The Impact of the Second Generation Everolimus-eluting Stent in Daily Clinical Practice

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Will it, then set to work briskly.
Friedrich Schiller

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The Impact of the Second Generation Everolimus-eluting Stent in Daily Clinical Practice

De impact van de tweede generatie everolimus-eluting stent in de dagelijkse klinische praktijk

Proefschrift

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Inhoud

Chapter 1

Introduction

INTRODUCTION

Clinical studies with first-generation sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) have demonstrate a dramatic reduction in restenosis rates compared with bare-metal stents (BMS)[1,2], however, reintervention rates were still high in patients with complex coronary artery disease[3], and an ongoing propensity for stent thrombosis (ST) beyond one year raised further concerns regarding safety issues with these devices[4]. Furthermore, as both of these devices were relatively high-profile stainless steel stents, they were difficult to deliver in complex anatomy, and the SES in particular was prone to a high fracture rate, contributing to late adverse events.

The everolimus-eluting stent (EES), (XIENCE V, Abbott Vascular, CA, USA; also distributed as the PROMUS stent by Boston Scientific, MA, USA) is a second-generation drug-eluting stent (DES) designed to overcome the limitations of earlier DES.

In the EES, everolimus, a rapamycin derivative, is released from a thin layer (7.8-μm) of a biocompatible fluoropolymer coated on an open-cell, thin-strut (81-μm) flexible and highly deliverable cobalt–chromium stent. The polymer is inert and non-inflammatory[5,6], and the stent is extremely resistant to fracture. Two moderate-sized trials with the EES demonstrated a significant reduction in angiographic in-stent and in-segment late lumen loss compared with the first-generation TAXUS Expres (PES, Boston Scientific), and noninferiority in major clinical end points[7,8]. These findings suggested that, if tested in larger populations, the EES might achieve superior clinical outcomes compared with the earlier predicate devices. However, given the favourable outcomes with PES, large studies would be required to elicit small differences in low frequency but important clinical end points. Toward this end, a large-scale randomized trial was performed, the SPIRIT IV[9] trial. SPIRIT IV was a prospective, multicenter trial that randomized 3690 patients throughout the USA in a 2:1 ratio to EES versus the TAXUS Express PES. The primary end point was a composite of target lesion failure (defined as cardiac death, target vessel myocardial infarction (MI) or ischemia-driven target lesion revascularization (TLR)). The trial was large enough to provide data on other secondary end points and important subgroups, particularly patients with diabetes mellitus, but excluded patients with acute coronary syndromes (ACS) and ST-segment elevation MI (STEMI), large bifurcations and other complex lesion subsets. We therefore compared the safety and efficacy of the second-generation everolimus-eluting and paclitaxel-eluting stents in unselected patients in real-life practice, in one other large, prospective and randomized trial: the COMPARE trial[10].

Chapter 2 describes the design as well as the one and two year results of the COMPARE trial. As there was a paucity of data evaluating the performance of EES in the high risk population of patients presenting with MI, we analysed the results of this subgroup of patients from the COMPARE trial database. A detailed analysis of two year outcomes of EES as compared to PES in all MI patients as well as stratified for non-ST elevation myocardial infarction and ST elevation myocardial infarction was performed and presented.

In **Chapter 3** the major findings of SPIRIT IV and COMPARE trials are summarized in a overview paper leading further to what is the focus of this chapter**:** the clinical impact of safety outcomes with EES. For this end, as none of these trials were adequately powered to examine the incidence and predictors of ST and of the combined safety endpoint of cardiac mortally and MI, as well as to evaluate the impact of dual antiplatelet therapy (DAPT) permanent interruption on ST outcomes in the EES and PES cohorts separately, we pooled patient-level data from four randomized trials in which the outcomes of EES compared to PES, in 6,789 patients, have been examined.

In **Chapter 4** we investigate the performance of the EES in DM patients. As known, patients with diabetes mellitus undergoing percutaneous coronary intervention with bare metal stents have higher rates of angiographic and clinical restenosis than patients without diabetes mellitus.[11,12] Compared with bare metal stents, drug-eluting stents (DES) have been shown to be safe[13] and to result in greater absolute reductions in target lesion revascularization (TLR) and target vessel revascularization in patients with versus those without diabetes mellitus.[14,15,16] However, whether the presence of diabetes mellitus differentially affects the relative clinical outcomes with different types of DES is a matter of considerable debate. Most prior studies have shown comparable rates of angiographic in-stent late loss and clinical restenosis with PES in patients with versus without diabetes mellitus.[17] In contrast, whether the relatively greater suppression of neointimal hyperplasia observed from stents that elute rapamycin analogs (such as sirolimus or everolimus) is preserved in patients with diabetes mellitus is unsettled. In this regard, several studies have provided conflicting results.[18,19] Moreover, none of these prior trials was powered to determine whether there are differences in safety outcomes between different DES according to the presence of diabetes mellitus.

To this end, we studied the safety and efficacy outcomes of the second generation EES and the first generation PES in patients with and without DM in the above mentioned patient-level pooled database from the SPIRIT II, III, IV and COMPARE trials. We also specifically examined the outcomes with these stents after stratifying for insulin dependence in each cohort.

To re-evaluate the findings of the previous here above mentioned, device comparison , as well as to study the impact of the stent design improvements when comparing two rapamycin – analog stents, respectively the second generation EES and the first generation SES, a second analysis in a much larger diabetes mellitus real life population, was performed, using the data of the Swedish Coronary Angiography and Angioplasty Register (SCAAR)

In **Chapter 5** the results of the studies presented in thesis are summarised, focusing particularly in the clinical impact, future perspectives, as well as in the designs of new trials, particularly the COMPARE-ACUTE[20] and DAPT-STEMI[21]. Both trials are designed and powered based on the findings and the clinical impact of the above mentioned studies, and intend to set a step ahead in the treatment approach of STEMI with multivessel disease at presentation as well as the duration of DAPT after primary PCI and stenting with modern DES.

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Chapter 2.1

Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial

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ABSTRACT

Background

Everolimus-eluting and paclitaxel-eluting stents, compared with bare metal stents, reduced the risk of restenosis in clinical trials with strict inclusion and exclusion criteria. We compared the safety and efficacy of the second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice.

Methods

We randomly assigned 1800 consecutive patients (aged 18–85 years) undergoing percutaneous coronary intervention at one centre to treatment with everolimus-eluting or paclitaxel-eluting stents. The primary endpoint was a composite of safety and efficacy (all-cause mortality, myocardial infarction, and target vessel revascularisation) within 12 months. Patients were not told which stent they had been allocated. Analysis was by intention to treat. The trial is registered with ClinicalTrials.gov, number NCT01016041.

Findings

Follow-up was completed in 1797 patients. The primary endpoint occurred in 56 (6%) of 897 patients in the everolimus-eluting stent group versus 82 (9%) of 903 in the paclitaxel-eluting stent group (relative risk 0,69 [95% CI 0,50–0,95], p value for superiority=0,02). The difference was attributable to a lower rate of stent thrombosis (6 [<1%] *vs* 23 [3%], 0,26 [0,11–0,64], p=0,002), myocardial infarction (25 [3%] *vs* 48 [5%], 0,52 [0,33–0,84], p=0,007), and target vessel revascularisation (21 [2%] *vs* 54 [6%], 0,39 [0,24–0,64], p=0,0001). Cardiac death, non-fatal myocardial infarction, or target lesion revascularisation occurred in 44 [5%] patients in the everolimus-eluting stent group versus 74 [8%] patients in the paclitaxel-eluting stent group, p value for superiority was 0,005.

Interpretation

The everolimus-eluting stent is better than the second generation paclitaxel-eluting stent in unselected patients in terms of safety and efficacy. On the basis of our results, we suggest that paclitaxel-eluting stents should no longer be used in everyday clinical practice.

INTRODUCTION

On the basis of results from randomised trials with strict inclusion and exclusion criteria, first-generation drug-eluting stents, coated with sirolimus or paclitaxel, were approved for clinical use in patients with coronary artery disease.[1–3] Early experience with use of first generation stents in patients in real-life practice showed that benefit, in terms of the need for reintervention, was most apparent in those with high risk of restenosis.[4] Widespread use of first-generation drug-eluting stents has drawn attention to several unresolved issues that are clinically relevant. First, although the risk is small, stent thrombosis is unpredictable, continues to increase with time, and has serious clinical consequences.[5,6] Second, the deliverability of first generation drug-eluting stents could be improved.

Third, although these stents are more effective than are bare metal stents in patients at high risk of restenosis, the need for reintervention is still a problem in patients with severe coronary disease, as shown in a randomised study in which individuals with complex coronary disease were given percutaneous treatment with the first-generation paclitaxel-eluting stent or coronary artery bypass surgery.[7]

Compared with the currently available first-generation drug-eluting stents, second-generation drug-eluting stents have been designed with the goal of improving safety, efficacy, and device performance. Everolimus, a semisynthetic sirolimus analogue, is released from a thin coating of a biocompatible fluoropolymer on an open cell, thin-strut, cobalt-chromium frame. A significant reduction in serious adverse cardiac events was noted in patients with the everolimus-eluting stent compared with those who had the first-generation paclitaxel-eluting stent.[8] This first-generation stent has been superseded in Europe by the new-generation paclitaxel-eluting stent since September, 2005. Whether such differences persist with a new-generation paclitaxel-eluting stent that consists of the same polymer but has a different stent platform is not known. We therefore compared the safety and efficacy of the second-generation everolimus-eluting and paclitaxel-eluting stents in unselected patients in real-life practice.

METHODS

Study design and patients

Consecutive patients (aged 18–85 years) referred to the Maasstad Ziekenhuis for elective or emergent percutaneous coronary intervention, were eligible to participate in the study. There were no limitations about the number of lesions or vessels, location of lesions, or their length. Exclusion criteria were contra-indications or expected non-adherence to dual antiplatelet drugs in the 12 months after the procedure; planned major surgery within 30 days; inability or refusal to comply with follow-up procedures; participation in other coronary-device trials; and inability to provide informed consent. All patients provided written informed consent. The study complied with the Declaration of Helsinki for investigation in human beings, and was approved by the institutional ethics committee of the Maasstad Ziekenhuis, Rotterdam, the Netherlands, and the Dutch Central Committee on Research Involving Human Subjects.

Randomisation and masking

The allocation schedule was based on computer-generated random numbers. The statistician involved in the design of the study generated the randomisation list. Patients were assigned in a one-to-one ratio to a polymer based, everolimus-eluting stent (Xience V, Abbott Vascular, Santa Clara, CA, USA) or a polymer-based, paclitaxel-eluting stent (Taxus Liberte, Boston Scientific, Natick, MA, USA), using sealed, opaque, sequentially numbered allocation envelopes after passage of the guide wire. The patients knew they had been randomly assigned in a trial of drug-eluting stents, but did not know which stent they had been allocated.

Procedures

Staged procedures were permitted and the same stent type, allocated at initial randomisation, was used. Everolimus-eluting stents were available in diameters of 2,25 mm, 2,50 mm, 3,00 mm, 3,50 mm, and 4,00 mm, and in lengths of 8 mm, 12 mm, 15 mm, 18 mm, 23 mm, and 28 mm. Paclitaxel-eluting stents were available in diameters of 2,25 mm, 2,50 mm, 3,00 mm, 3,50 mm, and 4,00 mm, and in lengths of 8 mm, 12 mm, 16 mm, 20 mm, 24 mm, 28 mm, and 32 mm. Percutaneous coronary intervention was done according to standard techniques. Crossover to another stent was allowed in the event of an inability to insert the assigned device. Technical details, such as the decision to stent without balloon predilatation, use of adjunctive techniques such as rotational atherectomy, and decision to postdilate the stent, were at the discretion of

the operator. Off -line quantitative coronary angiography analysis for the baseline data was done with an automated edge-detection system (CAAS, version 1.1, Pie Medical Imaging, Maastricht, Netherlands). The analyses were done by experienced technicians. All patients not on dual antiplatelet drugs were given aspirin (300 mg) and clopidogrel (300 mg or 600 mg) before the procedure. The high dose of clopidogrel was given to patients undergoing primary percutaneous intervention for ST-segment elevation myocardial infarction. An initial bolus of unfractionated heparin (70–100 IU/kg) was given to all patients, and additional boluses were given to achieve and maintain an activated clotting time of more than 250 s, which was checked every 30 min. The use of bivaluridin or low molecular-weight heparin was not allowed. The use of glycoprotein IIb/IIIa antagonists was at the discretion of the operator. A 12-lead electrocardiograph was done before and after the procedure; before discharge; and at 1 month, 6 months, and 12 months follow-up. Postprocedural measurements of cardiac biomarkers were obtained systematically only in patients in whom procedural complications, such as side-branch closure, residual dissection, or no reflow, occurred or when patients had chest pain or electrocardiographic changes after the procedure. At the time of discharge, all patients were given aspirin (100 mg once a day) for an indefinite period, as well as clopidogrel (75 mg per day) for 12 months.

Outcomes and data management

The prespecified primary endpoint was a composite of all-cause mortality, non-fatal myocardial infarction, and target vessel revascularisation within 12 months. The secondary endpoints were a composite of major adverse cardiac events (cardiac death, non-fatal myocardial infarction, and clinically justified target lesion revascularisation within 12 months of follow-up), and a composite of all-cause mortality, non-fatal myocardial infarction, and target vessel revascularisation at 3 years and 5 years. All deaths were regarded as cardiac unless an unequivocal non-cardiac cause was established. Periprocedural myocardial infarction, in patients without infarction at baseline, was defined as any elevation in concentrations of creatine kinase to more than double normal value, with elevated values of a confirmatory cardiac biomarker (creatine kinase-MB fraction or troponin). Spontaneous infarction was defined as a typical rise and fall in concentrations of troponin or creatinine kinase-MB with at least one of the following: ischaemic symptoms, development of pathological Q waves, ischaemic electrocardiographic changes, or pathological findings of an acute myocardial infarction.[9] Target lesion revascularisation was defined as revascularisation for a stenosis within the stent or within the 5-mm borders adjacent

to the stent. Revascularisation of the target lesion and vessel was regarded as clinically justified if the stenosis of any target lesion or vessel was at least 50% of vessel diameter on the basis of quantitative coronary angiography in the presence of objective evidence of ischaemia on non-invasive or invasive testing or symptoms, or if the stenosis was at least 70% of vessel diameter even in the absence of ischaemic signs or symptoms. Stent thrombosis was defined according to the definitions provided by the Academic Research Cnsortium.[10] Adverse events were assessed in the hospital, and at 1 month and 12 months. Data were gathered by study monitors who visited the hospitals in which follow-up was undertaken, reviewed the clinical notes, and collected the protocol-mandated electrocardiographs. Furthermore, medical questionnaires were posted to all patients at 1 month, 6 months, and 12 months to check for adverse events and establish current antiplatelet drugs. Data were stored in our institution. Data processing and adjudication of adverse events were done by an independent contract research organisation and core lab (Cardialysis, Rotterdam, Netherlands). An independent data and safety monitoring board reviewed the data after interim analyses with formal stopping rules.

Statistical analysis

On the basis of results from the T-SEARCH registry,[4] and SIRTAX[11] and SPIRIT II trials,[12] we assumed an incidence of the primary endpoint of 9% in the everolimus- eluting stent group and 14% in the paclitaxel-eluting stent group. Enrolment of 1800 patients would provide the study with a statistical power of 85% to detect this difference with a two-sided significance level of 0,05, allowing for 3–4% of patients lost to follow-up. All analyses were done according to the intention-to treat principle. Patients were censored from the Kaplan-Meier plots when they reached any component of the composite endpoint. Categorical variables were assessed with use of $\chi 2$ or Fisher's exact tests, whereas continuous variables were assessed with the Wilcoxon rank-sum test. The time to the primary endpoint was assessed according to the method of Kaplan-Meier, and the log-rank test was applied to compare the incidence of the endpoint between groups. Relative risks with 95% CIs, were calculated with the log-binomial method.[13] The Kaplan-Meier curves were drawn with the guidelines provided by Pocock and colleagues.[14] All p values were two-sided, and a p value of less than 0,05 was regarded as significant. Analyses were done with SAS (version 8.02).

The trial is registered with ClinicalTrials.gov, number NCT01016041.

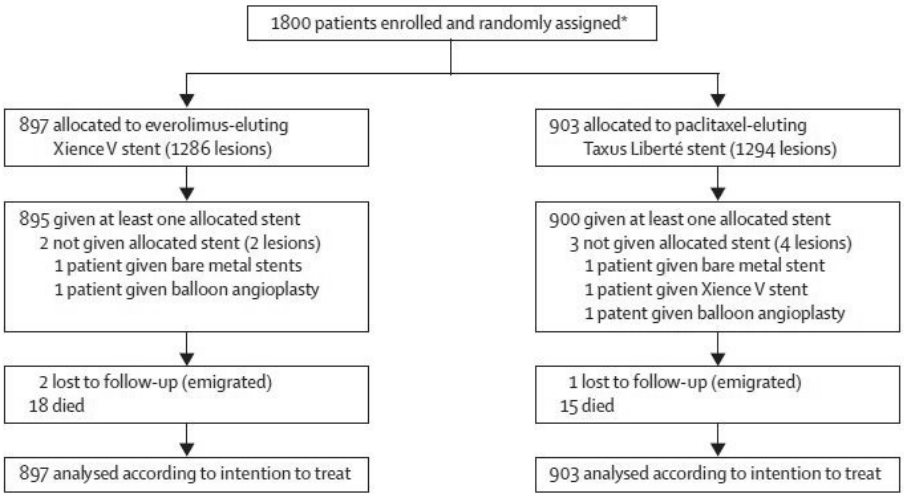

Figure 1 Trial profile
*We have no reliable data for patients assessed for eligibility.

Role of the funding source

The sponsors had no involvement in the design, conduct, or analysis of the study. The corresponding author had full access to all the data in the study, and had full responsibility for the decision to submit for publication.

RESULTS

Figure 1 shows the trial profile. 1800 patients were enrolled between February, 2007, and September, 2008. Five (<1%) were not given the designated stent. Staged procedures were done in 191 (21%) patients in the everolimus-eluting stent group and in 172 (19%) patients in the paclitaxel-eluting stent group (p=0,23). Three were lost to follow-up. The groups had similar baseline clinical (table 1), angiographic (table 2), and procedural characteristics (table 3).

Most patients presented with an acute coronary syndrome (table 1); the subtype of acute coronary syndrome was equally distributed in the two groups; 74% of lesions were complex (type B2 or C; table 2). The median total stent length per lesion, compared with previous studies, and the number of stents per lesion were high; the number of stents was slightly, but significantly, higher in the everolimus-eluting stent group because of a shorter available maximum stent length (table 3). Postprocedural cardiac biomarkers were assessed in 364 (41%) patients in the everolimus-eluting stent group and in 338

Table 1. Baseline Characteristics

	Everolimus- eluting stent (N=897)	**Paclitaxel- eluting stent** (N=903)
Age (years)	62.9 (11)	63.8 (11)
Men	619 (69%)	654 (72%)
Diabetes mellitus	153 (17%)	172 (19%)
Chronic renal failure *	25 (3%)	24 (3%)
Hypertension	417 (46%)	447 (49%)
Hypercholesterolaemia	477 (53.2%)	451 (49.9%)
Current smoker	295 (32.9%)	262 (29.0%)
Family history of CAD	399 (44%)	403 (45%)
History of MI	136 (15%)	159 (18%)
History of PCI	117 (13%)	123 (14%)
History of CABG	60 (6.7%)	53 (5.9%)
Stable angina pectoris	331 (37%)	349 (39%)
Silent ischemia	23 (3%)	17 (2%)
Acute coronary syndrome	541 (60%)	534 (59%)
Unstable angina	107 (12%)	105 (12%)
Non-ST segment elevation MI	194 (22%)	217 (24%)
ST segment elevation MI	240 (27%)	212 (23%)
Glycoprotein IIbIIIa antagonists	288 (32%)	290 (32%)
Multivessel treatment	244 (27%)	239 (26%)
Number of lesions treated per patient	1.4 (0.7)	1.4 (0.7)
Reference vessel diameter <2.75 mm	458 (51.%)	441 (49%)
Lesion length > 20 mm	290 (32.%)	263 (29.%)

Data are number (%), unless otherwise indicated. Percentages have been rounded. *Defi ned as treatment with diet or drugs for previously diagnosed diabetes. †Defined as serum creatinine greater than 130 µmol/L or patient on dialysis.

Table 2. Baseline Lesion and Procedural Characteristics

	Everolimus-eluting stent (1286 lesions)	**Paclitaxel-eluting stent** (1294 lesions)	p value
Target lesion coronary artery			
Left main	21 (1.6%)	21 (1.6%)	0.99
Left anterior descending	513 (39.9%)	485 (37.4%)	0.20
Left circumflex	299 (23.3%)	333 (25.7%)	0.15
Right	426 (33.2%)	431 (33.2%)	0.94
Bypass graft	27 (2.1%)	24 (1.8%)	0.69
ACC-AHA lesion class			
A	81 (6.3%)	61 (4.8%)	0.08
B1	255 (19.8%)	278 (21.5%)	0.31

B2	355 (27.6%)	379 (29.3%)	0.36
C	595 (46.3%)	576 (44.5%)	0.35
De novo lesions	1252 (97.4%)	1267 (97.9%)	0.34
Ostial lesion	242 (18.8%)	243 (18.8%)	0.31
Calcified lesion	422 (32.8%)	444 (34.3%)	0.55
Bifurcated lesion	223 (17.3%)	237 (18.3%)	0.24
Thrombus present	310 (24.1%)	314 (24.3%)	0.62
Chronic total occlusion	39 (3.0%)	53 (4.1%)	0.15
Pre procedure TIMI flow			
Grade 0	221 (17.2%)	213 (16.4%)	0.61
Grade 1	47 (3.6%)	56 (4.3%)	0.39
Grade 2	85 (6.6%)	102 (7.9%)	0.22
Grade 3	933 (72.5%)	926 (71.4%)	0.53

Data are mean (SD) or number (%). ACC denotes American College of Cardiology, AHA American Heart Association. TIMI= thrombolysis in myocardial infarction.

