PhD (when are you going to get it, finally?)! Paul Van den Heuvel, the first one I met, my first contact with Middelheim, I still have your email where you were explaining me what I could expect to do and to learn if I would have joined your group… actually I think you allowed me to realize at least two times what you were "promising" me in that email! Carl Convens and Dirk Stockman, albeit I worked a bit less with you, it was always nice to talk to you, share ideas and make jokes, the atmosphere was always nice!

Then there were the other fellows, the assistants and the other cardiologists coming as "guests" to perform PCIs: Nadia, Nathalie, Vanessa, Axel, Bert, Elvin, Kristoff, Oscar… it was always a great time either to work and to have fun with all of you!

A special thank goes also to all the people working in the cath lab and supporting me for my slowness and time-consuming procedures: An, Chris, Diana, Els, Françoise, Inge, Ilse, Katja, Katrin, Kristien, Linda, Martine, Micheline, Nancy, Sigrid, Sofie, Sonja, Stephanie, Wendy, Koen, Kristof, Josse, Peter; and those who left: Carine, Kim, Manola, Sandra and Jan… Another big, big thank goes also to the research department of the Middelheim hospital: Christine, Nancy and Petra, working (and also having funny chats about a lot of things, but mainly food…) with you was really, really, REALLY fantastic!

The planned 2 years of fellowship in Antwerp became almost 4 years… and I was thinking they would be more when Pieter Stella appeared… Pieter, my co-promotor… I still have your email in which you asked me if I wanted to join your interventional cardiology group in Utrecht as staff member (!!)… I could not believe that in the beginning… Staff member in the Netherlands, one of the countries with the greatest influence in interventional cardiology in the last 20 years! After a lot of thinking (the idea to leave Antwerp scared me a bit!), I decided to go for it! So we are almost at these days! Dear Pieter, I owe you so much! You believed in me almost without knowing me, you trusted my curriculum and my publications… I hope you do not regret your decision, I hope I can soon give you back all this trust and I hope we can bring Utrecht higher and higher in the sky of interventional cardiology (as Prof. Doevendans recently said: "the sky is NOT the limit!")!

In Utrecht I began in January 2009 and I had the opportunity to meet a great group of people, led by an extremely nice person, Prof. Pieter Doevendans, my promotor. Beste Pieter, thank you for your support and trust in these first months here in Utrecht. I always had the feeling you gave me a lot of "steun" and I am sure that everything "komt goed" in these future years of great development for the department of cardiology of UMCU.

A special quotation deserves all the group of interventional cardiologists of UMCU: Eric Van Belle, Siyrous Hoseyni Guyomi, and the two "Amersfoort guys", Bas Hamer and Thierry Wildbergh. This first year with all of you has been a great pleasure for me. And I am sure the future will become brighter and brighter! Eric and Siyrous, thank you for sharing with me all your thoughts about my stories related to my complex (and sometimes complicated) procedures, it has always been a fantastic opportunity for me to hear your insightful points of view and to follow your helpful teaching points! Looking forward for the new cath lab with all of you!

I would also like to thank the complete staff of the department of cardiology (Prof. Hauer, Barbara, Corinne, Bert, Folkert, Gertjan, Hans, Hendrik, Maarten-Jan, Matthias, Nicolaas, Peter, Rienk, Steven, Vincent, Giovanni, Jeroen, Yves) and cardiac surgery (Prof. Van Herwerden, Prof. Lahpor, Jolanda, Faiz, Guido, Marc, Ronald) and all the assistants in cardiology for the nice welcome they gave me when I arrived and for the very fruitful way of working together.

Last but not least, the extraordinary team in the cath lab of UMCU: Anique, Anna, Hermien, Henriette, Jettie, Manon, Margje, Marijke, Marion, Mieke, Mijke, Mirjam, the two Sandras, Selena, Silvia, Tinka, Tommy, Yvette, Willemijn, Bert, Cor, Hans, Henri, Herman, Ronald, and the "newcomers" Simone and Xavier; and the super R&D department: Ester, Jeanette, Yvonne, Han and Ellie (Ellie, you deserve an enormous thank for all the work you put in helping me for this thesis, without you I would have never been here!).

Besides my clinical work in different hospitals, I had (and still have) the great opportunity to work for a new and fast-growing Clinical Research Organization, based in Antwerp, genae associates NV, leaded by Bart and Aly Segers. Bart and Aly, it has been, and still is, a big pleasure working with you, I hope our collaboration will go

on for decades and I hope genae will grow stronger and stronger in the upcoming years! Beside this (and maybe more importantly) I would like to thank you for your real friendship and for all the help you gave me when I was in Antwerp! A big thank also to all the people, with whom I had the pleasure to work, involved in the activities of genae: Johannes, An, Anneleen (a special kiss to you!), Anouk, Deborah, Doreen, Giorgia, Maaike, Meroon, Tine, Valerie, Bavo, Bert, Dimitri, Stijn, Wouter.