Table 3. Quantitative coronary angiography and procedural results

	Everolimus-eluting stent (1286 lesions)	**Paclitaxel-eluting stent** (1294 lesions)	**p value**
Lesion length (mm)	16.8 (9.5-31.5)	16.0(9.2-31.0)	0.44
Diameter of reference vessel (mm)	2.56 (2.19-2.95)	2.55 (2.21-3.0)	0.61
Baseline minimal lumen diameter (mm)	0.90 (0.62-1.21)	0.91 (0.66-1.22)	0.66
Baseline stenosis (lumen diameter %)	64 (53-77)	64 (53-76)	0.98
Postprocedure stenosis (lumen diameter %)	17 (11-24)	16 (10-24)	0.39
Postprocedure minimum lumen diameter (mm)	2,14 (1,82– 2,51)	2,15 (1,80–2,55)	0,88
Acute gain (mm)	1.24 (0.82-1.76)	1.24 (0.81-1.71)	0.71
Number of stents per lesion	1.7 (0.9)	1.6 (0.9)	0.007
Total stent length per lesion (mm)	28 (18-46)	28 (18-44)	0.85
Direct stenting	432 (34%)	451 (35%)	0.37
Post dilatation	698 (54%)	668 (52%)	0.18

Data are median (IQR) or number (%), unless otherwise indicated. Data for quantitative coronary angiography (QCA) are presented only for lesions with matched views for QCA before and after procedure (1977 lesions).

(37%) in the paclitaxel-eluting stent group (p=0,17). Table 4 shows the major adverse cardiac events during

follow-up. The primary endpoint occurred in fewer patients in the everolimus-eluting stent group than in the paclitaxel-eluting stent group (table 4; figure 2A). The difference resulted from a lower rate of myocardial infarction and of target vessel revascularisation at 12 months in patients with

Table 4. Clinical events during follow-up

	Everolimus-eluting stent (n=897)	Paclitaxel-eluting stent (n=903)	Relative Risk (95% CI)	p value
Events at 30 days				
All cause mortality	7 (0.8%)	6 (0.7%)	1.17 (0.40-3.48)	0.77
Cardiac Death	7 (0.8%)	6 (0.7%)	1.17 (0.40-3.48)	0.77
Myocardial infarction	15 (2%)	28 (3%)	0.53 (0.29-1.00)	0.05
Q-wave	3 (0.3%)	8 (0.9%)	0.38 (0.10-1.42)	0.13
Non-Q-wave	12 (1%)	21 (2%)	0.57 (0.28-1.16)	0.12
Death or myocardial infarction	21 (2%)	33 (4%)	0.64 (0.37-1.10)	0.10
Cardiac death or myocardial infarction	21 (2%)	33 (4%)	0.64 (0.37-1.10)	0.10
Target vessel revascularisation (clinically justified)	4 (0.4%)	18 (2.0%)	0.22 (0.08-0.66)	0.003
Percutaneous	1 (0.1%)	16 (2%)	0.06 (0.01-0.47)	0.0003
Surgical	3 (0.3%)	2 (0.2%)	1.51 (0.25-9.02)	0.65
Target vessel revascularisation (Any)	5 (0.6%)	19 (2%)	0.26 (0.10-0.71)	0.004
Percutaneous	2 (0.2%)	17 (2%)	0.12 (0.03-0.51)	0.0006
Surgical	3 (0.3%)	2 (0.2%)	1.51 (0.25-9.02)	0.65
Target lesion revascularisation (Clinically Driven)	3 (0.3%)	16 (2%)	0.19 (0.06-0.65)	0.003
Percutaneous	0	14 (2%)	.	0.0005
Surgical	3 (0.3%)	2 (0.2%)	1.51 (0.25-9.02)	0.65
Target lesion revascularisation (Any)	4 (0.4%)	17 (2%)	0.24 (0.08-0.70)	0.005
Percutaneous	1 (0.1%)	15 (2%)	0.07 (0.01-0.51)	P<0.001
Surgical	3 (0.3%)	2 (0.2%)	1.51 (0.25-9.02)	0.65
Primary endpoint	25 (3%)	35 (4%)	0.72 (0.43-1.19)	0.20
Secondary endpoint	23 (3%)	34 (4%)	0.68 (0.40-1.15)	0.15
Stent Thrombosis (definite and probable)	2 (0.2%)	15 (2%)	0.13 (0.03-0.59)	0.002
Acute Stent Thrombosis (On date of procedure)	1 (0.1%)	1 (0.1%)	1.01 (0.06-16.07)	0.99
Sub-Acute Stent Thrombosis (1-30 days post procedure)	1 (0.1%)	14 (2%)	0.07 (0.01-0.55)	0.0008
Early Stent Thrombosis (0-30 days post procedure)	2 (0.2%)	15 (2%)	0.13 (0.03-0.59)	0.002
Definite Stent Thrombosis	2 (0.2%)	12 (1%)	0.17 (0.04-0.75)	0.008
Events at 12 months				
All-cause mortality	18 (2%)	15 (2%)	1.21 (0.61-2.38)	0.58
Cardiac Death	11 (1%)	10 (1%)	1.11 (0.47-2.59)	0.81
Myocardial infarction	25 (3%)	48 (5%)	0.52 (0.33-0.84)	0.007
Q-wave	3 (0.3%)	11 (1%)	0.27 (0.08-0.98)	0.03
Non Q-wave	22 (2%)	39 (4%)	0.57 (0.34-0.95)	0.03
All-cause mortality or myocardial infarction	42 (5%)	62 (7%)	0.68 (0.47-1.00) *	0.05 *

	Everolimus-eluting stent (n=897)	Paclitaxel-eluting stent (n=903)	Relative Risk (95% CI)	p value
Cardiac death or myocardial infarction	35 (4%)	57 (6%)	0.62 (0.41-0.93)	0.02
Target vessel revascularisation (Clinically justified)	19 (2%)	51 (6%)	0.38 (0.22-0.63)	0.0001
Percutaneous	13 (1%)	38 (4%)	0.34 (0.18-0.64)	0.0004
Surgical	6 (0.7%)	13 (1%)	0.46 (0.18-1.22)	0.11
Target vessel revascularisation (Any)	21 (2%)	54 (6%)	0.39 (0.24-0.64)	0.0001
Percutaneous	15 (2%)	41 (5%)	0.37 (0.21-0.66)	0.0005
Surgical	6 (0.7%)	13 (1%)	0.46 (0.18-1.22)	0.11
Target lesion revascularisation (Clinically justified)	15 (2%)	43 (5%)	0.35 (0.20-0.63)	0.0002
Percutaneous	9 (1.0%)	31 (3%)	0.29 (0.14-0.61)	0.0005
Surgical	6 (0.7%)	12 (1%)	0.50 (0.19-1.34)	0.16
Target lesion revascularisation (Any)	18 (2%)	48 (5%)	0.38 (0.22-0.64)	0.0002
Percutaneous	12 (1%)	36 (4%)	0.34 (0.18-0.64)	0.0005
Surgical	6 (0.7%)	12 (1%)	0.50 (0.19-1.34)	0.16
Primary endpoint	56 (6%)	82 (9%)	0.69 (0.50-0.95)	0.02
Secondary endpoint	44 (5%)	74 (8%)	0.60 (0.42-0.86)	0.005
Stent Thrombosis (definite and probable)	6 (0.7%)	23 (3%)	0.26 (0.11-0.64)	0.002
Late Stent Thrombosis (30 days – 1 year post procedure	4 (0.4%)	8 (0.9%)	0.50 (0.25-1.67)	0.25
Definite Stent Thrombosis	4 (0.4%)	18 (2%)	0.22 (0.08-0.66)	0.003

Data are number (%). Percentages have been rounded. *The 1,00 upper limit of 95% CI was 0,998, and p value was 0,047.

everolimus-eluting stents, whereas all-cause mortality did not differ between the groups (figure 2B–D). Periprocedural myocardial infarction occurred in 15 (2%) patients in the everolimus-eluting stent group and 19 (2%) patients in the paclitaxel-eluting stent group (p=0,49). The lower rate of non-fatal myocardial infarction during 12 months in patients given everolimus-eluting stents reflects a significant difference in early stent thrombosis (table 4; figure 3A). The rate of definite and probable stent thrombosis for up to 1 year remained significantly lower in the everolimus-eluting stent group compared with the paclitaxel-eluting stent group (table 4). There were more late-stent thromboses in the paclitaxel-eluting stent group than in the everolimus-eluting stent group at 1 year but the difference was not significant (figure 3B). The rate of target vessel revascularisation was significantly lower in patients who had everolimus-eluting stents. This difference between the groups was already apparent at 30 days, and remained significant at 1 year (figure 2D; table 4). The main secondary endpoint occurred in fewer patients in the everolimus-eluting stent group than in the paclitaxel-eluting stent group (table 4). We did an ex-

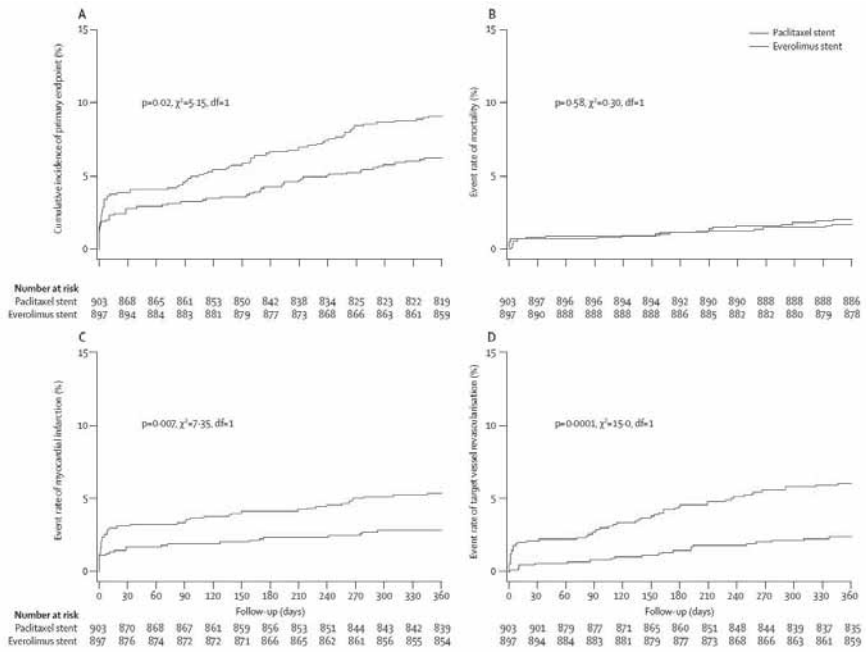

Figure 2 Kaplan-Meier cumulative events curves at 12 months for primary endpoint (A), mortality (B), myocardial infarction (C), and target vessel revascularisation (D)

ploratory stratified analysis of the primary endpoint that was not prespecified in the protocol (figure 4). The outcome of the primary endpoint was consistent across all but two subgroups ie, patients with diabetes (n=325) and those with long lesions (n=553). CIs were wide and the results of a test of interaction were not significant. Compliance with aspirin and clopidogrel was 809 (91%) in the everolimus-eluting stent group versus 829 (92%) in the paclitaxel-eluting stent group at 1 month; 805 (91%) and 815 (91%), respectively, at 6 months; and 611 (70%) in the everolimus-eluting stent group and 625 (70%) in the paclitaxel-eluting stent group at 1 year.

DISCUSSION

The use of second-generation everolimus-eluting stents, compared with paclitaxel-eluting stents, was associated with a significant reduction in the risk of major adverse cardiac events at 1 year. This difference was a result of reduction in the rate of myocardial infarction, a safety component of the primary endpoint, and reduction in repeat revascularisation of the target vessel. Rates of all-cause or cardiac mortality did not differ between the two groups; however

the rate of myocardial infarction was significantly reduced in the everolimus eluting stent group. This reduction was already apparent at 1 month. The significantly lower rate of myocardial infarction at 30 days with the everolimus stent was attributable to a significantly lower rate of early stent thrombosis because there was no significant difference between the groups in the rate of periprocedural myocardial infarction. Use of the paclitaxel-eluting stent was associated with a higher rate of early stent thrombosis in the unselected population we studied than that reported in previous randomised trials in selected patient populations.[8,12] A large proportion of the unselected patients enrolled had high-risk clinical or angiographic characteristics. Since the proportion of patients with such high-risk characteristics did not differ significantly between groups, differences between the devices—stent design, polymer coating, or the drug used—are the most plausible explanations for the high rate of stent

thrombosis with the paclitaxel stent. By contrast, the rate of stent thrombosis with the everolimus-eluting stent in our study was similar to that reported in the randomised trials of selected populations that led to marketing approval.[8,12] The significant difference in stent thrombosis at 12 months between the two groups was mainly attributable to early stent thrombosis. Because the groups did not differ in terms of baseline characteristics, preprocedural and postprocedural antiplatelet and antithrombotic drugs, or procedural technique, we believe that the noted difference in early stent thrombosis rates relate to differences between the two devices that become apparent in an unselected population. An open-cell, thin-strut stent frame mounted on a semicompliant balloon might result in better apposition and less side-branch compromise than would a closed-cell, thick-strut device on a non-compliant balloon. The thinner layer of polymer on the everolimus-eluting stent might also play a part. Preclinical data have shown that the everolimus -eluting stent has more rapid and more extensive re-endothelialisation than has the second-generation paclitaxel-eluting stent.[15] Numerically more stent thromboses were noted in the paclitaxel-eluting stent group than in the everolimus-eluting stent group between 1–12 months.

The absolute numbers were small and the differences were not significant. However, definitive conclusions about late stent thrombosis must await the prespecified analyses at 3 years and 5 years because results from several studies have shown a predictable, continued, risk of stent thrombosis with time, particularly with paclitaxel-eluting stents.[6]

As with safety, a significant difference in efficacy was also noted with the everolimus-eluting stent. Both target vessel and target lesion revascularisation

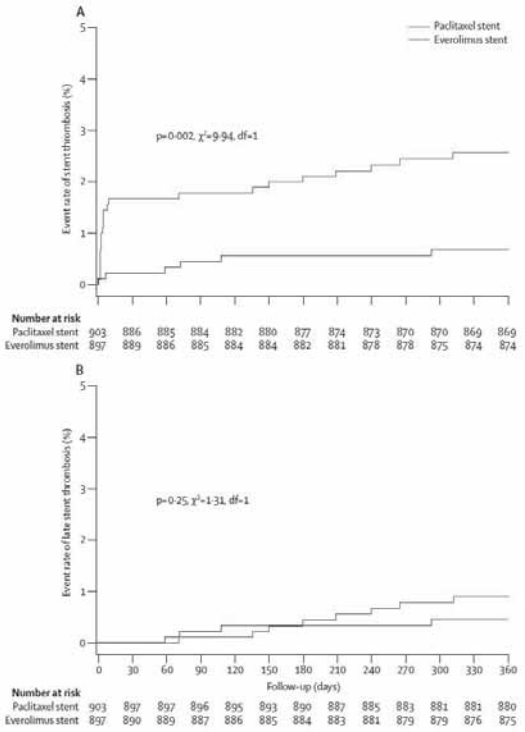

Figure 3 Kaplan-Meier event curves at 12 months for stent thrombosis (A) and late stent thrombosis (B)

were significantly reduced in the everolimus-eluting stent group compared with the paclitaxel-eluting stent group.

This difference was already evident at 30 days and continued to increase up to 1 year, with similar relative risk ratios at 30 days and at 12 months, consistent with a continued treatment effect. Up to 30 days, the difference in revascularisation between groups was related to the lower rate of stent thrombosis in the everolimus-eluting stent group than in the paclitaxel-eluting stent group. At 12 months, the difference suggested a significantly lower rate of clinically justified reinterventions for restenosis and lower rate of stent thrombosis in the everolimus-eluting stent group. The lower rate of reintervention might relate to the more potent reduction in neointimal hyperplasia with the everolimus-eluting stent than with the paclitaxel-eluting stent. The rate of major adverse cardiac events with the everolimus-eluting stent in our trial is similar to the rates reported in registries that also enrolled unselected populations—namely, the X-Search study[16] and the Spirit V registry (E Grube, Helios Heart Centre, personal communication). Since the test for interaction was not significant, the post-hoc exploratory subgroup analyses we did do not

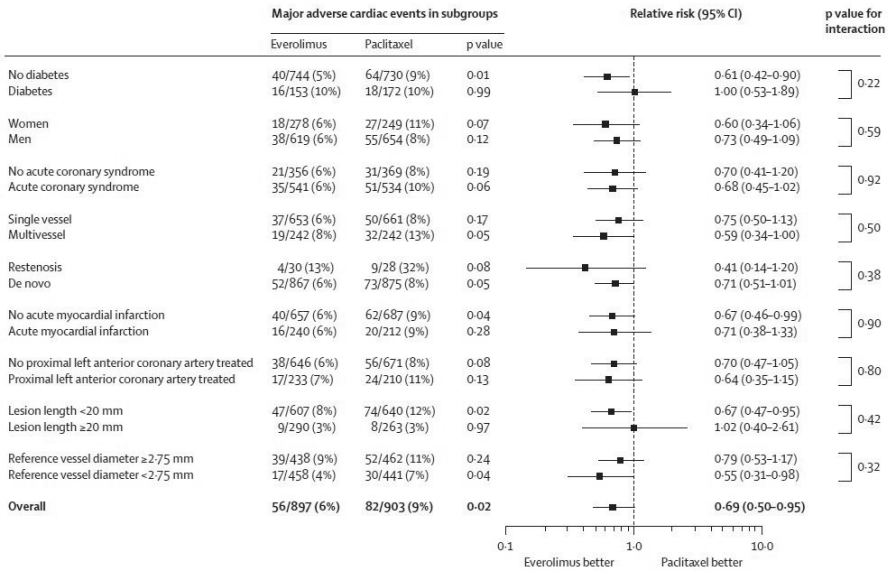

Figure 4 Subgroup analysis
Data are n/N (%). Percentages have been rounded.

allow us to infer whether the superiority of the everolimus-eluting stent differs between subgroups. However, in a similar analysis done in the SPIRIT IV trial (G Stone, New York-Presbyterian Hospital, Columbia University Medical Center, personal communication), the superiority of everolimus-eluting compared with paclitaxel-eluting stents was less apparent in patients with diabetes. This finding can only be regarded as exploratory. Patients with diabetes under going percutaneous coronary intervention have poorer outcomes overall than do those without diabetes even when treated with drug-eluting stents. However, results from previous studies have consistently suggested that stents eluting limus derivatives might offer an advantage over paclitaxel-eluting stents in patients with diabetes.[17,18] Enrolment of unselected patients and the entirely clinical follow-up were the strengths of our study. Further more, we studied the second-generation paclitaxel-eluting stent whereas the first-generation paclitaxel-eluting stent was used in previous comparisons.[19]

There are some limitations to our investigation. The trial was done in one, high-volume, tertiary centre in which implantation of drug-eluting stents was the default strategy for coronary intervention, and therefore the results might not be applicable in other settings.

Consistent with usual clinical practice in our institution, systematic sampling of cardiac biomarkers was not done for all patients, and is unlikely to have affected the outcome because the proportion of patients who had biomarkers

measured did not differ significantly between groups. In the Spirit III trial,[8] more postprocedure infarctions were noted in the paclitaxel-eluting stent group than in the everolimus-eluting stent group, whereas no significant difference was noted in the rate of periprocedural infarctions between groups in our study. Our conclusions about safety and efficacy are consistent with the outcome of previous studies of selected patient cohorts in which everolimus-eluting and paclitaxel-eluting stents were compared [8,12] and with the results of an all-comer registry in which the everolimus-eluting stent was compared with the first-generation paclitaxel-eluting stent.[16]

In conclusion, we have shown that the everolimus-eluting Xience V stent is better than the second-generation paclitaxel-eluting Taxus Liberte stent in treatment of patients in real-life practice in terms of safety and efficacy. On the basis of our results, we suggest that paclitaxel-eluting stents should no longer be used in everyday clinical practice.

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Chapter 2.2

2-Year Follow-Up of a Randomized Controlled Trial of Everolimus- and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice

COMPARE (Comparison of the everolimus eluting XIENCE-V stent with the paclitaxel eluting TAXUS LIBERTE´ stent in all-comers: a randomized open label trial)

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ABSTRACT

Objectives
The purpose of this study was to compare the safety and efficacy of the Xience V (Abbott Vascular, Santa Clara, California) everolimus-eluting stent (EES) with the Taxus Liberté (Boston Scientific, Natick, Massachusetts) paclitaxel-eluting stent (PES) at 2-year follow-up.

Background
COMPARE (Comparison of the everolimus eluting XIENCE-V stent with the paclitaxel eluting TAXUS LIBERTE´ stent in all-comers: a randomized open label trial) demonstrated a superior clinical outcome of EES over PES at 1 year in all comers. Whether this superiority is maintained after discontinuation, at 12 months, of dual antiplatelet therapy is unclear.

Methods
Patients undergoing percutaneous coronary intervention with limited exclusion criteria were randomly allocated to EES or PES. The 2-year pre-specified endpoints are composites of safety and efficacy and stent thrombosis.

Results
Follow-up was completed in 1,795 of 1,800 patients (99.7%). The groups had similar baseline characteristics. At 2 years, significantly fewer EES patients took dual antiplatelet therapy (11.4% vs. 15.4%, p =0.02). The primary composite of all death, nonfatal myocardial infarction, and target vessel revascularization occurred in 9.0% of EES patients and 13.7% of PES patients (relative risk [RR]: 0.66; 95% confidence interval [CI]: 0.50 to 0.86) driven by a lower rate of myocardial infarction (3.9% vs. 7.5%; RR: 0.52; 95% CI: 0.35 to 0.77) and target vessel revascularization (3.2% vs. 8.0%; RR: 0.41; 95% CI: 0.27 to 0.62), in parallel with a lower rate of definite or probable stent thrombosis (0.9% vs. 3.9%; RR: 0.23; 95% CI: 0.11 to 0.49). Differences significantly increased between 1- and 2-year follow-up for the primary composite endpoint (p = 0.04), target vessel revascularization (p = 0.02), and definite or probable stent thrombosis (p = 0.02).

Conclusions
The substantial clinical benefit of the EES over the PES with regard to measures of both safety and efficacy is maintained at 2 years in real-life practice with an increasing benefit in terms of safety and efficacy between 1 year and 2

years. Comparison of the everolimus eluting XIENCE-V stent with the paclitaxel eluting TAXUS LIBERTE´ stent in all-comers: a randomized open label trial: The COMPARE Trial [COMPARE 1]; NCT01016041) (J Am Coll Cardiol 2011; 58:11–8)

INTRODUCTION

Previous randomized trials involving highly selected patients with either 1 or 2 de novo coronary artery lesions have shown that the everolimus-eluting stent (EES) has a superior angiographic outcome in comparison with the paclitaxel-eluting stent (PES) (1,2). COMPARE (Comparison of the everolimus eluting XIENCE-V stent with the paclitaxel eluting TAXUS LIBERTE´ stent in all-comers: a randomized open label trial) and SPIRIT IV trials, in less selected patient populations, showed that the use of EES was associated with a significantly lower rate of the pre-specified primary endpoints compared to PES (3,4). In the COMPARE trial, the composite of all death, myocardial infarction (MI), and target vessel revascularization (TVR) was reduced by 31%. In the SPIRIT IV (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Subjects With de Novo Native Coronary Artery Lesions) trial, the rate of target lesion failure (TLF) at 12 months was reduced by 39%. In addition, both trials showed significant decreases in rates of MI, ischemia-driven target lesion revascularization (TLR), and definite or probable stent thrombosis (ST) with EES. Whether the demonstrated superiority of EES over PES at 1 year is maintained at 2 years remains unclear.

METHODS

The methodology of the trial has been published previously (3). In summary, consecutive patients, between 18 and 85 years of age, referred to Maasstad Ziekenhuis for elective or emergent percutaneous coronary intervention were eligible to participate. There were no limitations on the number of lesions or vessels, the location of lesions, or their length. Major exclusion criteria were contraindications to or expected nonadherence to dual antiplatelet therapy (DAPT) in the 12 months after the procedure, planned major surgery within 30 days, and inability to give informed consent. Patients were assigned on a 1:1 basis to EES or PES. All patients provided written informed consent. The study was investigator-initiated. Funding was provided by unrestricted

research grants from Abbott Vascular and Boston Scientific, which had no involvement in the study. The study was approved by the institutional ethics committee of the Maasstad Ziekenhuis, Rotterdam, the Netherlands, and the Dutch Central Committee on Research Involving Human Subjects (CCMO trial no. NL15206.101.06).

Medication

Details of periprocedural oral antiplatelet and anticoagulant therapy have been published (3). At discharge, all patients were receiving 100 mg of aspirin daily indefinitely and 75 mg of clopidogrel daily for 12 months.

Study endpoints and definitions

Adverse events were assessed in the hospital, and at 1, 12, and 24 months. Study monitors collected data by visits, phone calls, and postal questionnaires. Data were stored in our institution. Data processing and adjudication of adverse events, including ST, were done in a blinded fashion by an independent contract research organization and core laboratory (Cardialysis, Rotterdam, the Netherlands). The pre-specified primary endpoint was a composite of all death, nonfatal MI, and TVR at 12 months. The secondary endpoints were the primary composite endpoint at 2-year follow-up and the composite of major adverse cardiac events (cardiac death, nonfatal MI, and clinically driven TLR at 2-year follow-up). Definitions of endpoints are presented elsewhere (3).

Statistical analysis

Categorical variables, including events between 1 year and 2 years and up to 2 years, were evaluated using the chi-square test or Fisher's exact test, whereas continuous variables were evaluated with use of Wilcoxon ranksum test. Events between 1 year and 2 years were evaluated with Fisher's exact test after patients with the specified event up to 1 year were removed from the analysis. The time to the pre-specified endpoints was evaluated according to the Kaplan-Meier method, and the log-rank test was used to compare endpoint frequencies between groups. Relative risk (RR) with 95% confidence interval (CI) were calculated using the normal approximation to the binomial distribution. The statistical analysis was performed according to the intention-to-treat principle. All p values were 2-sided, and a p value < 0.05 was considered to indicate statistical significance. Analyses were performed using SAS version 8.02 (SAS Institute, Cary, North Carolina).

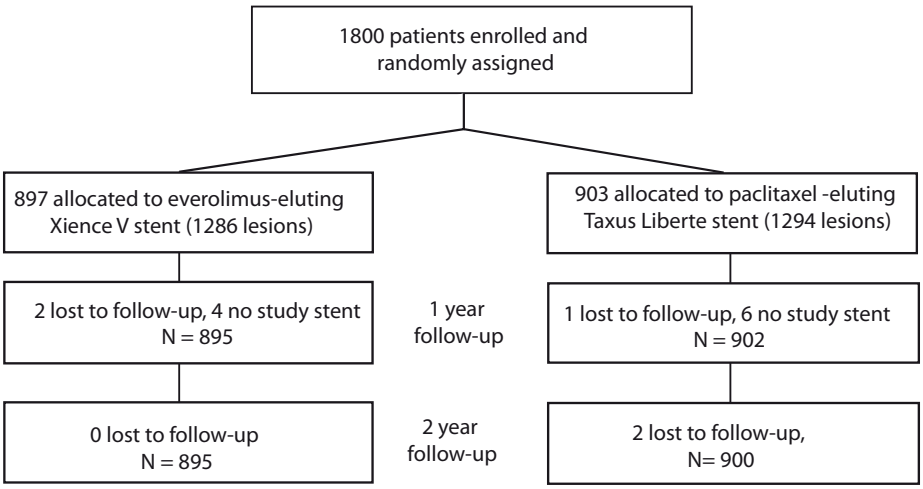

Figure 1 Patient diagram and follow-up

RESULTS

Between February 2007 and September 2008, 1,800 patients were enrolled. Randomization and patient flow is summarized in Figure 1.

Baseline demographic data

Baseline demographic data and lesion characteristics (Table 1) were comparable between groups (3). A high number of patients presented with an acute coronary syndrome (59% PES vs. 60% EES). Most lesions treated were complex (74% type B2 or C), resulting in a mean stented length of 28 mm in both groups.

Clinical outcomes

Table 2 shows clinical events at 1- and 2-year follow-up. At 2-year follow-up, the primary endpoint (Fig. 2A) occurred in 9.0% of the EES group versus 13.7% in the PES group (RR: 0.66, 95% CI: 0.50 to 0.86, p = 0.002). This reflected a lower rate of both MI and TVR in the EES group. All-cause mortality did not differ between groups (Figs. 2B to 2D). Between 1-year and 2-year follow-up, the event curves for the primary composite endpoint (p = 0.04) and TVR (p = 0.02) (Table 3) widened significantly. The secondary endpoint, a composite of cardiac death, nonfatal MI, and TLR, occurred in 7.4% of EES patients and

Table 1: Baseline patient and lesion characteristics

	Everolimus-eluting stent (N=897)	Paclitaxel-eluting stent (N=903)
Age (years; median)	62.9	63.6
Men	619 (69%)	654 (72%)
Diabetes mellitus *	153 (17%)	172 (19%)
Chronic renale failure †	25 (3%)	24 (3%)
Hypertension	417 (46%)	447 (50%)
Hypercholesterolaemia	(477 (53%)	451 (50%)
Current smoker	295 (33%)	262 (29%)
Family history of CAD	399 (44%)	403 (45%)
History of myocardial infarction	136 (15%)	159 (18%)
History of percutaneous coronary intervention	117 (13%)	123 (14%)
History of coronary artery bypass surgery	60 (7%)	53 (6%)
Stable angina pectoris	331 (37%)	349 (39%)
Acute coronary syndrome	541 (60%)	534 (59%)
Unstable angina	107 (12%)	105 (12%)
Non ST-segment elevation myocardial infarction	194 (22%)	217 (24%)
ST-segment elevation myocardial infarction	240 (27%)	212 (23%)
Multivessel treatment	244 (27%)	239 (26%)
Number of treated lesions per patient (SD)	1.4 (0.7)	1.4 (0.7)
Lesion Length ≥ 20mm	290 (32%)	263 (29%)
Number of lesions	1286	1294
Number of stents per lesion (mean, SD)	1.7 (0.9)	1.6 (0.9)
Total stent length per lesion (mm)	28 (18-46)	28 (18-44)
Direct stenting	432 (34%)	451 (35%)
Type B2 or C lesion	950 (74%)	955 (74%)
Bifurcation lesions	223 (17%)	237 (18%)
Thrombus present	310 (24%)	314 (24%)
Chronic total occlusion	39 (3%)	53 (4%)

Data are median, n (%), or mean ± SD. Percentages have been rounded. *Defined as treatment with diet or drugs for previously diagnosed diabetes mellitus. †Defined as serum creatinine >130 µmol/l or patient on dialysis. CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; EES = everolimus-eluting stent(s); MI = myocardial infarction; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent(s).

Table 2. Clinical Events during Follow-up

	Everolimus eluting stent (897 Patients)	Paclitaxel eluting stent (903 patients)	Relative Risk	Lower Limit RR*	Upper Limit RR*	P Value
Events at 12 months						
Death	18 (2.0)	15 (1.7)	1.21	0.61	2.38	0.58
Cardiac Death	11 (1.2)	10 (1.1)	1.11	0.47	2.59	0.81
MI	25 (2.8)	49 (5.4)	0.51	0.32	0.82	0.005
Q-wave	3 (0.3)	11 (1.2)	0.27	0.08	0.98	0.03
Non Q-wave	22 (2.5)	40 (4.4)	0.55	0.33	0.92	0.02
Death or MI	42 (4.7)	63 (7.0)	0.67	0.46	0.98	0.04
Cardiac death or MI	35 (3.9)	58 (6.4)	0.61	0.40	0.91	0.02
TVR , clinically riven	19 (2.1)	49 (5.4)	0.39	0.23	0.66	<0.001
Percutaneous	13 (1.4)	36 (4.0)	0.36	0.19	0.68	<0.001
Surgical	6 (0.7)	13 (1.4)	0.46	0.18	1.22	0.11
TVR, any	21 (2.3)	52 (5.8)	0.41	0.25	0.67	<0.001
Percutaneous	15 (1.7)	39 (4.3)	0.39	0.22	0.70	0.001
Surgical	6 (0.7)	13 (1.4)	0.46	0.18	1.22	0.11
TLR, clinically driven	15 (1.7)	40 (4.4)	0.38	0.21	0.68	<0.001
Percutaneous	9 (1.0)	28 (3.1)	0.32	0.15	0.68	0.002
Surgical	6 (0.7)	12 (1.3)	0.50	0.19	1.34	0.16
TLR, any	18 (2.0)	45 (5.0)	0.40	0.24	0.69	<0.001
Percutaneous	12 (1.3)	33 (3.7)	0.37	0.19	0.70	0.002
Surgical	6 (0.7)	12 (1.3)	0.50	0.19	1.34	0.16
Primary endpoint †	56 (6.2)	83 (9.2)	0.68	0.49	0.94	0.02
Secondary endpoint ‡	44 (4.9)	74 (8.2)	0.60	0.42	0.86	0.005
ST, definite and probable	5 (0.6)	23 (2.5)	0.22	0.08	0.57	<0.001
Early ST, 0-30 days after procedure	2 (0.2)	15 (1.7)	0.13	0.03	0.59	0.002
Late ST, 30 days – 1 yr after procedure	3 (0.3)	8 (0.9)	0.38	0.10	1.42	0.13
Definite ST	3 (0.3)	18 (2.0)	0.17	0.05	0.57	0.001
Events at 24 months						
Death	30 (3.3)	27 (3.0)	1.12	0.67	1.87	0.67
Cardiac Death	20 (2.2)	16 (1.8)	1.26	0.66	2.41	0.49
MI	35 (3.9)	68 (7.5)	0.52	0.35	0.77	<0.001
Q-wave	3 (0.3)	17 (1.9)	0.18	0.05	0.60	0.002
Non Q-wave	32 (3.6)	53 (5.9)	0.61	0.40	0.93	0.02
Death or MI	63 (7.0)	93 (10.3)	0.68	0.50	0.93	0.01
Cardiac death or MI	53 (5.9)	82 (9.1)	0.65	0.47	0.91	0.01
TVR, clinically driven	27 (3.0)	69 (7.6)	0.39	0.25	0.61	<0.001

	Everolimus eluting stent (897 Patients)	Paclitaxel eluting stent (903 patients)	Relative Risk	Lower Limit RR*	Upper Limit RR*	P Value
Percutaneous	20 (2.2)	52 (5.8)	0.39	0.23	0.64	<0.001
Surgical	7 (0.8)	19 (2.1)	0.37	0.16	0.88	0.02
TVR, any	29 (3.2)	72 (8.0)	0.41	0.27	0.62	<0.001
Percutaneous	22 (2.5)	55 (6.1)	0.40	0.25	0.65	<0.001
Surgical	7 (0.8)	19 (2.1)	0.37	0.16	0.88	0.02
TLR, clinically driven	23 (2.6)	53 (5.9)	0.44	0.27	0.71	<0.001
Percutaneous	16 (1.8)	40 (4.4)	0.40	0.23	0.71	0.001
Surgical	7 (0.8)	15 (1.7)	0.47	0.19	1.15	0.09
TLR, any	26 (2.9)	58 (6.4)	0.45	0.29	0.71	<0.001
Percutaneous	19 (2.1)	45 (5.0)	0.43	0.25	0.72	0.001
Surgical	7 (0.8)	15 (1.7)	0.47	0.19	1.15	0.09
Primary endpoint †	81 (9.0)	124 (13.7)	0.66	0.50	0.86	0.002
Secondary endpoint ‡	66 (7.4)	102 (11.3)	0.65	0.48	0.88	0.004
ST, definite and probable	8 (0.9)	35 (3.9)	0.23	0.11	0.49	<0.001
Very late ST >1 yr after procedure	3 (0.3)	13 (1.4)	0.23	0.07	0.81	0.01
Definite ST	5 (0.6)	24 (2.7)	0.21	0.08	0.55	<0.001

Values are n (%). *Relative risk (RR) and p values are from the chi-square test. Lower and upper limit of RR represent the 95% confidence intervals. †The pre-specified primary endpoint was a composite of all death, nonfatal MI and target vessel revascularization (TVR). ‡The principal secondary endpoint was a composite of cardiac death, nonfatal MI, and clinically driven target lesion revascularization (TLR).
ST = stent thrombosis; other abbreviations as in Table 1

Table 3. Outcome differences between 1 and 2 year.

	Everolimus eluting stent	Paclitaxel eluting stent			
	% Patients With Event Between 1and 2 yrs No Event First Year		OR	95% CI	p Value
Primary endpoint	3.0 (25/841)	5.0 (41/820)	0.58	0.34-0.99	0.04
Death	1.4 (12/879)	1.4 (12/888)	1.01	0.41-2.47	1.00
Cardiac death	1.0 (9/879)	0.7 (6/888)	1.52	0.45-5.21	0.45
TVR, clinically driven	0.9 (8/878)	2.3 (20/854)	0.38	0.15-0.92	0.02
TLR, clinically driven	0.9 (8/882)	1.5 (13/863)	0.60	0.21-1.57	0.28
MI	1.2 (10/872)	2.2 (19/854)	0.51	0.21-1.16	0.09
ST, definite and probable	0.3 (3/892)	1.4 (12/880)	0.24	0.04-0.91	0.02

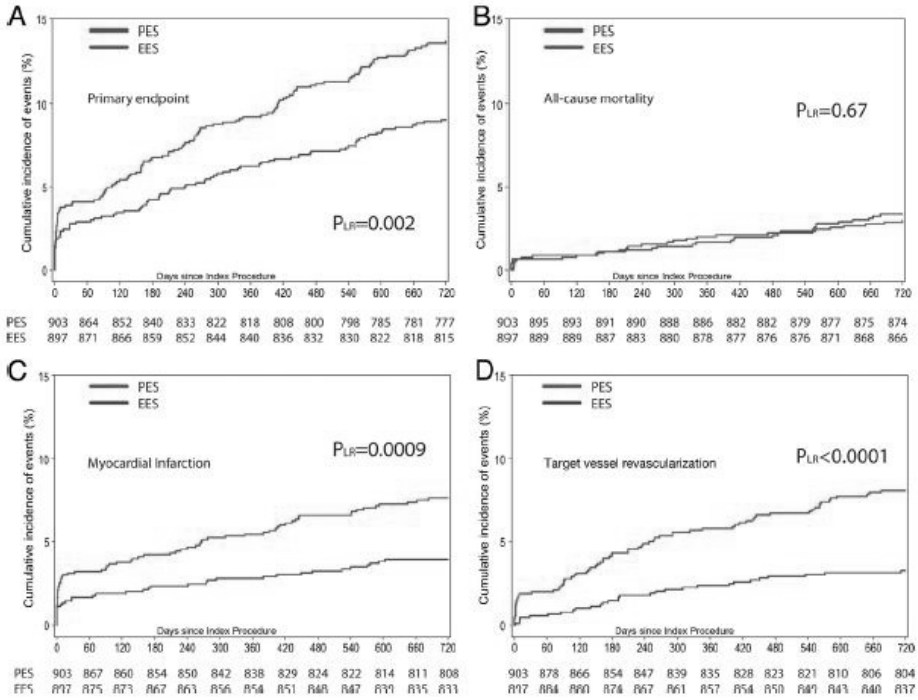

Figure 2 Kaplan-Meier Cumulative Event Curves for Primary Endpoints
Kaplan-Meier cumulative event curves for (A) the primary endpoint, (B) all death, (C) myocardial infarction (MI), and (D) target vessel revascularization (TVR). The absolute
difference in the primary endpoint between groups was 3.0% at 1 year, which significantly increased to 4.7% at 2 years. The absolute difference in MI increased from 2.6% at 1 year to 3.6% at 2 years. The absolute difference in TVR significantly increased from 3.5% at 1 year to 4.8% at 2 years. Red lines indicate paclitaxel-eluting
stent (PES); blue lines indicate everolimus-eluting stent (EES). PLR _ p value according to the log-rank test.

11.3% of PES patients at 2 years (RR: 0.65, 95% CI: 0.48 to 0.88, p = 0.004). As for the primary endpoint, this difference was driven by a reduction in MI and TLR. The rate of cardiac death did not differ between groups. In accordance with European percutaneous coronary intervention guidelines, the protocol specified that DAPT should be prescribed for 1 year after stent implantation. At 1 year of follow-up, 70% of patients in both groups were receiving DAPT. At 2 years, 11.4% of patients in the EES group and 15.2% in the PES group (p = 0.02) were receiving DAPT (Fig. 3). Definite and probable ST rate differed significantly between groups at 1 year (0.6% for EES vs. 2.5% for PES, RR: 0.22, 95% CI: 0.08 to 0.57, p = 0.001). At 2 years of follow-up, this absolute difference increased to 3.0% (0.9% for EES vs. 3.9% for PES, RR: 0.23, 95% CI: 0.11 to

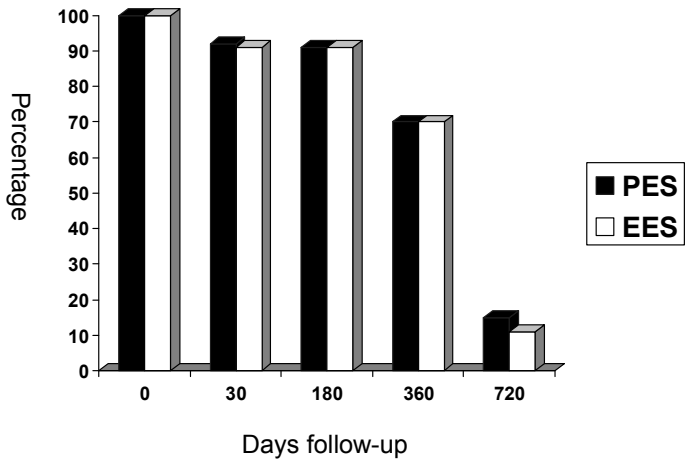

Figure 3 Baseline and Follow-Up DAPT
Dual antiplatelet therapy (DAPT) at baseline and at 1, 6, 12, and 24 months of follow-up in the paclitaxel-eluting stent (PES) group (red bars) and the everolimus- eluting stent (EES) group (blue bars). At 2 years, significantly more patients were on DAPT in the PES group (*p = 0.02).

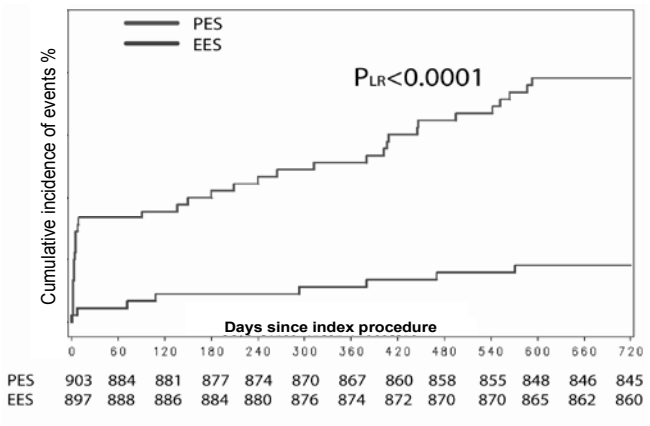

Figure 4 Kaplan-Meier Cumulative Event Curves for ST at 2-Year Follow-Up
Kaplan-Meier cumulative event curves for definite and probable stent thrombosis (ST) at 2 year follow-up as defined by the Academic Research Consortium. The absolute difference in rates of definite and probable ST between stent groups was 1.9% at 1 year, which significantly increased to 3.9% at 2 years. Red line indicates PES; blue line indicates EES. Abbreviations as in Figure 2.

0.49, p = 0.001) (Fig. 4). Between 1-year and 2-year follow-up, this event curve widened significantly (p = 0.02) (Table 3).

Early definite and probable ST occurred significantly more often in the PES group (0.2% EES vs. 1.7% PES, RR: 0.13, 95% CI: 0.03 to 0.59, p = 0.002). The rate of late definite and probable ST was numerically higher in the PES group, but did not differ significantly between groups. The rate of very late definite and probable ST was significantly higher in the PES group (0.3% EES vs. 1.4% PES, RR: 0.23, 95% CI: 0.07 to 0.81, p = 0.01) (Fig. 5).

Subgroup analysis

In a stratified analysis of the primary endpoint, the difference between EES and PES was consistent across all subgroups apart from patients with diabetes mellitus, for whom no difference in the primary composite outcome was noted at 1- or 2-year follow-up; however, the test of interaction was not significant (Fig. 6). In a more detailed analysis of the diabetic population, no differences were found in mortality, MI, and ST at 2 years; however, significantly more patients had clinically indicated TVR (9.3% vs. 2.0%, RR: 0.20, 95% CI: 0.04 to 0.70, p = 0.008), and there was a trend toward more TLR in the PES group compared with the EES group (5.8% vs. 2.0%, respectively; p = 0.09).