I would moreover thank also all the people working for the different companies manufacturing the devices we daily use in the cath lab… thank you all for being good friends independently from the fact you "need" to sell your products (and you all know I tell this without conflicts of interests!): Barbara, Carmen, Chantal, Christina, Isabel, Isabelle, Leen, Linda, Mieke, Odette, Bart, Dirk, Frank, Karl, Kim, Ivo, Peter, Stephane…

Biotronik (Ivo) thank you very much for the financial support.

Alongside my "medicine world", I have a world of friends not linked to medicine, also if some people do not believe this… Unfortunately I could not always dedicate them all the time I wanted (and it is getting worse and worse… but to defend myself I want to say that also the distance –Utrecht-Milan– plays a little role…), but they always supported me in the good and in the bad times… I would not be here without them all!

Dani V., amico da sempre e a amico di sempre, le nostre strade si son fisicamente divise, ma il nostro legame rimane sempre, e sempre più solido.

Nico L., prima compagno di scuola poi grande amico, abbiamo diviso quasi tutto, dalle vacanze estive ai weekend di divertimento puro, fino al tuo matrimonio… che altro dire?

Claudia C., anche tu all'estero… finalmente felice con i tuoi due splendidi bimbi! E' sempre bello rincontrarti quando vado per congressi a Barça!

Marco A., insieme all'università, insieme a militare… poi io ho lasciato la psichiatria per la cardiologia (e non me ne pento!) e tutti e due abbiamo lasciato l'Italia… Viva l'Abruzzo!

Luca P., grandissimo, ricordo ancora, ai tempi del liceo e dell'università, le ore spese al telefono a raccontarsi tremila stupidate! E le vacanze a Ravenna pure!
Gianbattista C., alla fine tu ti sei sposato ed io no… incredibile!!! In bocca al lupo a Bruxelles con il tuo "guru" Pedro!
Fede M., anche tu sposato e già con un bimbo! Aspetto ancora una tua visita a Utrecht!
Luca D'E., dalla filosofia ad un'altra "cosa" che inizia e finisce con le stesse lettere, le nostre lunghe discussioni "teorizzatrici della vita" son sempre state di altissimo livello intellettuale… o sbaglio?
Luca T., dopo anni ad Oxford (ricordo ancora le lunghe telefonate quando io ero ad Anversa), adesso sei rientrato in Italia, in bocca al lupo per la tua carriera! E grazie per tutto il lavoro per la meta-analisi del capitolo 5 di questa tesi!
Andrea C., mio nuovo amico qui ad Utrecht (e non solo, viste le nostre peregrinazioni in giro per l'Europa!)… hai "salvato" la mia vita privata in terra olandese facendomi conoscere tutti i locali migliori di Utrecht! Mi raccomando, aspetta ancora un po' prima di sposarti, dobbiamo ancora finire di metter Utrecht "a ferro e fuoco" (sai a cosa mi riferisco…)!

Finally, my family… Papà, mamma, Rosy grazie per avermi sopportato in tutti questi anni e per aver sempre assecondato (magari a volte controvoglia) i miei umori e le mie decisioni. Siete eccezionali! E anche se ve lo dimostro poco, posso assicurarvi che vi voglio un bene immenso! Infine, posso solo ringraziar Dio di avermi dato una famiglia così!

CV

Curriculum vitae

List of publications

Curriculum vitae

Pierfrancesco Agostoni was born in Trescore Balneario (Bergamo, Italy) the 3rd of October 1975. After his infancy in Bergamo, he moved with his family to Novate Milanese (Milan, Italy). In Milan he obtained his high school degree at the San Carlo College in 1993. He then became Doctor in Medicine magna cum laude at the State University of Milan in 1999. After completing compulsory military service in 2000 as medical officer, he moved to Verona, Italy, where he became Cardiologist magna cum laude in the local State University, in 2004, under the supervision of Prof. Zardini. He spent periods of training in clinical research applied to Interventional Cardiology at the Thoraxcenter – Erasmus Medical Center in Rotterdam, The Netherlands in 2004, under the supervision of Prof. Serruys, and at the Centro Cuore Columbus and S. Raffaele hospitals in Milan, Italy in 2004-2005, under the supervision of Prof. Colombo. He then moved to Antwerp, Belgium where he had formal training in Interventional Cardiology at the Antwerp Cardiovascular Institute Middelheim of the Middelheim General Hospital between 2005 and 2008, under the supervision of Dr. Van den Branden. From January 2009, he joined the staff of the Department of Cardiology of the University Medical Center in Utrecht, The Netherlands, as University Medical Specialist in Cardiology, with specific clinical and scientific tasks in Interventional Cardiology.

Pierfrancesco's clinical and research interests in percutaneous interventions, together with a passion for statistics, have resulted in more than 120 publications in major peer-reviewed international journals and several lectures to national and international congresses. He is also reviewer for numerous international journals. Additionally, he has been involved as investigator in several national and international Clinical Trials.

Finally, Pierfrancesco has a strong interest in Clinical Trials planning and management and in Cinical Research Organization and Core Laboratory activities. He worked as a Senior Analyst for Quantitative Coronary Angiography and Intravascular Ultrasound for different Core Laboratories in Italy and in Belgium, and he has been part of Data Safety and Monitoring Boards and Clinical Events Committees for several international Clinical Trials.

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