DISCUSSION

Our major finding was that the demonstrated superiority at 1 year of EES over PES in terms of safety and efficacy was maintained at 2 years. Indeed, the event curves continued to diverge in favor of the EES. This difference, at 2 years, was driven by reductions in both MI and TVR. At 1 year, the EES group showed a significant absolute risk reduction of 2.6% compared with the PES group in the rate of a first MI. The magnitude of the difference for this safety endpoint widened in the subsequent year, resulting in an absolute risk reduction of 3.6% at 2 years for the EES group. The COMPARE, SPIRIT III, and SPIRIT IV trials all showed either a significant reduction or a trend toward fewer MIs with the EES in the first 30 days (2– 4). That might reflect differences in stent design, leading to less side branch compromise with the EES (4). Our results suggest that other mechanisms may also contribute. When periprocedural and early (30 days) events were excluded, we observed that event curves significantly diverged from the 30-day timepoint up to 2 years (data not shown). A similar trend (p = 0.22) was noted in the pooled SPIRIT II and III trial reports; between 1- year and 2-year follow-up, MI occurred in 0.8% of EES patients versus 1.7%

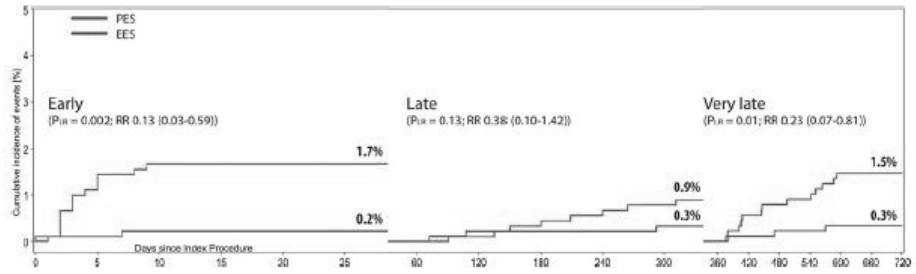

Figure 5 Kaplan-Meier Cumulative Event Curves for Early, Late, and Very Late ST

Kaplan-Meier cumulative event curves for definite and probable stent thrombosis (ST) in the (A) early, (B) late, and (C) very late time periods, as defined by the Academic Research Consortium. Red lines indicate PES; blue lines indicate EES. RR = relative risk; other abbreviations as in Figure 2.

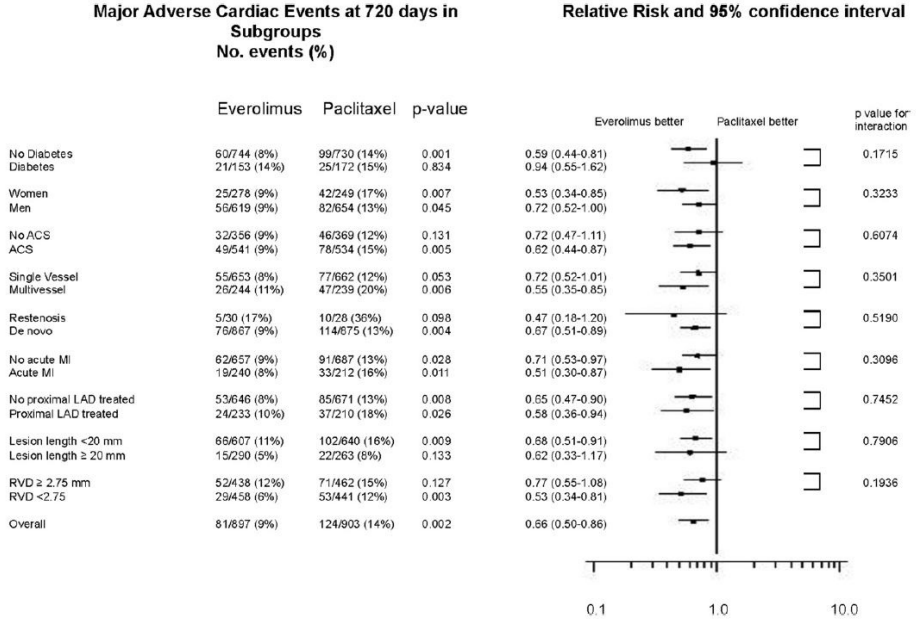

Figure 6 Post-Hoc Subgroup Analysis

Results of a post-hoc subgroup analysis performed with 9 clinical or angiographic variables. The treatment effect was consistent across subgroups, apart from patients with diabetes mellitus. However, the test for interaction was not significant. ACS = acute coronary syndrome; LAD = left anterior descending artery; MI = myocardial infarction; RVD = reference vessel diameter.

of PES patients (5). As previously reported, the rate of ST in the COMPARE study at 1 year was significantly lower with EES. Between 1 and 2 years, there was a further significant divergence of the event curves due to a significantly lower definite and probable ST in the EES group, despite low rates of DAPT, which were not protocol mandated after 1 year. The small, but significantly higher rate of DAPT in the PES group at 2 years parallels differences in MI and ST rates, events that likely led to prolongation or reinstitution of DAPT. With first-generation DES, the promising low ST rates in initial clinical trials (6) have shown a consistent increase as the patient populations enrolled expanded from those with favourable "research" lesions to "real-world" lesions. Registry studies have clearly demonstrated a continuing risk of very late ST, with annual increments in ST of 0.4% and 0.6% for SES and PES, respectively (7,8). In our all-comer trial, the annual increase of definite ST with PES was comparable (0.7%). Against this background, the ST rates reported with EES to date are much lower and of the same order of magnitude as for bare-metal stents (6,7,9). Two-year pooled (892 patients) STrates for the SPIRIT II and III studies, with restrictive inclusion criteria, showed a 1.2% rate of probable or definite ST, remarkably similar to that of COMPARE (0.9%) (5).

Differences in stent design, strut thickness, delivery platform, polymer coating, drug, and drug release profile could all play a role in the difference in ST rates between PES and EES.

Other potential explanations may be more rapid reendothelialization with EES, documented in the rabbit iliac model, or the more biocompatible fluorinated copolymer (10–12). Both TLR and TVR were significantly lower for EES at 2 years, with relative risk reductions of 55% and 60%, respectively. Between 1 and 2 years, the absolute difference for TVR between the PES and EES groups increased significantly from 3.5 to 4.8%. The recently published SPIRIT IV trial showed results for safety and efficacy endpoints similar to those for the COMPARE trial at 1 year of follow-up (4). At 2-year follow-up, there was a continuing benefit of EES in TLF and ST rates. However, no divergence of the curves between 1 and 2 years was observed. Whether the inclusion of patients and lesions at lower risk in the SPIRIT IV study or the very high rate (72%) of DAPT at 2-year follow-up might account for this discordance is unclear (13).

CONCLUSIONS

In summary, we have shown that the substantial clinical benefit of the EES Xience V stent over the PES Taxus Liberté with regard to measures of both

safety and efficacy is maintained at 2 years in real-life practice with an increasing benefit in terms of safety and efficacy

between 1 and 2 years. Further research is required to understand the lack of benefit of EES over PES in the diabetic population.

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Chapter 2.3

Everolimus-eluting stents and paclitaxel-eluting stents in patients presenting with myocardial infarction: insights from the two year results of the COMPARE prospective randomised controlled trial

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ABSTRACT

Aims:
Although large clinical trials have shown that everolimus-eluting stents (EES) significantly reduce target vessel revascularisation (TVR), myocardial infarction (MI) and stent thrombosis (ST) compared to paclitaxel-eluting stents (PES) in diverse populations, there is a paucity of data comparing EES and PES in patients presenting with MI.

Methods and results:
We performed a *post hoc* subgroup analysis on COMPARE, an all-comer trial comparing EES to PES. We identified 863 patients (EES=434, PES=429 treated for MI: 452 ST-elevation MI (STEMI) and 411 non ST-elevation MI (NSTEMI). EES was associated with a significant reduction in the primary endpoint, a composite of all-cause mortality, MI, and TVR, at two years (RR=0.57; 95% CI: 0.40- 0.83, p=0.002). While the effect was more marked in the STEMI (RR=0.51; 95%CI: 0.30-0.87, p=0.01) than the NSTEMI subgroup (RR=0.65; 95% CI: 0.39-1.08, p=0.09), the interaction p value (0.5) suggests that a difference in treatment effect between presentations is unlikely. ST rates were significantly lower with EES (RR=0.30; 95% CI: 0.12-0.73, p=0.005).

Conclusions:
At two years, EES results are superior to PES in terms of safety and efficacy endpoints in treatment of MI.

INTRODUCTION

Paclitaxel-eluting stents (PES) and sirolimus-eluting stents (SES) substantially reduce the need for re-intervention compared to bare metal stents.[1,2] However, increased rates and ongoing propensity for stent thrombosis (ST) remain a matter of concern.[3-7] Specific concerns have been raised with respect to the unrestricted use of first generation DES in patient populations presenting with AMI.[8] Second generation drug-eluting stents were designed to improve safety, efficacy and procedural success rates. Specifically, a second generation, thin-strut, cobalt-chromium, everolimus-eluting stent (EES) demonstrated significant improvements in angiographic and clinical outcomes when compared to PES in two early randomised trials.[9,10] Thereafter, two large clinical trials, SPIRIT IV and COMPARE, independently demonstrated that the EES was superior to the PES with regard to broadly similar primary composite safety and efficacy endpoints in less selected populations.[11-14] Both trials showed strikingly similar relative risk reductions in thrombotic events with EES compared with PES at 30 day, 1- and 2-year follow- up. No study has compared EES with PES in patients presenting with myocardial infarction (MI). To investigate whether these promising results with EES can be replicated in this high risk category of patients, we performed a *post hoc* subgroup analysis comparing the outcomes of EES and PES in patients treated for MI in the COMPARE trial.

METHODS

We performed a subgroup analysis of patients presenting with myocardial infarction from the population of the COMPARE trial.[12] The methodology of the COMPARE trial has been published previously.[12] In summary, consecutive patients, between 18 and 85 years, referred to the Maasstad Ziekenhuis (Hospital) Cardiology Centre for elective or emergent percutaneous coronary intervention, were eligible to participate in the study. There were no limitations on the number of lesions or vessels, on the location of lesions, or on their length. Exclusion criteria were contraindications or expected nonadherence to dual antiplatelet drug therapy in the 12 months after the procedure; planned major surgery within 30 days; inability or refusal to comply with follow-up procedures; participation in other coronary-device trials; and inability to give informed consent. For the present analysis, the same primary and secondary endpoints as well as the same definitions as for the COMPARE trial were used[12].

As the majority of patients were treated in the setting of an evolving MI, the periprocedural infarctions were adjudicated in the following manner: If the peak total CK (or CK-MB) from the index infarction had not yet been reached: recurrent chest pain lasting >20 minutes (or new ECG changes consistent with MI) AND the peak CK (or CK-MB in absence of CK) level measured within 24 hours after the event is elevated by at least 50% above the previous level.

If the elevated CK (or CK-MB) levels from the index infarction are falling or have returned to normal within 24 hours post-index PCI: either a new elevation of CK >2 x ULN within 24 hours post-index PCI if the CK level has returned to <ULN or a rise by >50% above the previous nadir level if the CK level has not returned to <ULN. Randomisation was performed by means of sealed, opaque, sequentially numbered allocation envelopes after passage of the guidewire. The allocation schedule was based on computer-generated random numbers. (SAS, release 8.02; Cary, NC, USA). Patients were assigned on a 1:1 basis to treatment with a polymer-based, everolimus-eluting stent (XIENCE V®, Abbott Vascular, Santa Clara, CA, USA) or a polymer-based, paclitaxel-eluting stent (Taxus Liberté™, Boston Scientific, Natick, MA, USA). Staged procedures were permitted, and the same stent type, allocated at initial randomisation, was used. All patients provided written informed consent. The study was investigator-initiated. Funding for the study was provided by unrestricted research grants from Abbott Vascular and Boston Scientific, who had no involvement in the design, conduct or analysis of the study. The study complied with the Declaration of Helsinki regarding investigation in humans and was approved by the Institutional Ethics committee of the Maasstad Ziekenhuis, Rotterdam, Netherlands and the Dutch Central Committee on Research Involving Human Subjects (CCMO trial nr: NL15206.101.06).

Medication

All patients not on dual antiplatelet therapy received a dose of 100 or 300 mg aspirin and 300 or 600 mg of clopidogrel before the procedure. The higher doses of aspirin and clopidogrel were given to patients in acute settings. An initial bolus of unfractionated heparin (70 to 100 IU/kg) was given to all patients, and additional boluses given to achieve and maintain an activated clotting time of >250 seconds, which was checked every 30 minutes. The use of bivalirudin or low-molecular heparin was prohibited. The use of glycoprotein

IIb/IIIa antagonists was at the discretion of the operator, even in the setting of primary PCI. At the time of discharge, all patients were receiving 100 mg of aspirin once daily for an indefinite period, as well as 75 mg of clopidogrel daily for 12 months.

Study endpoints and definitions

Adverse events were assessed in the hospital, and at 1, 12 and 24 months. Data were collected by study monitors who visited the hospitals where follow-up was undertaken, reviewed the patients' clinical notes, and collected the source documents. Furthermore, medical questionnaires were posted to all patients at 1, 6, 12 and 24 months to check for adverse events and establish current antiplatelet medication. In case of no response, information was obtained by telephone contact. Data were stored in our institution. Data processing and adjudication of adverse events, including stent thrombosis, were done by an independent contract research organisation and corelab (Cardialysis, Rotterdam, The Netherlands).

The pre-specified primary endpoint was a composite of all death, non-fatal myocardial infarction and target vessel revascularisation at 12 months. The secondary endpoints were the primary endpoint at two year follow-up and the composite of major adverse cardiac events (cardiac death, non-fatal myocardial infarction and clinically driven target-lesion revascularisation at two year follow-up). The same endpoints and definitions were used as well in this current study. Definitions of endpoints are presented elsewhere.[12] Acute myocardial infarction was defined as a typical rise and fall in concentrations of troponin or creatinine kinase-MB with at least one of the following: ischaemic symptoms, development of pathological Q-waves, ischaemic electrocardiographic changes or pathological findings of an acute myocardial infarction. ST-elevation MI was defined as patients with ST segment elevation: new or presumed new ST segment elevation at the J point in two or more contiguous leads with the cut-off points $\geq$0.2 mV in leads V1, V2, or V3 and $\geq$0.1 mV in other leads (contiguity in the frontal plane is defined by the lead sequence aVL, I, inverted aVR, II, aVF, III).[15]

Statistical analysis

A new database with only patients presenting with MI was created. Categorical variables of all AMI patients were evaluated using the chi-square or Fisher's exact tests, whereas continuous variables were evaluated using the Wilcoxon rank-sum test. The time to the pre-specified endpoints was evaluated according to the Kaplan-Meier method and the log-rank test was applied to compare the incidence of the endpoints between groups. Relative risks with 95% confidence intervals, were calculated using the delta method for binomially distributed data. This analysis was performed for all MI patients as well as for patients presenting with non-ST elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI) separately. Formal interaction

testing was performed to determine whether treatment for NSTEMI or STEMI influenced the relative risk of EES versus PES for the occurrence of primary and secondary endpoints at two years. The statistical analysis was performed according to the intention to treat principle. All p values were two-sided, and a p value of less than 0.05 was considered to indicate statistical significance. Analyses were performed using SAS version 8.02 (SAS Institute Inc. Cary, NC, USA).

RESULTS

From the COMPARE database we identified 863 patients (EES=434, PES=429) that were treated with PCI for MI. From these patients 452 (EES=240, PES=212) had a STEMI at presentation and 411 patients were treated for NSTEMI (EES=217, PES=194). Baseline demographic and angiographic data. The baseline demographic data is presented in Table 1. Baseline characteristics did not differ significantly between groups. The use of DAPT was also similarly distributed in both groups (Table 2). The use of glycoprotein IIbIIIa blockers did not differ significantly between groups in the overall population (49.8% vs. 49.6% in EES and PES, respectively) or in the subgroup undergoing primary PCI for STEMI (62.6% vs. 61.1% in EES and PES, respectively). In addition, the angiographic findings were similar between groups. No significant differences were observed in lesion numbers and distribution, lesions quantified coronary analysis results, TIMI flow at baseline and presence of thrombus. Although the total stent length was similar between the two groups, a slight, but not significantly, higher number of stents was used in the EES group (Table 3). This dissimilarity can be attributed to the difference in the maximal device length available for use (32 mm for PES and 28 mm for EES) during the trial. TIMI flow 0 (60% vs. 55.2%, p=0.3) and the use of thrombosuction catheters (47.3% vs. 46.2% p=0.6) during primary PCI for STEMI did not differ significantly in EES and PES respectively. There were no statistical differences in angiographic baseline characteristics between EES and PES groups in either STEMI or NSTEMI subgroups.

Clinical outcomes

Table 4 shows the clinical outcomes at 30 days, one year and two years follow-up. At one year, the primary endpoint, a patient oriented composite of all-cause mortality, non-fatal MI and TVR, occurred in 28 (6.4%) of patients in the EES group versus 45 (10.5%) in the PES (RR=0.62; 95% CI:0.39-0.97, p=0.03). At

Table 1: Baseline characteristics:

	Everolimus- eluting stent (n=434)	Paclitaxel-eluting stent (n=429)	P-value
Age (years)	61.5 ±11.5	62.4± 11.8	0.23
Men	302 (69.6%)	318 (74.1%)	0.14
Diabetes mellitus	62 (14.3%)	63 (14.7%)	0.87
- not insulin dependent	52 (12.0%)	45 (10.5%)	0.49
- insulin dependent	10 (2.3%)	18 (4.2%)	0.12
Hypertension	180 (41.5%)	184 (43.0%)	0.65
Hypercholesterolaemia	180 (41.5%)	162 (37.8%)	0.26
Current smoker	191 (44.0%)	166 (38.7%)	0.11
Family History of CAD	189 (43.6%)	192 (44.8%)	0.72
History of MI	52 (12.0%)	52 (12.1%)	0.95
History of PCI	33 (7.6%)	30 (7.0%)	0.73
History of CABG	15 (3.5%)	16 (3.7%)	0.83
Non-ST segment elevation MI	194 (44.7)	217(50.6)	0.08
ST segment elevation MI	240 (55.3)	212 (49.4)	0.08
Glycoprotein IIbIIIa antagonists	213 (49.8%)	213 (49.6%)	0.89
Multivessel treatment	111 (25.6)	101 (23.6)	0.50
Number of lesions treated per patient	1.4 (0.7)	1.4 (0.7)	0.27

Values are percentages or mean ±SD; CABG: coronary artery bypass grafting; CAD: coronary artery disease; MI: myocardial infarction; PCI: percutaneous coronary intervention

the two year follow-up, the primary endpoint occurred in 40 (9.2%) of patients assigned to EES and 69 (16.1%) of patients assigned to PES (RR=0.57; 95% CI: 0.40-0.83, p=<0.002). This difference was mainly driven by a significantly lower rate of both non-fatal myocardial infarction and target vessel revascularisation at one and two years in patients with EES; all-cause mortality did not differ significantly between treatment groups **(Figure 1)**. At two years, the primary endpoint remained significantly lower for EES treated patients in STEMI (EES: 19 (7.9%) vs. PES: 33 (15.6%); RR=0.51; 95% CI: 0.30-0.87, p=0.01) where it was mainly driven by a significant reduction in TVR and a trend towards less non-fatal MI. The primary endpoint was also lower for EES treated patients in NSTEMI (EES: 21 (10.8%) vs. PES 36 (16.6%); RR=0.65; 95% CI: 0.39-1.08, p=0.09) but failed to reach significance. The same trend was observed also for the TVR and non-fatal MI in this subgroup whereas no clinically relevant differences were observed in all-cause mortality. However, the results of formal interaction testing for the primary and secondary endpoint resulted in a RR for interaction of 1.13; 95% CI: 0.79-1.63, interaction p=0.5 and 1.05; 95% CI: 0.70-1.56 interaction p=0.8, respectively, suggesting that a difference in

Table 2: Antiplatelet therapy for the entire patient population presenting with AMI and in the subgroups presenting with NSTEMI and STEMI

	All AMI			NSTEMI			STEMI		
	Everolimus-eluting stent (n=434)	Paclitaxel-eluting stent (n=429)	p value	Everolimus-eluting stent (n=194)	Paclitaxel-eluting stent (n=217)	p value	Everolimus-eluting stent (n=240)	Paclitaxel-eluting stent (n=212)	p value
Discharge									
Aspirin	94·8% (404/426)	95.7% (403/421)	0·54	95·8% (184/192)	95.3% (202/212)	0·79	94·0% (220/234)	96.2% (201/209)	0·30
Clopidogrel	99·1% (422/426)	99·8% (420/421)	0·37	99·5% (191/192)	99·5% (211/212)	1.00	98·7% (231/234)	100·0% (209/209)	0·25
Aspirin + Clopidogrel	94.4% (402/426)	95·5% (402/421)	0·46	95.3% (183/192)	94.8% (201/212)	0·82	93.6% (219/234)	96.2% (201/209)	0·22
6-months									
Aspirin	93·9% (398/424)	93·0% (386/415)	0·62	96·3% (184/191)	92·9% (196/211)	0·13	91·8% (214/233)	93·1% (190/204)	0·61
Clopidogrel	96·9% (411/424)	98·3% (408/415)	0·19	95·8% (183/191)	97·2% (205/211)	0·46	97·8% (228/233)	99·5% (203/204)	0·22
Aspirin + Clopidogrel	91·8% (389/424)	91·3% (379/415)	0·83	92·7% (177/191)	90·0% (190/211)	0·35	91·0% (212/233)	92·6% (189/204)	0·53
1-Year									
Aspirin	94·8% (400/422)	91·9% (376/409)	0·10	98·9% (187/189)	92·2% (190/206)	0·001	91·4% (213/233)	91·6% (186/203)	0·94
Clopidogrel	77·7% (328/422)	77·3% (316/409)	0·87	73.5% (139/189)	76·2% (157/206)	0·54	81·1% (189/233)	78·3% (159/203)	0·47
Aspirin + Clopidogrel	73·9% (312/422)	70·2% (287/409)	0·23	72·5% (137/189)	69·9% (144/206)	0·57	75·1% (175/233)	70·4% (143/203)	0·27
2-Years									
Aspirin	91·1% (379/416)	92·8% (373/402)	0·38	95·1% (174/183)	93·6% (189/202)	0·52	88·0% (205/233)	92·0% (184/200)	0·17
Clopidogrel	14·9% (62/416)	17·7% (71/402)	0.29	12.6% (23/183)	16·8% (34/202)	0.24	16·7% (39/233)	18·5% (37/200)	0.63
Aspirin + Clopidogrel	12·5% (52/416)	15·9% (64/402)	0.16	10·9% (20/183)	14·8% (30/202)	0.25	13·7% (32/233)	17·0% (34/200)	0.35

Table 3: Lesion characteristics

Characteristic	Everolimus- eluting stent (619 lesions)	Paclitaxel- eluting stent (589 lesions)	p value
Target lesion coronary artery			
Left main	7 (1.1%)	8 (1.4%)	0.72
Left anterior descending	245 (39.6%)	213 (36.2%)	0.14
Left circumflex	152 (24.6%)	161 (27.3%)	0.22
Right	215 (34.7%)	207 (35.1%)	0.87
Bypass graft	15 (2.4%)	9 (1.5%)	0.67
ACC-AHA lesion class			
A	37 (6.0%)	16 (2.7%)	0.01
B1	117 (18.9%)	122 (20.7%)	0.43
B2	176 (28.4%)	188 (31.9%)	0.21
C	289 (46.7%)	263 (44.6%)	0.51
De novo lesions	602 (97.2%)	582 (98.6%)	0.14
Thrombus present	272 (43.9%)	262 (44.5%)	0.87
Calcified lesion	172 (27.8%)	174 (29.5%)	0.47
Lesion length, mm (N)	22.3±17.2 (346)	22.8±19.1 (354)	0.68
Reference vessel diameter, mm (N)	2.67±0.58 (419)	2.70±0.65 (412)	0.55
Baseline minimal luminal diameter., mm (N)	0.78±0.58 (436)	0.84±0.58 (435)	0.10
Baseline stenosis, % lumen diameter (N)	72.4±21.2 (469)	70.7±20.4 (452)	0.22
Pre procedure TIMI flow			
Grade 0	171 (27.6%)	151 (25.6%)	0.45
Grade 1	32 (5.2%)	36 (6.1%)	0.49
Grade 2	58 (9.4%)	66 (11.2%)	0.20
Grade 3	358 (57.8%)	336 (57.0%)	0.78
Number of stents per lesion*	1.6±0.8	1.5±0.8	0.06
Total stent length per lesion (mm)*	33.5±19,0)	33.0±21.5	0.70

TIMI flow: Thrombolysis in myocardial infarction flow. * data presented as mean± standard deviation

Table 4. Events and Endpoints

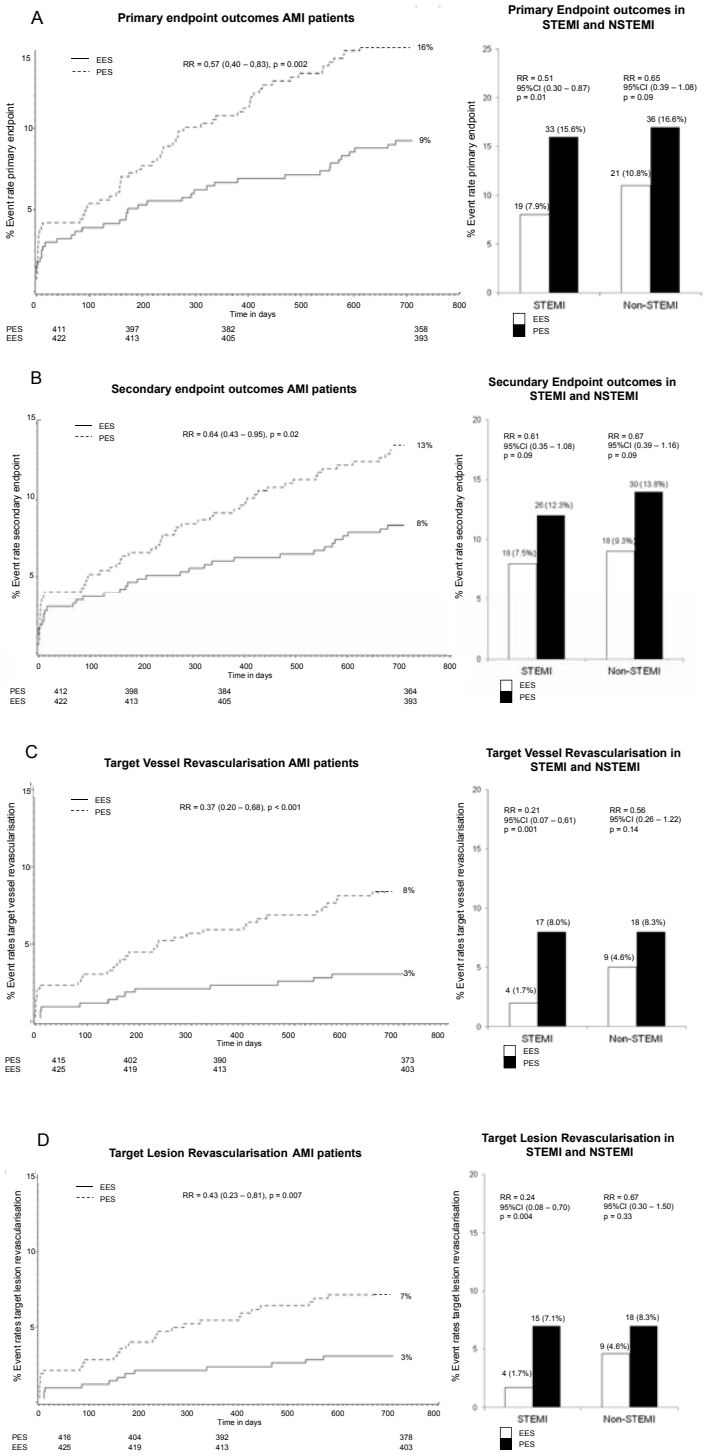
	Everolimus-eluting stent (N=434)	Paclitaxel-eluting stent (N=429)	Relative Risk (95% CI)	p value
Events at 30 days				
All-cause death	6 (1.4%)	5 (1.2%)	1.19 (0.36-3.86)	0.78
Cardiac death	6 (1.4%)	5 (1.2%)	1.19 (0.36-3.86)	0.78
Myocardial infarction	5 (1.2%)	11 (2.6%)	0.44 (0.16-1.28)	0.12
Q-wave	2 (0.5%)	3 (0.7%)	0.66 (0.11-3.92)	0.69
Non-Q-wave	3 (0.7%)	8 (1.9%)	0.37 (0..10-1.39)	0.12
Mortality or myocardial infarction	10 (2.3%)	15 (3.5%)	0.66 (0.30-1.45)	0.30
Cardiac mortality or myocardial infarction	10 (2.3%)	15 (3.5%)	0.66 (0.30-1.45)	0.30
TVR (Clinically Driven)	3 (0.7%)	9 (2.1%)	0.33 (0.09-1.21)	0.08
Percutaneous	0 (0.0%)	8 (1.9%)	N.A.	0.004
Surgical	3 (0.7%)	1 (0.2%)	2.97 (0.31-28.4)	0.62
TVR (Any)	3 (0.7%)	9 (2.1%)	0.32 (0.09-1.21)	0.078
Percutaneous	0 (0.0%)	8 (1.9%)	N.A.	0.004
Surgical	3 (0.7%)	1 (0.2%)	2.97 (0.31-28.4)	0.62
TLR (Clinically Driven)	3 (0.7%)	8 (1.9%)	0.37 (0.10-1.39)	0.12
Percutaneous	0 (0.0%)	7 (1.6%)	N.A.	0.007
Surgical	3 (0.7%)	1 (0.2%)	2.97 (0.31-28.4)	0.62
TLR (Any)	3 (0.7%)	8 (1.9%)	0.37 (0.10-1.39)	0.12
Percutaneous	0 (0.0%)	7 (1.6%)	N.A.	0.007
Surgical	3 (0.7%)	1 (0.2%)	2.97 (0.31-28.4)	0.62
Primary endpoint †	12 (2.8%)	17 (4.0%)	0.70 (0.34-1.44)	0.33
Secondary endpoint ‡	12 (2.8%)	16 (3.7%)	0.74 (0.35-1.55)	0.42
ST *(Definite and Probable)*	1 (0.2%)	9 (2.1%)	0.11 (0.01-0.86)	0.01
Acute (On date of procedure)	0 (0.0%)	1 (0.2%)	N.A.	0.50
Sub-Acute (1-30 days post-procedure)	1 (0.2%)	8 (1.9%)	0.12 (0.02-0.98)	0.020
(Definite)	1 (0.2%)	7 (1.6%)	0.14 (0.02-1.14)	0.037
Acute (On date of procedure)	0 (0.0%)	1 (0.2%)	N.A.	0.50
Sub-Acute (1-30 days post-procedure)	1 (0.2%)	6 (1.4%)	0.16 (0.02-1.36)	0.068
Events at 12 months				
All-cause death	11 (2.5%)	14 (3.3%)	0.78 (0.36-1.69)	0.52
Cardiac death	8 (1.8%)	9 (2.1%)	0.88 (0.34-2.26)	0.79
Myocardial infarction	13 (3.0%)	24 (5.6%)	0.54(0.28-1.04)	0.06
Q-wave	2 (0.5%)	4 (0.9%)	0.49 (0.09-2.68)	0.45
Non Q-wave	11 (2.5%)	20 (4.7%)	0.54 (0.26-1.12)	0.09
mortality or myocardial infarction	23 (5.3%)	37 (8.6%)	0.61 (0.37-1.02)	0.06
Cardiac mortality or myocardial infarction	20 (4.6%)	32 (7.5%)	0.62 (0.36-1.06)	0.08

	Everolimus-eluting stent (N=434)	Paclitaxel-eluting stent (N=429)	Relative Risk (95% CI)	p value
TVR (Clinically Driven)	9 (2.1%)	23 (5.4%)	0.39 (0.18-0.83)	0.01
Percutaneous	5 (1.2%)	18 (4.2%)	0.27 (0.10-0.73)	0.006
Surgical	4 (0.9%)	5 (1.2%)	0.79 (0.21-2.92)	0.75
TVR (Any)	9 (2.1%)	24 (5.6%)	0.37 (0.17-0.79)	0.007
Percutaneous	5 (1.2%)	19 (4.4%)	0.26 (0.10-0.69)	0.003
Surgical	4 (0.9%)	5 (1.2%)	0.79 (0.21-2.92)	0.75
TLR (Clinically Driven)	9 (2.1%)	20 (4.7%)	0.44 (0.20-0.97)	0.03
Percutaneous	5 (1.2%)	16 (3.7%)	0.31 (0.11-0.84)	0.01
Surgical	4 (0.9%)	4 (0.9%)	0.99 (0.25-3.93)	1.0
TLR (Any)	9 (2.1%)	22 (5.1%)	0.40 (0.19-0.87)	0.02
Percutaneous	5 (1.2%)	18 (4.2%)	0.27 (0.10-0.73)	0.006
Surgical	4 (0.9%)	4 (0.9%)	0.99 (0.25-3.93)	1.0
Primary endpoint †	28 (6.4%)	45 (10.5%)	0.62 (0.39-0.97)	0.03
Secondary endpoint ‡	25 (5.8%)	38 (8.9%)	0.65 (0.40-1.06)	0.08
ST (Definite and Probable)	3 (0.7%)	13 (3.0%)	0.23 (0.07-0.79)	0.012
Late (30 days – 1 year post procedure)	2 (0.5%)	4 (0.9%)	0.49 (0.09-2.68)	0.45
Definite	1 (0.2%)	10 (2.3%)	0.10 (0.01-0.77)	0.006
Late (30 days – 1 year post procedure)	0 (0.0%)	3 (0.7%)	N.A.	0.12
Events at 24 months				
All-cause death	17 (3.9%)	21 (4.9%)	0.80 (0.43-1.50)	0.48
Cardiac death	13 (3.0%)	13 (3.0%)	0.99 (0.46-2.11)	0.98
Myocardial infarction	18 (4.2%)	35 (8.2%)	0.51 (0.29-0.88)	0.01
Q-wave	2 (0.5%)	8 (1.9%)	0.25 (0.05-1.16)	0.06
Non Q-wave	16 (3.7%)	27 (6.3%)	0.59 (0.32-1.07)	0.08
Mortality or myocardial infarction	33 (7.6%)	55 (12.8%)	0.59 (0.39-0.89)	0.01
Cardiac mortality or myocardial infarction	29 (6.7%)	47 (11.0%)	0.61 (0.39-0.95)	0.03
TVR (Clinically Driven)	13 (3.0%)	34 (7.9%)	0.38 (0.20-0.71)	0.001
Percutaneous	9 (2.1%)	26 (6.1%)	0.34 (0.16-0.72)	0.003
Surgical	4 (0.9%)	9 (2.1%)	0.44 (0.14-1.42)	0.16
TVR (Any)	13 (3.0%)	35 (8.2%)	0.37 (0.20-0.68)	< 0.001
Percutaneous	9 (2.1%)	27 (6.3%)	0.33 (0.16-0.69)	0.002
Surgical	4 (0.9%)	9 (2.1%)	0.44 (0.14-1.42)	0.16
TLR (Clinically Driven)	13 (3.0%)	28 (6.5%)	0.46 (0.24-0.87)	0.02
Percutaneous	9 (2.1%)	23 (5.4%)	0.39 (0.18-0.83)	0.01
Surgical	4 (0.9%)	6 (1.4%)	0.66 (0.19-2.32)	0.54
TLR (Any)	13 (3.0%)	30 (7.0%)	0.43 (0.23-0.81)	0.007
Percutaneous	9 (2.1%)	25 (5.8%)	0.36 (0.17-0.75)	0.005

	Everolimus-eluting stent (N=434)	Paclitaxel-eluting stent (N=429)	Relative Risk (95% CI)	p value
Surgical	4 (0.9%)	6 (1.4%)	0.66 (0.19-2.32)	0.54
Primary endpoint †	40 (9.2%)	69 (16.1%)	0.57 (0.40-0.83)	0.002
Secondary endpoint ‡	36 (8.3%)	56 (13.1%)	0.64 (0.43-0.95)	0.02
Stent Thrombosis ARC *(Definite and Probable)*	6 (1.4%)	20 (4.7%)	0.30 (0.12-0.73)	0.005
Late (30 days – 1 year)	2 (0.5%)	4 (0.9%)	0.49 (0.09-2.68)	0.45
Very late (1year – 2 year)	3 (0.7%)	7 (1.6%)	0.42 (0.11-1.63)	0.22
(Definite)	3 (0.7%)	14 (3.3%)	0.21 (0.06-0.73)	0.007
Late (30 days – 1 year)	0 (0.0%)	3 (0.7%)	N.A.	0.12
Very late (1year – 2 year)	2 (0.5%)	4 (0.9%)	0.49 (0.09-2.68)	0.45

ST = stent thrombosis; TLR = target lesion revascularisation; TVR = target vessel revascularisation; ARC = Academic Research Consortium

treatment effect in the NSTEMI subgroup and the remaining patients from the MI population (STEMI subgroup) is unlikely. The secondary endpoint, a device-oriented composite of cardiac death, non-fatal MI and TLR, at two years, occurred in 36 (8.3%) of patients assigned to EES and in 56 (13.1%) assigned to PES, (RR=0.64; 95% CI: 0.43-0.95, p=0.02). Similar to the primary endpoint, this difference was driven by a reduction in rates of both nonfatal MI and TLR, while no differences were observed in the rates of cardiac death **(Figure 1 and Table 4)**. The stent thrombosis (definite and probable) rate at two years was significantly lower in the EES group: six (1.4%) compared to PES group: 20 (4.7%); RR=0.30; 95%CI: 0.12-0.73, p=0.005). As was the case in the general COMPARE population, a significant reduction in ST (definite and probable) was already evident at 30 days (EES: 1 (0.2%) vs. PES: 9 (2.1%); RR=0.11; 95%CI: 0.01-0.86, p=0.01) and the curves continued to diverge to the end of the second year **(Figure 2A)**. A significant reduction in ST (definite and probable) was also observed **(Figure 2B)** also in the NSTEMI group at one year (EES: one (0.5%) vs. PES: nine (4.2%); RR=0.12; 95%CI: 0.02-0.97, p=0.02) and two years (EES: three (1.6%) vs. PES 13(6.0%); RR=0.26; 95%CI: 0.07-0.89, p=0.02). In the STEMI subgroup, the ST rates were lower in the EES group but the observed reduction in ST did not reach statistical significance **(Figure 2C)**. The lower rates of ST in the overall MI population treated with EES paralleled significantly better outcomes in the safety endpoint of all-cause mortality and/or MI, with differences that continued to enhance during the two year follow-up **(Table 4)**.


A
Primary endpoint outcomes AMI patients
EES
PES
RR = 0,57 (0,40 – 0,83), p = 0.002
16%
9%
% Event rate primary endpoint
Time in days
PES 411 397 382 358
EES 422 413 405 393
Primary Endpoint outcomes in STEMI and NSTEMI
RR = 0.51 95%CI (0.30 – 0.87) p = 0.01
RR = 0.65 95%CI (0.39 – 1.08) p = 0.09
19 (7.9%)
33 (15.6%)
21 (10.8%)
36 (16.6%)
STEMI
Non-STEMI
B
Secondary endpoint outcomes AMI patients
RR = 0.64 (0.43 – 0.95), p = 0.02
13%
8%
% Event rate secondary endpoint
PES 412 398 384 364
EES 422 413 405 393
Secundary Endpoint outcomes in STEMI and NSTEMI
RR = 0.61 95%CI (0.35 – 1.08) p = 0.09
RR = 0.67 95%CI (0.39 – 1.16) p = 0.09
18 (7.5%)
26 (12.3%)
18 (9.3%)
30 (13.8%)
C
Target Vessel Revascularisation AMI patients
RR = 0.37 (0.20 – 0.68), p < 0.001
8%
3%
% Event rates target vessel revascularisation
PES 415 402 390 373
EES 425 419 413 403
Target Vessel Revascularisation in STEMI and NSTEMI
RR = 0.21 95%CI (0.07 – 0.61) p = 0.001
RR = 0.56 95%CI (0.26 – 1.22) p = 0.14
4 (1.7%)
17 (8.0%)
9 (4.6%)
18 (8.3%)
D
Target Lesion Revascularisation AMI patients
RR = 0.43 (0.23 – 0.81), p = 0.007
7%
3%
% Event rates target lesion revascularisation
PES 416 404 392 378
EES 425 419 413 403
Target Lesion Revascularisation in STEMI and NSTEMI
RR = 0.24 95%CI (0.08 – 0.70) p = 0.004
RR = 0.67 95%CI (0.30 – 1.50) p = 0.33
4 (1.7%)
15 (7.1%)
9 (4.6%)
18 (8.3%)

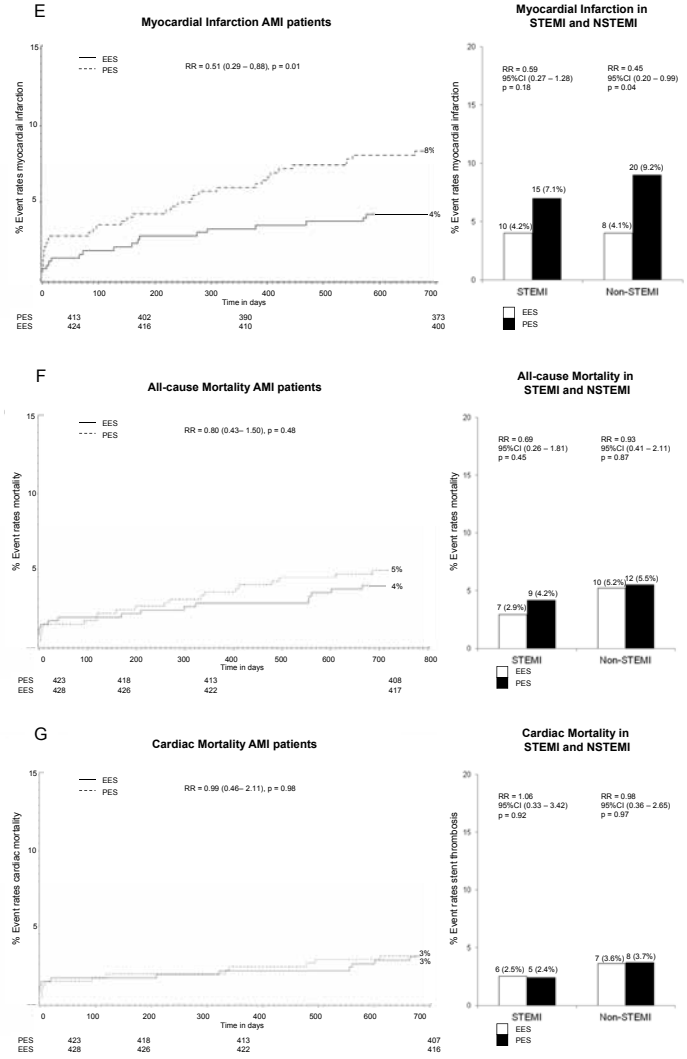


Figure 1 Kaplan-Meier cumulative event curves for all AMI patients and events rates split between STEMI and non-STEMI patients (bars) for **(A)** the primary endpoint, **(B)** secondary endpoint, **(C)** target vessel revascularization (TVR), **(D)** target lesion revascularization (TLR), **(E)** myocardial infarction (MI) and **(F**) All-cause mortality, **(G**) Cardiac mortality.

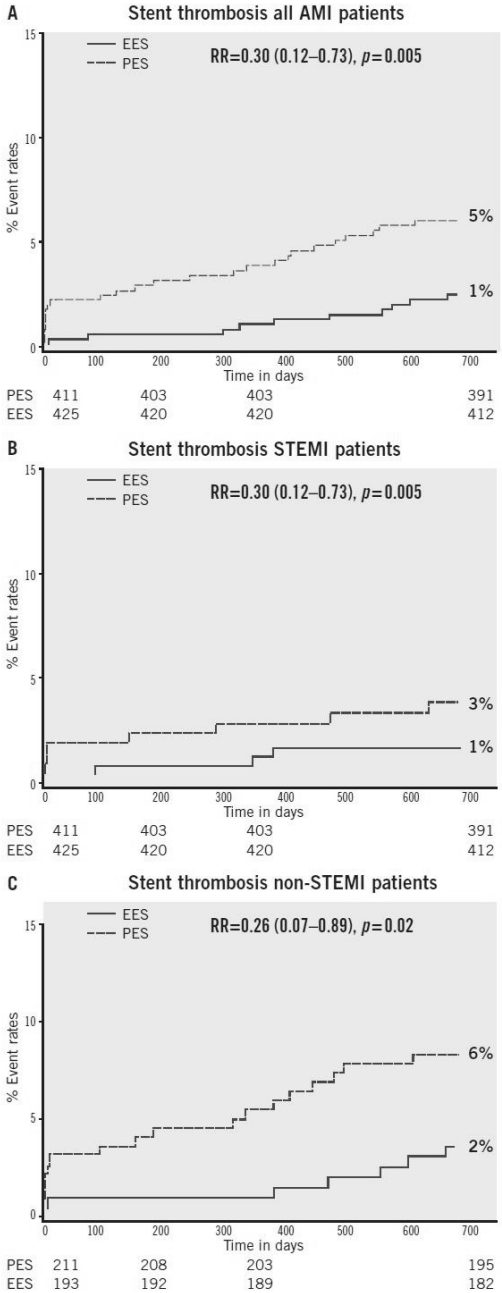


Figure 2 Kaplan-Meier cumulative event curves for stent thrombosis (ST) for **(A)** all AMI patients, **(B)** STEMI patients, **(C)** non-STEMI patients.

DISCUSSION

The major finding of this study is that the use of the second generation EES, compared to PES, during percutaneous coronary intervention for myocardial infarction was associated with a significant reduction in the risk of both the primary endpoint –a patient-oriented composite of all-cause mortality, non-fatal MI and TVR– and the principal secondary endpoint –a device-oriented composite of cardiac mortality, non-fatal MI and TLR. The improvement in event-free survival with the EES was driven by a reduction in repeat TVR, reflecting superiority in terms of efficacy, as well as a reduction in non-fatal MI, a safety component of the primary and secondary endpoint. There were no significant differences in rates of all-cause or cardiac mortality. With respect to the primary and secondary endpoints, the curves separated early and the effect grew in magnitude over the 2-year follow-up period. Another notable finding of this study is that the use of EES was associated with a significant reduction in ST, when compared to PES. The difference in ST outcomes between devices was apparent early and persisted at the end of the second year. As no significant differences were observed in baseline demographic or angiographic outcomes, the pathophysiologic mechanism(s) underlying the marked reduction in ST following EES, although speculative, may relate to specific design features of this stent. The combination of thin fracture-resistant struts, the low dose of everolimus, and the thromboresistant non-inflammatory proprieties of the fluorinated polymer, may contribute to the lower rates of early ST with EES.[16,17] The lower rates of ST following EES at 30 days, one year and two years may be explained by more rapid and complete stent reendothelialisation as observed in pre-clinical animal models.[18] As expected, the reduction in ST was paralleled by a significant reduction in the safety composite of cardiac death or MI. The use of EES was associated with a reduction in major adverse cardiac events in the subgroup of patients presenting with STEMI. This is the first study in which the outcome with EES has been shown to be superior to PES for a composite of all-cause mortality, non-fatal myocardial infarction and target vessel revascularisation, in the setting of STEMI. However, our findings are consistent with the results of other studies that used the same stents in this setting. The PES subgroup of the HORIZONS-AMI trial had similar clinical outcomes to the PES subgroup of the present trial.[3] Similarly, the outcomes with EES in our study are consistent with those observed in the STEMI subgroup of the RESOLUTE ALL-COMER trial.[19] In the NSTEMI subgroup, a clear trend towards significance, with respect to the primary and secondary endpoint, was observed with EES. As the interaction p values for the primary and second-

ary endpoints, were not significant, it appears reasonable to conclude that a difference in the treatment effect tendency between STEMI and NSTEMI is unlikely. Taken together, these findings suggest that the previously documented superiority, with regards to efficacy and safety endpoints, observed with EES can be extended to a high risk patient population presenting with AMI[11,12]. The ST rates with EES in the current study are comparable and numerically superior to those reported with BMS in historical comparisons[20-22]. This conclusion is also supported by the findings of the recently presented EXAMINATION trail, where EES is associated with significantly lower rates of definite as well as definite and probable ST compared to identically designed BMS, in setting of STEMI.[23] More widespread use of DES for treatment of AMI should be guided by cost effectiveness trials now that safety concerns have been largely resolved. This study has several limitations. This study presents a subgroup analysis from the randomised COMPARE study. However, randomisation was not stratified for the current subgroups, and therefore the number of patients in each treatment arm is not completely balanced. Nevertheless, the baseline characteristics were well matched between groups. The study was not powered for any of the individual endpoints therefore, for certain endpoint components, this may result in beta-errors, especially when data are further divided and analysed in STEMI and NSTEMI subgroups. Therefore, larger randomised trials will be needed in the setting of MI. Finally, these results reflect the outcomes of PCI for treatment of MI from a single tertiary centre.

In conclusion, we have shown that the use of second-generation EES as compared to PES, is associated with significantly better outcomes, in terms of safety and efficacy endpoints at two year follow-up in patients presenting with MI. The use of EES compared to PES, is also associated with a significant reduction in rates of ST in MI patients. However, larger randomised trials, as well as cost-effectiveness analysis are required to further guide device choice in this setting.

CONFLICT OF INTEREST STATEMENT

E. Kedhi reports having received lecture fees from Abbott Vascular, Saint Jude Medical and Terumo Europe. P.C. Smits reports having received lecture fees from Abbott Vascular and Terumo Europe. All the other authors report no disclosures.

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Chapter 3.1

Everolimus-eluting stents: insights from the SPIRIT IV and COMPARE trials

Elvin Kedhi & Gregg W. Stone

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The XIENCE V (Abbott Vascular, CA, USA; also distributed as the PROMUS stent by Boston Scientific, MA, USA) everolimus-eluting stent (EES) is a second-generation drug-eluting stent (DES) designed to overcome the limitations of earlier DESs. Clinical studies with first-generation sirolimus-eluting stents (SESs) and paclitaxel-eluting stents (PESs) demonstrated a dramatic reduction in restenosis rates compared with bare-metal stents (BMSs) [1,2]; however, reintervention rates were still high in patients with complex coronary artery disease[3], and an ongoing propensity for stent thrombosis beyond 1 year raised further concerns regarding safety issues with these devices[4] . Furthermore, as both of these devices were relatively high-profile stainless steel stents, they were difficult to deliver in complex anatomy, and the SES in particular was prone to a high fracture rate, contributing to late adverse events.

In the EES, everolimus, a rapamycin derivative, is released from a thin layer (7.8-μm) of a biocompatible fluoropolymer coated on an open-cell, thin-strut (81-μm) flexible and highly deliverable cobalt–chromium stent. The polymer is inert and noninflammatory, and the stent is extremely resistant to fracture. Two moderate-sized trials with the EES demonstrated a significant reduction in angiographic in-stent and in-segment late lumen loss compared with the first-generation TAXUS Express (PES) (Boston Scientific), and noninferiority in major clinical end points [5,6]. These findings suggested that, if tested in larger populations, the EES might achieve superior clinical outcomes compared with the earlier predicate devices. However, given the favorable outcomes with PES, large studies would be required to elicit small differences in low frequency but important clinical end points. Toward this end, two large-scale randomized trials have been performed, the SPIRIT IV and COMPARE trials.

SPIRIT IV was a prospective, multicenter trial that randomized 3690 US patients in a 2:1 ratio to EES versus the TAXUS Express PES [7]. The primary end point was a composite of target lesion failure (defined as cardiac death, target vessel myocardial infarction [MI] or ischemia-driven target lesion revascularization [TLR]); the major secondary end points were ischemia-driven TLR and a composite end point of cardiac death or target vessel MI at 1 year. SPIRIT IV is the largest completed randomized controlled trial comparing two DESs to date, and was powered for sequential testing of noninferiority and superiority in its primary and both major secondary end points. The trial was large enough to provide data on other secondary end points and important subgroups, particularly patients with diabetes mellitus, but excluded patients with acute coronary syndromes (ACSs) and ST-segment elevation MI (STEMI), large bifurcations and other complex lesion subsets.

Almost simultaneously, another prospective, randomized investigator-initiated, single-center study, the COMPARE trial, was performed in The Netherlands [8]. This trial randomized 1800 'all-comer' patients (i.e., with limited exclusion criteria) in a 1:1 ratio between the EES and TAXUS Liberté PES, which shares the same polymer, drug and release kinetics with the TAXUS Express PES, but has thinner struts and more uniform scaffolding. The primary end point of COMPARE was a composite of all-cause mortality, non-fatal MI and clinically driven target vessel revascularization (TVR). Like SPIRIT IV, COMPARE was also powered for both noninferiority and superiority testing. This trial population represents a real-world population as there were no exclusion criteria other than general contraindications for DES (e.g., inability to take dual antiplatelet therapy), and was large enough to provide data on complex patient subsets including those with ACS and STEMI. In contrast to many prior DES studies, routine angiographic follow-up was not performed in either SPIRIT IV or COMPARE to avoid unnecessary and unplanned revascularization procedures [9–11].

Both trials independently showed that the EES was superior to the PES (regardless of the TAXUS platform) with regard to their respective primary composite safety and efficacy end points (Table 1). These results were driven by

Table 1. One year clinical outcomes in the SPIRIT IV and COMPARE traials

Outcomes	SPIRIT IV			COMPARE		
	EES (n = 2458)	PES (n = 1229)	p value	EES (n = 897)	PES (n = 903)	p value
Death	1.0%	1.3%	0.61	2.0%	1.7%	0.58
Cardiac death	0.4%	0.4%	1.00	1.2%	1.1%	0.81
Non cardiac death	0.6%	0.8%	0.52			
MI	1.9%	3.1%	0.02	2.8%	5.3%	0.007
-Q-wave	0.1%	0.4%	0.13	0.3%	1.2%	0.03
-Non-Q-wave	1.7%	2.8%	0.05	2.5%	4.3%	0.03
Target vessel MI	1.8%	2.9%	0.04			
Ischemic TLR	2.5%	4.6%	0.001	1.7%	4.8%	<0.001
Ischemic TVR	3.9%	5.9%	0.009	2.1%	5.6%	<0.001
Stent thrombosis (ARC def/prob†)	0.3%	1.1%	0.003	0.7%	2.5%	0.002
Major adverse cardiac events (death, MI or ischemic TLR)				6.2%	9.1%	0.02
Target lesion failure (cardiac death, target vessel MI or ischemic TLR)	4.2%	6.9%	<0.001			

†Definite and probable stent thrombosis referring to ARC definitions. ARC: Academic Research Consortium; EES: Everolimus-eluting stent; MI: Myocardial infarction; PES: Paclitaxel-eluting stent; TLR: Target lesion revascularization; TVR: Target vessel revascularization.

significant reductions in clinically driven TLR and MI, findings that were in part due to a significant reduction in the rates of stent thrombosis with the EES, as well as to reduced late recurrent ischemia necessitating repeat percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG). No significant differences were observed in the rates of all-cause or cardiac mortality between the different stent platforms at 1 year.

Based on the results of these two trials, the belief that had previously been held by some that clinically relevant differences between DES of various designs do not exist has clearly been discredited. These trials have also shown that low angiographic late loss (resulting in greater efficacy) as well as improved safety may be simultaneously achieved in a single DES platform. Although the lower rates of TLR and TVR with EES were predictable from previous studies in which late loss with EES was significantly lower than with PES, the marked (nearly 75%) reduction in stent thrombosis observed with the EES was a surprising finding in its magnitude. Both trials showed strikingly similar relative risk reductions in thrombotic events with EES compared with PES at 30-day and 1-year follow-up, with the majority of the stent thromboses occurring during the first 30 days. EES reduced stent thrombosis compared with PES in both the early (<30-day) and late (30-day to 1-year) phases. Until recently, the interventional community has been focused on very late stent thrombosis (after 1 year) given the ongoing propensity of first-generation DES to occlude acutely after 1 year when compared with BMS [4,12]. However, early stent thrombosis accounts for the majority of stent thrombosis events during follow-up[13]. This is even more evident in complex populations. In the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) [14] and Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) [3] trials, stent thrombosis rates at 1 year were 3.2 and 3.3%, respectively; 30-day stent thrombosis was responsible for approximately two-thirds of the events in both trials. SPIRIT IV and COMPARE have now demonstrated that use of EES during this critical time period can markedly reduce the incidence of stent thrombosis. Longer-term follow-up from both studies is required to determine whether these findings persist or become even more pronounced. The mechanistic underpinnings of the marked reduction in stent thrombosis with EES (despite low angiographic late loss) are speculative, but may relate to certain stent design features. Specifically, the thinner stent struts in combination with a biocompatible fluoropolymer may result in more rapid strut coverage with functional endothelium[15]. Fluorinated polymers are also known to resist platelet and thrombus deposition[16, 17]. Because these trials

were not designed to study these issues, additional mechanistic studies are required to confirm the reasons underlying the enhanced safety of EES.

Another important finding from the SPIRIT IV and COMPARE trials is that significantly fewer adverse events were observed with EES in complex patient and lesion subgroups, such as multivessel and small-vessel disease, chronic total occlusions, long lesions and ACS. Based on data from the SPIRIT IV and COMPARE trials, we examined how the results of the randomized SYNTAX trial [3], a 1700-patient study of PES versus CABG in patients with left main and three-vessel coronary artery disease, might have been influenced if EES was used in place of PES. SYNTAX showed superiority of CABG compared with PES at 1 year, a finding driven by more revascularization procedures in the PCI arm. In order to reach noninferiority between the PCI and CABG groups, a reduction of 20 events with PCI was needed. Use of EES rather than PES in SYNTAX might have led to a total reduction of 81 events in the PCI group, such that the SYNTAX trial could have declared noninferiority for PCI. This analysis, of course, is only a hypothesis-generating exercise; whether PCI with the EES is truly noninferior (or superior) to CABG in patients with complex coronary artery disease can only be determined by a dedicated large randomized controlled trial. Such a study has recently been announced. The international Evaluation of XIENCE Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial, set to begin in late 2010, will randomize approximately 2500 patients with unprotected left main disease to CABG versus PCI with the next-generation EES (XIENCE Prime). For many years the relative clinical utility of rapamycin analogue-based DES compared with PES in patients with diabetes mellitus has been debated. With nearly 5500 randomized patients in SPIRIT IV and COMPARE (1510 [28%] of whom had diabetes), these trials had significant power to examine clinical outcomes in this subgroup. Of note, while there was marked reduction in death or MI, stent thrombosis and TLR in nondiabetic patients in both studies with EES compared with PES, no statistically significant benefits were apparent with EES in diabetic patients. While differences may emerge between these devices with longer follow-up from SPIRIT IV and COMPARE, currently there is no conclusive clinical evidence that one stent is superior in diabetic patients. Larger dedicated randomized trials in diabetic patients would be useful. Considering that approximately 1 million patients with diabetes worldwide are treated with PCI each year, even small differences in treatment outcomes would have important implications for global health. Conversely, for every 1000 nondiabetic patients treated with the EES rather than the PES, approximately 14 stent thromboses and 52 occurrences of death, MI or TLR within 1 year would be prevented.

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Chapter 3.2

Stent Thrombosis: Insights on Outcomes, Predictors and Impact of Dual Antiplatelet Therapy Interruption from the SPIRIT II, SPIRIT III, SPIRIT IV and COMPARE Trials

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Eurointervention *In Press*

Dr. Kedhi reports receiving lecture fees from Abbott Vascular and Sint Jude Medical. Dr. Smits reports receiving lecture fees from Abbott Vascular. Dr. Kereiakes reports serving on the advisory boards for Abbott Vascular and Boston Scientific. Dr. Stone reports having serving as a consultant for Boston Scientific, Abbott Vascular, The Medicines Company, Merck, Eli Lilly, AstraZeneca, Bristol-Meyers-Squibb and Medtronic. Charles A. Simonton, Krishnankutty Sudhir and Poornima Sood are employees of Abbott Vascular.

ABSTRACT

Aims:
Recent studies have suggested that EES may reduce ST compared to PES, but no individual trial has been adequately powered for this endpoint. The incidence of stent thrombosis, as well as the impact of dual antiplatelet therapy (DAPT) discontinuation during the first 2 years following everolimus-eluting stent (EES) and paclitaxel-eluting stent (PES) deployment were therefore analyzed from a pooled, patient-level database derived from four randomized clinical trials.

Methods and Results:
Data from the SPIRIT II, SPIRIT III, SPIRIT IV and COMPARE trials (n=6,789 patients) were analyzed. Two-year ST rates were determined using time-to-event methods and compared with the log-rank test. ST rates were also determined after DAPT discontinuation. EES compared to PES significantly reduced the 2-year rates of ST (0.7% versus 2.3%, p=0.0001), including the interval rates of ST up to 30 days (0.2% versus 1.0%, p<0.0001), between 31 days and 1 year (0.2% versus 0.6%, p=0.02), and after 1 year (0.3% versus 0.8%, p=0.001). EES also reduced the 2-year composite rate of cardiac death or MI (4.0% versus 6.6%, p=0.0001). Increased rates of ST after DAPT discontinuation beyond 6 months were observed in the PES cohort, but not in the EES cohort.

Conclusion:
In this large pooled analysis from four randomised trials, treatment with EES compared to PES significantly reduced the rates of ST through 2 years of follow-up, with a concomitant reduction in cardiac death or MI. DAPT discontinuation beyond 6 months may be safe with EES.

Key words
Everolimus-eluting stent, paclitaxel-eluting stent, stent thrombosis, dual antiplatelet therapy discontinuation, prognosis

INTRODUCTION

Paclitaxel-eluting stents (PES) and sirolimus-eluting stents (SES) substantially reduce target lesion and vessel re-intervention rates compared to bare metal stents.[1,2] However, increased rates of very late stent thrombosis (ST), particularly in high risk patient populations,[3,4] remain a matter of concern with these first generation drug-eluting stents.[5]

Second generation drug-eluting stents have been designed to improve procedural performance as well as safety and efficacy of the first generation devices. Specifically, a second generation, thin-strut, cobalt-chromium, everolimus-eluting stent (EES) demonstrated significant improvements in angiographic and clinical outcomes when compared to PES in two small to moderate sized randomised trials[6,7]. Thereafter two large clinical trials, SPIRIT IV[8] and COMPARE[9], tested the same hypothesis in greater numbers of patients with either non-complex coronary artery disease or all-comers, respectively. Both trials reported significant improvements in safety and efficacy endpoints as well as reductions in definite ST and definite/probable ST rates, in favour of EES. However, no individual trial was adequately powered to examine the incidence rates of ST, or to determine the impact of dual antiplatelet therapy (DAPT) interruption on ST outcomes in the EES and PES cohorts separately. For this purpose we pooled patient-level data from the four randomized trials in which the outcomes of EES compared to PES in 6,789 patients have been examined.

METHODS

The designs of SPIRIT II, SPIRIT III, IV and COMPARE trials have previously been described.[6-9] Briefly, each study was a prospective, single-blind, randomized controlled clinical trial in which patients were assigned to receive either EES (manufactured and distributed as Xience V by Abbott Vascular, Santa Clara, CA; also distributed as Promus by Boston Scientific, Natick, MA) or PES (TAXUS Express2, or TAXUS Liberté, Boston Scientific). The SPIRIT trials enrolled patients with simple and moderately complex coronary lesions, excluding those

with acute or recent myocardial infarction and difficult or high-risk lesions such as chronic total occlusions, true bifurcations, thrombus, and lesions in the left main coronary artery or a saphenous vein graft. COMPARE was an "all-comers" trial, excluding from randomization only patients unable to comply with DAPT for a period of 12 months, and those presenting in cardiogenic shock. Aspirin ≥75 mg daily was recommended for a minimum of 1 year in SPIRIT II and indefinitely in the other trials. Clopidogrel (75 mg daily) was prescribed by protocol for ≥6 months in SPIRIT II and III and for ≥12 months in SPIRIT IV and COMPARE. Each study employed an independent, angiographic core laboratory as well as independent clinical event adjudication committees, blinded to stent assignment. Follow-up is planned for 5 years in each trial, and is currently complete through at least 2 years in all four studies.

For the present analysis, baseline clinical, angiographic and procedural data of these four trials were pooled to allow for a patient-level analysis. Events as adjudicated in each trial were utilized. The purpose of this analysis was to examine the incidence rates of ST as defined by the ARC definite and/or probable definition,[10] including examining the outcomes after DAPT discontinuation. The rates of definite ST and definite/probable ST were examined in the following periods: early (0-30 days); late (31 days to 1 year); cumulative to 1 year; very late (1-2 years); and cumulative to 2 years.

To analyze the impact of DAPT interruption on subsequent, definite ST and definite/probable ST, four groups of patients were identified: patients who permanently discontinued DAPT (either aspirin and/or a thienopyridine) between 1 and 6 months, between 6 and 12 months, between 12 and 24 months, and those who were still taking DAPT at 24 months. DAPT compliance was ascertained for all studies at discharge, 1, 6, 12, and 24 months, as well as at the time of adverse events. Patients in whom a ST occurred while not on DAPT were included in the respective DAPT interruption group based on their DAPT status at the time of the event, regardless of DAPT usage afterwards. Moreover, only patients with definitely known DAPT status at each time point through the 2-year follow-up were included in the present analysis. Thus, 183 patients (2,7%), including seven of whom (0,1%) who had a ST (all between 0-30 days) were not included in this analysis due to unknown DAPT status after the event. Only 36 patients (0,5%), discontinued DAPT before 1 month; given the small size of this group these patients were excluded from the analysis. Only the first ST episode was considered; patients with ST were not included in the denominator of subsequent time periods. Finally, to test whether DAPT may be safely permanently discontinued beyond 6 months after DES implantation, definite ST and definite/probable ST rates at 2 years were compared in

following groups using a landmark analysis beyond 6 months: patients who permanently discontinued DAPT between 6 and 12 months, those who permanently discontinued DAPT between 12 and 24 months, and those who were still taking DAPT at 24 months.

All analyses were done by intention to treat. Categorical outcomes were compared by chi-square or Fisher's exact test. Continuous variables are presented as mean ± S.D. and were compared by t-test. The 2-year event analyses were performed using time-to-event data, are displayed using Kaplan-Meier plots, and were compared with the log-rank test. To adjust for slight differences in the baseline characteristics of the study population, a propensity score matching analysis was performed using the covariates in Tables 1 and 2. The propensity score estimates were entered into the multivariable model, and adjusted Kaplan-Meier curves and HR were derived. A two-sided α=0.05 was used for all superiority testing. All statistical analyses were performed by SAS version 9.1.3 (SAS Institute, Cary, NC).

RESULTS

Baseline characteristics.

Pooling the four trials resulted in a total of 6,789 patients randomized to treatment with EES (n=4247; 63%) or PES (n=2542; 37%). Clinical follow-up at 2 years was available in 96,2% EES and 96,1% PES treated patients. Baseline patient demographic characteristics as well as angiographic and procedural characteristics are shown in Tables 1 and 2 respectively. Baseline coronary risk factors were similar between randomly assigned stent types except that EES patients had a slightly higher incidence of hyperlipidemia and hypertension, while PES patients had a slightly higher rate of ACS at presentation. Minor imbalances in several angiographic variables, including the rates of total occlusion, presence of thrombus, moderate or severe calcification, modified ACC/AHA Class C lesion morphology, target lesion length and stented length were also present. Compliance with DAPT was similar between the randomly assigned stent types through 1-year of follow-up; at 2 years, aspirin usage was not significantly different between the groups, but thienopyridine usage was slightly more common in the EES group (Table 3).

Clinical events.

Outcomes of unadjusted early, late and very late definite ST and definite/probable ST as well as rates of cardiac death or MI with follow-up to 2 years

Table 1. Baseline patient demographic characteristics

	Everolimus-eluting stents	Paclitaxel-eluting stents	P-Value
Age (years)	63.09 ± 10.61 (4247)	63.36 ± 10,68 (2541)	0.30
Gender: Male	68.5% (2911/4247)	69.5% (1766/2541)	0.42
Diabetes mellitus	28.0% (1188/4244)	26.9% (681/2536)	0.31
- Insulin-treated	7.3% (310/4244)	7.3% (184/2536)	0.96
Smoking During Past Year	25.0% (1042/4176)	25.0% (624/2493)	0.95
Hypertension	70.1% (2976/4243)	66.1% (1677/2537)	0.0006
Hyperlipidemia	70.5% (2949/4184)	65.8% (1658/2518)	<0.0001
Prior CABG	7.2% (306/4244)	6.0% (153/2541)	0.06
Prior myocardial infarction	20.4% (847/4157)	19.0% (476/2508)	0.17
Prior percutaneous intervention	14.5% (610/4194)	13.9% (350/2516)	0.49
Stable angina	53.8% (2254/4193)	49.8% (1248/2506)	0.002
Unstable angina	22.9% (959/4193)	22.3% (559/2506)	0.61
Stable ischemic heart disease	67.2% (2854/4247)	61.1% (1551/2539)	<0.0001
Acute coronary syndrome	32.8% (1393/4247)	38.9% (988/2539)	<0.0001

Table 2. Baseline angiographic and procedural characteristics.

	Everolimus-eluting stents	Paclitaxel-eluting stents	P-Value
Vessel Location--RCA	34.2% (1865/5460)	33.8% (1132/3353)	0.71
Vessel Location--LAD	40.5% (2209/5460)	39.6% (1329/3353)	0.45
Vessel Location--LCX	25.0% (1364/5460)	25.9% (870/3353)	0.31
Vessel Location--LM	0.4% (22/5460)	0.7% (22/3353)	0.12
Vessel Location--SVG	0.5% (27/5460)	0.7% (24/3353)	0.19
Total Occlusion - Baseline	2.0% (109/5460)	3.5% (117/3353)	<0.0001
Calcification, Mod-Severe	14.3% (775/5433)	17.8% (596/3341)	<0.0001
Thrombus	7.2% (392/5434)	10.3% (346/3345)	<0.0001
Modified ACC/AHA Lesion Class A	9.0% (487/5417)	9.3% (309/3334)	0.67
Modified ACC/AHA Lesion Class B1	33.6% (1820/5417)	31.8% (1060/3334)	0.08
Modified ACC/AHA Lesion Class B2	31.7% (1716/5417)	31.0% (1034/3334)	0.52
Modified ACC/AHA Lesion Class C	25.7% (1394/5417)	27.9% (931/3334)	0.02
Baseline TIMI Flow: 0	4.8% (241/5068)	7.0% (217/3095)	<0.0001
Baseline TIMI Flow: 1	2.2% (110/5068)	2.6% (80/3095)	0.23
Baseline TIMI Flow: 2	6.6% (337/5068)	7.9% (246/3095)	0.03
Baseline TIMI Flow: 3	86.4% (4380/5068)	82.5% (2552/3095)	<0.0001
Number treated lesions	1.29 ± 0.53 (4246)	1.32 ± 0.57 (2540)	0.02
Number treated vessels	1.20 ± 0.43 (4246)	1.22 ± 0.44 (2541)	0.04
Pre-procedure lesion length (mm)	15.96 ± 9.50 (4963)	16.78 ± 11.60 (2867)	0.001
Pre-procedure reference vessel diameter (mm)	2.68 ± 0.51 (5077)	2.68 ± 0.54 (2958)	0.88

Pre-procedure MLD (mm)	0.80 ± 0.42 (5103)	0.83 ± 0.44 (2986)	0.01
Pre-procedure% diameter stenosis	70.3 ± 14.7 (5147)	69.5 ± 15.5 (3007)	0.03
Total stent length implanted (mm)	32.2 ± 21.6 (4227)	34.0 ± 25.8 (2530)	0.004
Total number stents implanted	1.7 ± 1.0 (4238)	1.7 ± 1.1 (2538)	0.05

RCA = Right coronary artery; LAD = Left anterior descending; LCX= Left circumflex; LM = Left main; MLD = Minimal lumen diameter SVG = Saphenous vein graft; TIMI score = Thrombolysis In Myocardial Infarction score.

Table 3. Dual antiplatelet therapy compliance according to stent type

	Everolimus-eluting stents	Paclitaxel-eluting stents	P-Value
Discharge			
Aspirin	97.3% (4123/4238)	96.9% (2454/2533)	0.33
Clopidogrel	98.9% (4191/4238)	99.1% (2509/2533)	0.62
Ticlopidine	0.4% (15/4238)	0.3% (8/2533)	1.00
Any thienopyridine	99.3% (4208/4238)	99.4% (2517/2533)	0.76
Aspirin + any thienopyridine	96.9% (4106/4238)	96.7% (2449/2533)	0.67
6-months			
Aspirin	95.9% (4047/4220)	94.5% (2379/2517)	0.01
Clopidogrel	95.3% (4021/4220)	95.7% (2408/2517)	0.51
Ticlopidine	0.2% (10/4220)	0.2% (5/2517)	1.00
Any Thienopyridine	96.8% (4085/4220)	96.9% (2439/2517)	0.89
Aspirin + any thienopyridine	93.6% (3964/4233)	92.5% (2338/2528)	0.07
1-Year			
Aspirin	93.7% (3929/4194)	92.7% (2318/2501)	0.12
Clopidogrel	80.6% (3379/4194)	80.4% (2010/2501)	0.85
Ticlopidine	0.2% (9/4194)	0.2% (5/2501)	1.00
Any thienopyridine	81.7% (3428/4194)	81.3% (2033/2501)	0.65
Aspirin + any thienopyridine	78.3% (3310/4230)	77.0% (1941/2522)	0.23
2-Year			
Aspirin	91.0% (3772/4144)	91.1% (2243/2461)	0.89
Clopidogrel	52.4% (2170/4144)	47.3% (1163/2461)	<0.0001
Ticlopidine	0.2% (8/4144)	0.1% (2/2461)	0.34
Any thienopyridine	53.3% (2209/4144)	47.8% (1177/2461)	<0.0001
Aspirin + any thienopyridine	50.0% (2107/4215)	44.5% (1117/2508)	<0.0001

are shown in Table 4 and Figure 1a and 1b. EES resulted in a 70% reduction in the rate of definite/probable ST at 2 years compared to PES, with significant interval reductions in early, late and very late ST. Similarly, EES resulted in a 70% reduction in the rate of angiographically confirmed definite ST at 2 years compared to PES, with significant reductions in definite ST during each interval, including at 30 days and 1 year. After propensity adjustment for differences in the baseline clinical and angiographic characteristics, EES showed comparable reductions in rates of definite/probable ST at 30 days (0.3% (8) versus 1.0% (24), HR: 0.33, 95% CI [0.15,0.74], p=0.005), 1 year (0.6% (13) versus 1.5% (35); HR: 0.37; 95% CI: [0.20, 0.70], p=0.0001) and 2 years (0.9% (19) versus 2.2% (51); HR: 0.37; 95% CI [0.22,0.63], p=0.0001), (Figure 1c and 1d).

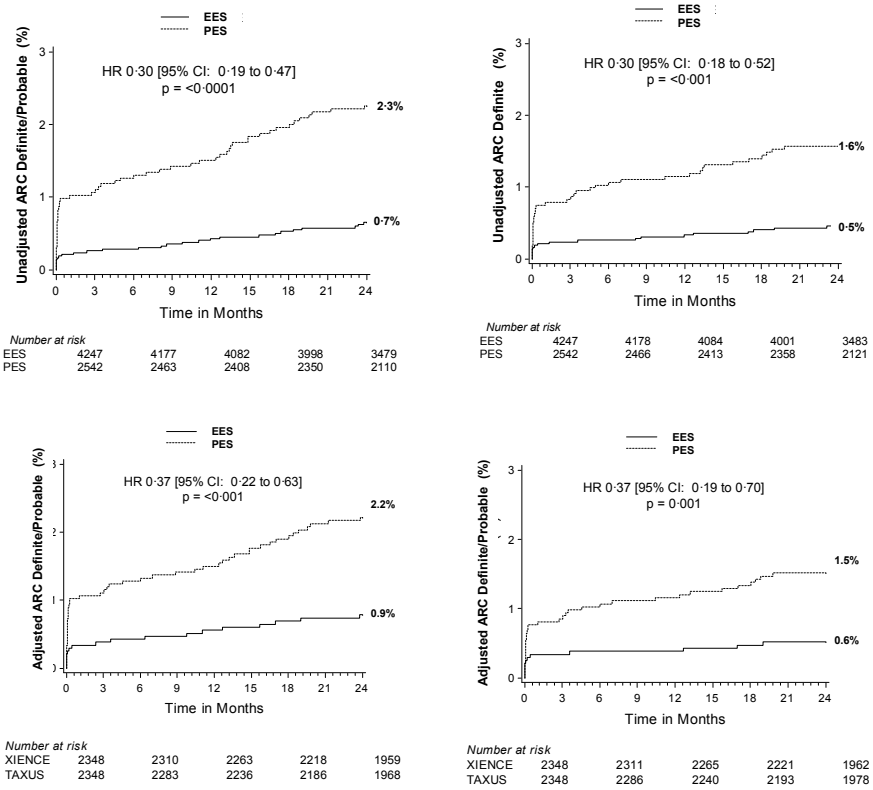

Figure 1 Time-to-event curves for ARC definite/probable stent thrombosis (A) and ARC definite stent thrombosis (B), propensity score adjusted ARC definite/probable stent thrombosis (C) and propensity score adjusted ARC definite stent thrombosis (D) through 2-year follow-up. EES denotes everolimus-eluting stents. PES denotes paclitaxel-eluting stents.

Table 4. Unadjusted rates of stent thrombosis, cardiac death and myocardial infarction

	Everolimus-eluting stents	Paclitaxel-eluting stents	Hazard Ratio [95% C.I.]	P-Value
Early Stent Thrombosis (0-30 Days)				
ARC Definite	0.2% (9)	0.8% (19)	0.28 [0.13,0.63]	0.0009
ARC Probable	0.0% (0)	0.2% (6)	-	0.001
ARC Definite/Probable	0.2% (9)	1.0% (25)	0.21 [0.10,0.46]	<0.0001
Late Stent Thrombosis (31-365 Days)				
ARC Definite	0.1% (5)	0.4% (10)	0.30 [0.10,0.87]	0.02
ARC Probable	0.1% (4)	0.2% (5)	0.48 [0.13,1.77]	0.26
ARC Definite/Probable	0.2% (9)	0.6% (14)	0.38 [0.17,0.88]	0.02
Stent Thrombosis (0-365 Days)				
ARC Definite	0.3% (14)	1.2% (29)	0.29 [0.15,0.54]	<0.0001
ARC Probable	0.1% (4)	0.4% (11)	0.22 [0.07,0.68]	0.004
ARC Definite/Probable	0.4% (18)	1.5% (38)	0.28 [0.16,0.49]	<0.0001
Very Late Stent Thrombosis (366-730 Days)				
ARC Definite	0.2% (6)	0.5% (11)	0.32 [0.12,0.87]	0.02
ARC Probable	0.1% (4)	0.3% (8)	0.30 [0.09,0.99]	0.04
ARC Definite/Probable	0.3% (10)	0.8% (19)	0.31 [0.14,0.67]	0.001
Stent Thrombosis (0-730 Days)				
ARC Definite	0.5% (20)	1.6% (39)	0.30 [0.18,0.52]	<0.0001
ARC Probable	0.2% (8)	0.8% (19)	0.25 [0.11,0.57]	0.0004
ARC Definite/Probable	0.7% (28)	2.3% (56)	0.30 [0.19,0.47]	<0.0001
Cardiac Death or MI (0-30 Days)	1.6% (68)	2.8% (70)	0.58 [0.41,0.81]	0.001
Cardiac Death or MI (0-365 Days)	2.7% (113)	4.5% (114)	0.59 [0.45,0.76]	<0.0001
Cardiac Death or MI (0-730 Days)	4.0% (166)	6.6% (163)	0.60 [0.48,0.74]	<0.0001

ARC = Academic Research Consortium; MI = Myocardial Infarction

Reduced definite ST and definite/probable ST rates with EES paralleled a significant reduction in the composite rate of cardiac death or MI in each time period and at 2 years (Table 4).

Stent thrombosis according to dual anti-platelet therapy use.

The 2-year ST rates from the four groups according to DAPT compliance in the EES and PES cohorts are presented in Table 5. No significant differences in 2-year definite ST and definite/probable rates according to early DAPT discontinuation were observed between the four groups in the EES cohort. In contrast, a significant increase in the rate of definite/probable ST was observed in the PES patients who interrupted DAPT between 1 and 6 months. After excluding the ST events of the first 6 months, the overall 2-year definite/prob-

Table 5. Stent thrombosis rates at 2 years according to randomized stent type and dual antiplatelet therapy compliance

	Group a	Group b	Group c	Group d	Combined	p value
EES cohort*	75.0% (75/100)	92.3% (562/609)	97.8% (1168/1194)	97.5% (1969/2019)	96.2% (3774/3922)	<0.0001
ARC Definite	1.1% (1)	0.2% (1)	0.3% (4)	0.6% (11)	0.5% (17)	0.43
ARC Probable	0.0% (0)	0.3% (2)	0.2% (2)	0.2% (4)	0.2% (8)	0.86
ARC Def/Prob	1.1% (1)	0.5% (3)	0.5% (6)	0.8% (15)	0.7% (25)	0.75
PES cohort*	74.3% (55/74)	94.6% (336/355)	98.2% (808/823)	97.1% (1023/1054)	96.4% (2222/2306)	<0.0001
ARC Definite	6.2% (4)	1.1% (4)	1.4% (11)	1.3% (14)	1.5% (33)	0.01
ARC Probable	0.0% (0)	1.2% (4)	1.0% (8)	0.3% (3)	0.7% (15)	0.16
ARC Def/Prob	6.2% (4)	2.3% (8)	2.3% (19)	1.5% (16)	2.1% (47)	0.05

* Patients without events that had at least 700 days of follow-up. Group a: DAPT interrupted between 1-6 months; Group b: DAPT interrupted between 6-12 months; Group c: DAPT interrupted between 12-24 months; Group d: No DAPT interruption up to 24 months; EES denotes everolimus-eluting stent. PES denotes paclitaxel-eluting stent; ST : Stent Thrombosis; ARC : Academic Research Consortium; DAPT : Dual Antiplatelet Therapy; Def/Prob: Definite and Probable

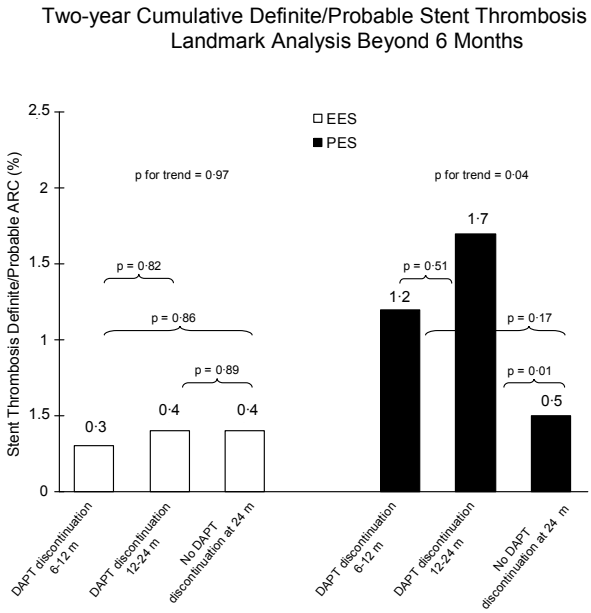

Figure 2 Cumulative 2 year rates of definite or probable stent thrombosis after excluding events from the first 6 months in subjects that discontinued dual antiplatelet therapy (DAPT) between 6-12 months, between 12-24 months, and subjects still on DAPT at 24 months in the everolimus-eluting stent EES and paclitaxel-eluting stent cohorts respectively. EES denotes everolimus-eluting stents. PES denotes paclitaxel-eluting stents.

able ST rates in the groups of patients who permanently discontinued DAPT between 6-12 months, between 12-24 months and who were still on DAPT at 24 months were 0.3% (n=2), 0.4% (n=5) and 0.4% (n=8), respectively in the EES cohort (p for trend=0.97), and 1.2% (n=4), 1.7% (n=14) and 0.5% (n=5) in the PES cohort (p for trend=0.04) (Figure 2).

DISCUSSION

The major finding of the present pooled analysis from 4 randomized trials is that EES markedly reduced the 2-year rates of definite ST and definite/probable ST compared to PES. A significant difference in ST frequency was present at every interval examined through the 2-year follow-up period. The reduction in definite ST and definite/probable ST was accompanied by a reduction in the composite occurrence of cardiac death or MI. Finally, DAPT discontinuation beyond 6 months (and any time before 2 years) was associated with an increased risk of ST with PES, but not with EES.

The benefits of reduced clinical restenosis achieved with first generation DES compared to BMS were offset in many studies by higher rates of very late ST.[4,5] Furthermore, the on-going propensity for ST with first generation DES has generated reluctance regarding unrestricted use of DES, and recommendations for long-term use of DAPT, despite the lack of evidence that such an approach improves clinical outcomes post PCI. The present study establishes that gains in safety as well as efficacy[11,12] may be achieved by a single stent platform (EES). Of note, however, the present pooled analysis refers only to the results of EES vs PES; further study is required to determine whether these results apply to other second and third generation DES.

Stent Thrombosis.

Both unadjusted and propensity score adjusted multivariable analysis, showed significant and important reductions on rates of definite ST and definite/probable ST. The pathophysiologic mechanism(s) underlying the marked reduction in ST following EES are speculative, but may relate to specific stent design features. The combination of thin fracture-resistant struts with everolimus released from a thromboresistant non-inflammatory fluorinated polymer[13,14] may contribute to the lower rates of early ST with EES. In pre-clinical animal models more rapid and complete stent re-endothelialization has been seen with EES compared to other DES.[15] Reduction in inflammation along with the faster and more complete reendothelialisation may result in lower rates of

early, late and very late ST. Moreover, despite the focus of the physician and public on very late ST (beyond 1 year) with first-generation DES when compared with BMS,[3,16] early ST accounts for a substantial proportion of total ST events. While low rates of late and very late ST have been reported with other new DES,[17-19] the EES is the only second generation DES which has repeatedly shown a reduced rate of definite ST events, especially in the early period.[9,18].

DAPT interruption analysis.

The premise that EES-treated patients may require shorter durations of DAPT is supported by the findings of the current analyses. Interruption of DAPT at any time point after the first month did not influence the rate of ST at two years in the EES cohort. After excluding events within the first 6 months, no difference was observed with regard to definite ST and definite/probable ST rates in the EES cohort regardless of DAPT compliance, suggesting that permanent DAPT interruption beyond 6 months following EES implantation may be safe. This observation is consistent with the Xience USA registry where DAPT interruption at any time point beyond 180 days following EES implantation was safe in an unselected (all-comers) population.[20] Continued exposure to DAPT after 6 months may expose EES-treated patients to increased bleeding risk without efficacy benefit.[21] However, large-scale randomized trials are required to confirm the safety of permanent DAPT discontinuation at 6 months (or earlier) in EES-treated patients before this practice can be routinely recommended.

In contradistinction, we found that discontinuation of DAPT following PES deployment any time before 24 months (but especially between 1 and 6 months) was associated with increased rates of definite/probable ST. Similarly, Eisenstein and colleagues reported increased rates of death or myocardial infarction when DAPT was discontinued after 6 months or after 12 months with first generation DES.[22] In contrast, Airoldi et al reported that ST rates with first generation DES were increased when DAPT discontinuation occurred prior to 6 months (compared with continued DAPT therapy), but not after 6 months,[23] and Park and colleagues did not find that extended clopidogrel use after 1 year prevented ST.[24] Additional large-scale randomized trials are underway to clarify the relative risks and benefits of prolonged DAPT use after first generation DES.[25]

Limitations.

This study has several limitations. Despite the randomized design of the 4 component trials, slight imbalances in baseline covariates between the two randomly assigned stents were observed after pooling. However, after propensity score adjustment the HRs for definite ST and definite/probable ST did

not directionally differ from the unadjusted HRs. Additional confounding variables (either measured or unmeasured) not incorporated in this analysis may have influenced the study observations as well. Angiographic measures of reference vessel diameter and lesion length were assessed by an independent core laboratory in the SPIRIT trials, and by operator assessment in COMPARE. Outcomes of ST in high risk categories of patients presenting with acute coronary syndromes or diabetes mellitus were not the focus of this analysis, as they have previously been. [26,27] Subjects in the present analysis were not randomized by duration of DAPT compliance. A small percentage of patients with definite ST and definite/probable ST were excluded from this analysis due to unknown DAPT status at multiple time points after the event; however all patients in whom ST occurred between 0-30 days were taking DAPT at the time of the event. Finally, bleeding was not a focus of these trials, and long-term DAPT may entail hemorrhagic risks which may offset their advantages. For all of these reasons the findings of the present study should be considered hypothesis-generating, requiring confirmation in appropriately designed and powered randomized trials.

Conclusions.

The present large-scale patient-level pooled database from four randomized trials has shown that EES significantly reduces definite ST and definite/probable ST rates compared to PES. This major safety benefit was evident early (within 30 days) and increased in magnitude during the 2-year follow-up duration. The reduction in ST was paralleled by a reduction in the combined rate of cardiac death or MI with EES compared to PES. Finally the present analysis suggests that permanent DAPT discontinuation beyond 6 months may be safe following EES implantation.

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Chapter 4.1

Differential Clinical Responses to Everolimus-Eluting and Paclitaxel-Eluting Coronary Stents in Patients With and Without Diabetes Mellitus

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ABSTRACT

Background

Some (but not all) prior trials have reported differential outcomes after percutaneous coronary intervention with paclitaxel-eluting stents versus stents eluting rapamycin analogs according to the presence of diabetes mellitus These studies lacked sufficient power to examine individual safety and efficacy end points.

Methods and Results

To determine whether an interaction exists between the presence of diabetes mellitus and treatment with everolimus-eluting stents compared with paclitaxel-eluting stents, we pooled the databases from the Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions (SPIRIT) II, SPIRIT III, SPIRIT IV, and A Trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice (COMPARE) trials in which percutaneous coronary intervention was performed in 6780 patients, 1869 (27.6%) of whom had diabetes mellitus. Patients without diabetes mellitus treated with everolimus-eluting stents compared with paclitaxel-eluting stents had significantly reduced 2-year rates of mortality (1.9% versus 3.1%; P=0.01), myocardial infarction (2.5% versus 5.8%; P<0.0001), stent thrombosis (0.3% versus 2.4%; P<0.0001), and ischemia-driven target lesion revascularization (3.6% versus 6.9%; P<0.0001). In contrast, among patients with diabetes mellitus, there were no significant differences between the 2 stent types in any measured safety or efficacy parameter. Significant interactions were present between diabetic status and stent type for the 2-year end points of myocardial infarction (P=0.01), stent thrombosis (P=0.0006), and target lesion revascularization (P=0.02).

Conclusions

We have identified a substantial interaction between diabetes mellitus and stent type on clinical outcomes after percutaneous coronary intervention. In patients without diabetes mellitus, everolimus-eluting stents compared with paclitaxel-eluting stents resulted in substantial 2-year reductions in death, myocardial infarction, stent thrombosis, and target lesion revascularization, whereas no significant differences in safety or efficacy outcomes were present in diabetic patients.

Clinical Trial Registration
URL: http://www.clinicaltrials.gov. Unique identifiers: NCT00180310 (SPIRIT II), NCT00180479 (SPIRIT III), NCT00307047 (SPIRIT IV), and NCT01016041 (COMPARE).
(*Circulation*. 2011;124:893-900.)

Key Words:
coronary artery disease , diabetes mellitus , prognosis , restenosis , stents

INTRODUCTION

Patients with diabetes mellitus undergoing percutaneous coronary intervention with bare metal stents have higher rates of angiographic and clinical restenosis than patients without diabetes mellitus.[1,2] Compared with bare metal stents, drug-eluting stents (DES) have been shown to be safe[3] and to result in greater absolute reductions in target lesion revascularization (TLR) and target vessel revascularization in patients with versus those without diabetes mellitus.[4–6] However, whether the presence of diabetes mellitus differentially affects the relative clinical outcomes with different types of DES is a matter of considerable debate. Most prior studies have shown comparable rates of angiographic in-stent late loss and clinical restenosis with paclitaxel-eluting stents (PES) in patients with versus without diabetes mellitus.[7] In contrast, whether the relatively greater suppression of neointimal hyperplasia observed from stents that elute rapamycin analogs (such as sirolimus or everolimus) is preserved in patients with diabetes mellitus is unsettled. In this regard, several small to moderate-sized studies have provided conflicting results.[8,9] Moreover, none of these prior trials was powered to deter-mine whether there are differences in safety outcomes between different DES according to the presence of diabetes mellitus.

The outcomes of patients undergoing percutaneous coronary intervention with PES compared with everolimuseluting stents (EES) have been examined in 4 prospective randomized trials that have demonstrated that EES is both safer and more effective over a broad cross section of patients and lesion types.[10–15] We therefore pooled the databases from these 4 trials to determine whether an interaction exists between the presence of diabetes mellitus and treatment with EES compared with PES.

METHODS

Study Protocols

The features of the Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions (SPIRIT) II, SPIRIT III, SPIRIT IV, and A Trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice (COMPARE) trials are shown in Table 1. As previously described, [10–15] each study was a prospective, randomized, single-blind trial of EES versus PES. Randomization in the SPIRIT II, SPIRIT III, and SPIRIT IV trials was stratified by the presence of medically treated diabetes mellitus. The PES platform used in the SPIRIT trials was the TAXUS EXPRESS; the TAXUS Liberte´ was used in COMPARE. The SPIRIT trials enrolled patients with simple and moderately complex coronary artery disease, excluding patients with acute or recent myocardial

Table 1. Description of the prospective, randomized SPIRIT and COMPARE trials

	SPIRIT II	SPIRIT III	SPIRIT IV	COMPARE
Geography	EU, India, and New Zealand	US	US	Netherlands
Number of sites	28	65	66	1
Number of ITT patients	300	1,002	3,687	1,800
Number of patients with diabetes mellitus*	69/299 (23.1%)	290/999 (29.0%)	1195/3683 (32.4%)	325/1799 (18.1%)
Randomization EES:PES	3:1	2:1	2:1	1:1
PES platform	Express	Express	Express	Liberté
Primary endpoint(s)	In-stent LL at 6 months	In-segment LL at 8 months and TVF at 9 months	TLF at 12 months	MACE at 12 months
Recruitment period	July, 2005 - November, 2005	June, 2005 -March, 2006	August, 2006 - July, 2008	February, 2007 -September, 2008
RVD (mm)	2.5-4.25	2.5-3.75	2.5-3.75	No pre-specified criteria
Lesion length (mm)	≤28	≤28	≤28	No limit
Maximum lesions/patient	2	2	3	No limit
Major patient and lesion exclusion criteria**	Complex or high-risk†	Complex or high-risk†	Complex or high-risk†	None
Routine angiographic follow-up				
- Timing	6 and 24 months	8 months	None	None
- Number intended	300 and 152	564	0	0
- Number completed	275 and 115	436	0	0

*Medically treated; 9 patients in whom the diabetic status prior to enrollment was unknown were excluded. **Patients in all trials were also excluded if unable to take an extended course of dual antiplatelet therapy. †Including acute or recent myocardial infarction, left ventricular ejection fraction <30%, lesions which were in a bypass graft conduit, occluded, bifurcations (minor bifurcations were included in SPIRIT IV), ostial (ostial RCA lesions were included in SPIRIT IV), severe calcification or tortuosity. EES denotes everolimus-eluting stent; EU denotes Europe; ITT denotes intention to treat; LL denotes late loss; MACE denotes major adverse cardiac events (all-cause death, myocardial infarction or target vessel revascularization); PES denotes paclitaxel-eluting stent; RVD denotes reference vessel diameter; TLF denotes target lesion failure (cardiac death, target-vessel-related myocardial infarction or target lesion revascularization); TVF denotes target vessel failure (cardiac death, myocardial infarction or target vessel revascularization); US denotes United States.

infarction and difficult or high-risk lesions such as chronic total occlusions, true bifurcations, and lesions in the left main coronary segment or a saphenous vein graft. In contrast, COMPARE was an "all-comers" trial, excluding from randomization only patients unable to comply with dual antiplatelet therapy or study procedures, those who required major surgery within 30 days, and those who were unable to provide informed consent. A proportion of enrolled patients underwent protocol specified routine angiographic follow-up in the SPIRIT II and SPIRIT III trials, whereas only clinical follow-up was performed in the larger SPIRIT IV and COMPARE trials (Table 1). Follow-up is planned for 5 years in each trial and is currently complete through 2 years in all 4 studies.

End Points and Statistical Methods

For the present analysis, the databases from the 4 trials were pooled to provide a patient-level analysis. The principal end points of interest included safety parameters (principally cardiac death, myocardial infarction [MI], and stent thrombosis according to the Academic Research Consortium definition of definite or probable)[16]; efficacy parameters, including ischemia-driven TLR; and major adverse cardiac events (MACE), a composite measure of safety and efficacy consisting of cardiac death, MI, or ischemia-driven TLR. Other end points examined included all-cause mortality, Q-wave and non–Q-wave MI, and ischemia-driven target vessel revascularization. The definitions used for the end points assessed in the present analysis were similar in the SPIRIT and COMPARE trials.[10–15] Events as adjudicated in each trial were used for the pooled analysis. All end points were assessed at 2 years. Outcomes of patients randomized to EES versus PES were evaluated stratified by the presence of medically treated diabetes mellitus. All analyses are by intention to treat. Categorical outcomes were compared by the χ^2 test, unless the expected number of values in any cell of the 2x2 contingency table was < 5, in which case the Fisher exact test was used. Continuous variables are presented as mean SD and were compared by

the *t* test. Cumulative event rates were determined from time-to-event data (for which patients were censored at the time of withdrawal from the study or at last follow-up), are displayed through the use of Kaplan-Meier plots, and were compared by use of the log-rank test. A 2-sided α= 0.05 was used for all superiority testing.

Multivariable analyses were performed with the use of stepwise logistic regression to adjust for differences in baseline variables. The following variables were entered into the multivariable models: age, sex, hypertension, hyperlipidemia, prior MI, prior percutaneous coronary intervention, prior coronary artery bypass graft surgery, presentation with acute coronary syndromes, number of treated lesions, and randomization to EES versus PES. Formal interaction testing was performed to determine whether the presence of diabetes mellitus influenced the relative risk of EES versus PES for the occurrence of safety or efficacy end points at 2 years. Among patients with medically treated diabetes mellitus, possible interactions between insulin treatment and stent type were also examined.

Poolability across the 4 trials was confirmed for the 2-year measures of cardiac death, cardiac death or MI, MACE, and stent thrombosis (for the study-by-treatment interaction, *P*=0.53, *P*=0.91, *P*=0.83, and *P*=0.32, respectively). Poolability of the 3 SPIRIT trials versus

the COMPARE trial was also confirmed for these end points (for the study-by-treatment interaction, *P*=0.15, *P*=0.84, *P*=0.91, and *P*=0.16, respectively). All statistical analyses were performed with SAS version 9.1.3 (SAS Institute, Inc, Cary, NC).

RESULTS

Patients, Procedures, and Overall Impact of Diabetes Mellitus

Of the 6789 patients enrolled in the SPIRIT II, SPIRIT III, SPIRIT IV, and COMPARE trials, diabetic status at the time of admission was known for 6780 patients (99.9%), 1869 (27.6%) of whom had medically treated diabetes mellitus (Table 1). As shown in Table 2, the 2-year rates of all-cause and cardiac mortality, ischemia-driven target vessel revascularization, stent thrombosis, and MACE were significantly greater in patients with versus without diabetes mellitus. Among patients with diabetes mellitus, 1188 were randomly assigned to EES and 681 were randomly assigned to PES. Among patients without diabetes mellitus (n=4911), random assignment to EES and PES occurred in 3056 and 1855 patients, respectively. The baseline clinical and angiographic characteristics of

Table 2. Two-year clinical outcomes in patients with vs. without diabetes mellitus, regardless of stent type

	Diabetes (n=1,869)	No diabetes (n=4,911)	P value
Death	3.6% (64)	2.3% (110)	0.004
- Cardiac	2.1% (37)	1.0% (49)	0.0009
- Non-cardiac	1.5% (27)	1.3% (61)	0.45
MI	4.4% (80)	3.7% (179)	0.19
Ischemia-driven TLR	5.7% (101)	4.8% (228)	0.14
Ischemia-driven TVR	8.9% (157)	6.8% (319)	0.003
Stent thrombosis*	1.8% (31)	1.1% (53)	0.046
- Definite	1.2% (22)	0.8% (37)	0.08
- Probable	0.5% (9)	0.4% (18)	0.47
MACE	10.2% (182)	8.2% (391)	0.01

Event rates are shown as Kaplan-Meier estimates, % (number of events). MI denotes myocardial infarction denotes; TLR denotes ischemia-driven target lesion revascularization; TVR denotes ischemia-drive target vessel revascularization; MACE denotes major adverse cardiovascular events (cardiac death, MI, or ischemia-driven TLR). *According to the Academic Research Consortium (ARC) definite or probable definition.

the stent-assigned patients in each group were well matched (Table 3). Patients assigned to EES, compared with PES had hyperlipidemia more frequently and fewer totally occluded lesions. Among patients without diabetes mellitus, those assigned to EES had hypertension more frequently, were less likely to present with acute coronary syndromes or with thrombotic or calcified lesions, and had slightly shorter lesion length.

Clinical Outcomes

As shown in Figure 1 and Table 4, patients without diabetes mellitus randomized to EES rather than PES had significantly lower 2-year rates of mortality, MI, stent thrombosis, ischemia- driven TLR and target vessel revascularization, and MACE. In contrast, there were no significant differences in any measured parameters of safety or efficacy in patients with diabetes mellitus randomized to EES versus PES. These findings were unchanged after multivariable correction for differences in baseline characteristics (Table 5). Statistically significant interactions were present between diabetic status and stent type for the end points of MACE (P=0.0009), MI (P=0.01), stent thrombosis (P=0.0006), and ischemia-driven TLR (P=0.02) but not for cardiac death (P=0.25).

Influence of Insulin Treatment

Of the 1869 patients with diabetes mellitus at baseline, 494 (26.4%) were treated with insulin. Among patients treated with EES, a gradient was present so that the 2-year rates of most adverse events were greatest among

Table 3. Baseline characteristics and anti-platelet agent use in the randomized groups according to diabetic status

	Patients without diabetes (n=4,811)			Patients with diabetes (n=1,869)		
	EES (N=3,056)	PES (N=1,855)	P value	EES (N=1,188)	PES (N=681)	P value
Age (years)	62.9 ± 10.8	63.1 ± 10.9	0.58	63.5 ± 10.1	64.1 ± 10.2	0.23
Male	2151/3056 (70.4%)	1337/1855 (72.1%)	0.22	757/1188 (63.7%)	426/681 (62.6%)	0.62
Insulin-treatment	-	-	-	310/1188 (26.1%)	184/681 (27.0%)	0.66
Smoking within past year	808/3013 (26.8%)	498/1827 (27.3%)	0.74	234/1160 (20.2%)	125/662 (18.9%)	0.54
Hypertension	1975/3054 (64.7%)	1116/1852 (60.3%)	0.002	999/1186 (84.2%)	558/681 (81.9%)	0.22
Hyperlipidemia	1988/3004 (66.2%)	1133/1837 (61.7%)	0.002	960/1177 (81.6%)	552/677 (77.1%)	0.02
Prior myocardial infarction	588/3001 (19.6%)	343/1838 (18.7%)	0.43	258/1153 (22.4%)	133/666 (20.0%)	0.24
Prior PCI	409/3029 (13.5%)	241/1842 (13.1%)	0.70	201/1162 (17.3%)	109/670 (16.3%)	0.61
Prior CABG	185/3054 (6.1%)	92/1855 (5.0%)	0.11	121/1187 (10.2%)	61/681 (9.0%)	0.42
Presentation with ACS	1031/3056 (33.7%)	762/1854 (41.1%)	<0.0001	362/1188 (30.5%)	224/680 (32.9%)	0.28
# treated lesions	1.29 ± 0.53	1.32 ± 0.56	0.052	1.29 ± 0.53	1.33 ± 0.58	0.15
# treated vessels	1.20 ± 0.43	1.22 ± 0.44	0.13	1.20 ± 0.42	1.23 ± 0.46	0.14
Lesion location (core laboratory)						
- Native coronary artery	3907/3925 (99.5%)	2426/2442 (99.3%)	0.29	1522/1531 (99.4%)	897/905 (99.1%)	0.45
- Saphenous vein graft	18/3925 (0.5%)	16/2442 (0.7%)	0.29	9/1531 (0.6%)	8/905 (0.9%)	0.45
- Left main	12/3925 (0.3%)	18/2442 (0.7%)	0.02	10/1531 (0.7%)	4/905 (0.4%)	0.59*
- Left anterior descending	1597/3925 (40.7%)	970/2442 (39.7%)	0.45	611/1531 (39.9%)	356/905 (39.3%)	0.80
- Left circumflex	957/3925 (24.4%)	627/2442 (25.7%)	0.25	406/1531 (26.5%)	240/905 (26.5%)	1.0
- Right	1359/3925 (24.4%)	827/2442 (25.7%)	0.55	504/1531 (32.9%)	305/905 (33.7%)	0.72
Total occlusion	90/3925 (2.3%)	91/2442 (3.7%)	0.001	19/1531 (1.2%)	26/905 (2.9%)	0.005
Moderate or severe calcification	575/3905 (14.7%)	449/2436 (18.4%)	0.0001	200/1524 (13.1%)	145/899 (16.1%)	0.05
Thrombus	317/3908 (8.1%)	298/2437 (12.2%)	<0.0001	75/1522 (4.9%)	48/902 (5.3%)	0.70
Baseline QCA						

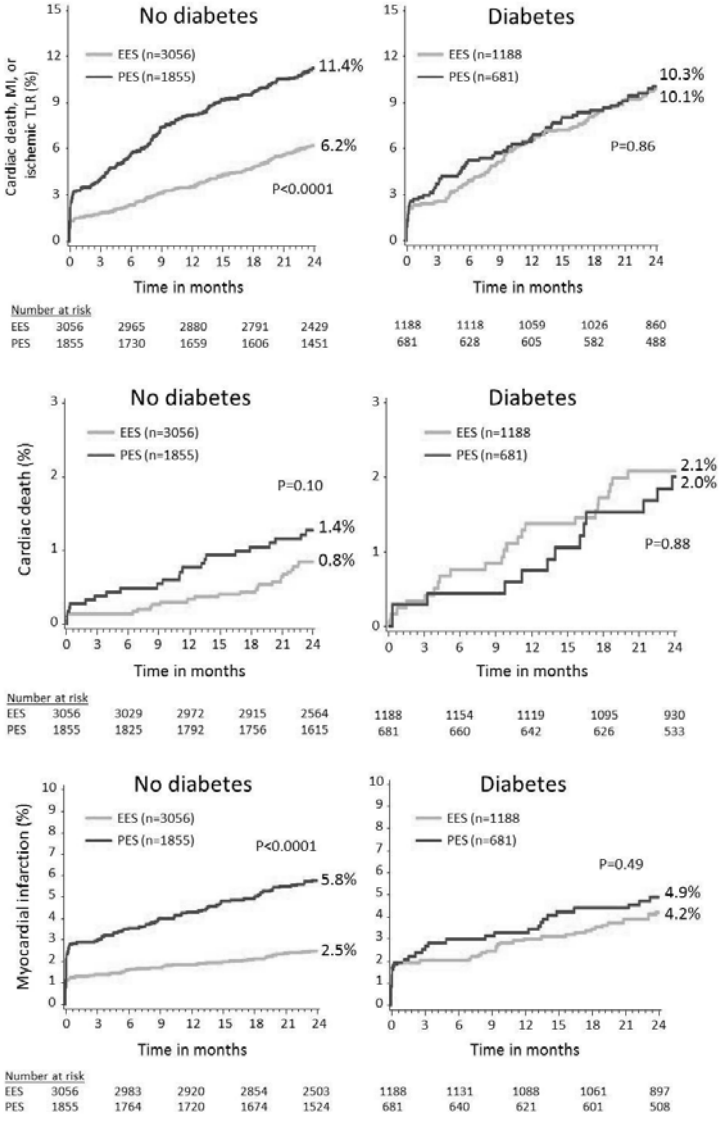
Reference vessel diameter (mm)	2.69 ± 0.51	2.69 ± 0.55	0.66	2.66 ± 0.52	2.65 ± 0.51	0.70
Minimal luminal diameter (mm)	0.81 ± 0.43	0.83 ± 0.46	0.04	0.78 ± 0.41	0.81 ± 0.41	0.16
Diameter stenosis %	70.2 ± 14.9	69.5 ± 15.8	0.10	70.5 ± 13.9	69.6 ± 14.4	0.17
Lesion length (mm)	16.0 ± 9.8	17.1 ± 12.0	0.0006	15.8 ± 8.7	16.0 ± 10.5	0.69
Dual anti-platelet therapy[†]						
- At discharge	2960/3050 (97.0%)	1789/1849 (96.8%)	0.61	1143/1185 (96.5%)	655/678 (96.6%)	0.90
- At 6 months	2864/3045 (94.1%)	1703/1834 (92.9%)	0.10	1097/1172 (93.6%)	628/677 (92.8%)	0.50
- At 1 year	2384/3030 (78.7%)	1413/1822 (77.6%)	0.37	922/1161 (79.4%)	523/673 (77.7%)	0.41

*Fisher's Exact test; all other comparisons were Chi-square test. [†] Patient taking both aspirin and a thienopyridine. EES denotes everolimus-eluting stent; PES denotes paclitaxel-eluting stent; ACS denotes acute coronary syndrome; CABG denotes coronary artery bypass graft surgery; PCI denotes percutaneous coronary intervention; QCA denotes quantitative coronary angiography.

insulin-treated diabetic patients, intermediate in non–insulin-treated diabetic patients, and lowest in nondiabetic patients (Figure 2, top). In contrast, among patients treated with PES, the 2-year rates of adverse events were independent of diabetic status or insulin treatment (Figure 2, bottom). Among patients with diabetes mellitus, there were no significant differences in the 2-year rates of cardiac death, MI, or stent thrombosis for patients randomized to EES versus PES, regardless of treatment with insulin (Table 6). However, ischemia-driven TLR was reduced among non–insulin-treated diabetic patients assigned to EES compared with PES (3.7% versus 6.3%; *P*=0.04) but not in insulin-treated diabetic patients, in whom a trend was present for less TLR with PES (10.8% versus 5.5%; *P*=0.08). Thus, a significant interaction was present in diabetic patients between the use of insulin and stent type for the occurrence of ischemia-driven TLR at 2 years (*P*=0.01).

DISCUSSION

The major findings from the present analysis, the largest study to date evaluating the relative safety and efficacy of different DES types stratified by the presence of diabetes mellitus, are (1) that a significant interaction was present between diabetic status and treatment with EES compared with PES on the relative risk of 2-year clinical outcomes, reflecting measures of both safety and efficacy; (2) that inpatients without diabetes mellitus, treatment with EES compared with PES reduced the 2-year rates of death, MI, stent thrombosis,


No diabetes
Diabetes
Cardiac death, MI, or ischemic TLR (%)
EES (n=3056)
PES (n=1855)
11.4%
6.2%
P<0.0001
EES (n=1188)
PES (n=681)
10.3%
10.1%
P=0.86
Time in months
Number at risk
EES 3056 2965 2880 2791 2429
PES 1855 1730 1659 1606 1451
1188 1118 1059 1026 860
681 628 605 582 488
Cardiac death (%)
P=0.10
1.4%
0.8%
2.1%
2.0%
P=0.88
EES 3056 3029 2972 2915 2564
PES 1855 1825 1792 1756 1615
1188 1154 1119 1095 930
681 660 642 626 533
Myocardial infarction (%)
P<0.0001
5.8%
2.5%
P=0.49
4.9%
4.2%
EES 3056 2983 2920 2854 2503
PES 1855 1764 1720 1674 1524
1188 1131 1088 1061 897
681 640 621 601 508

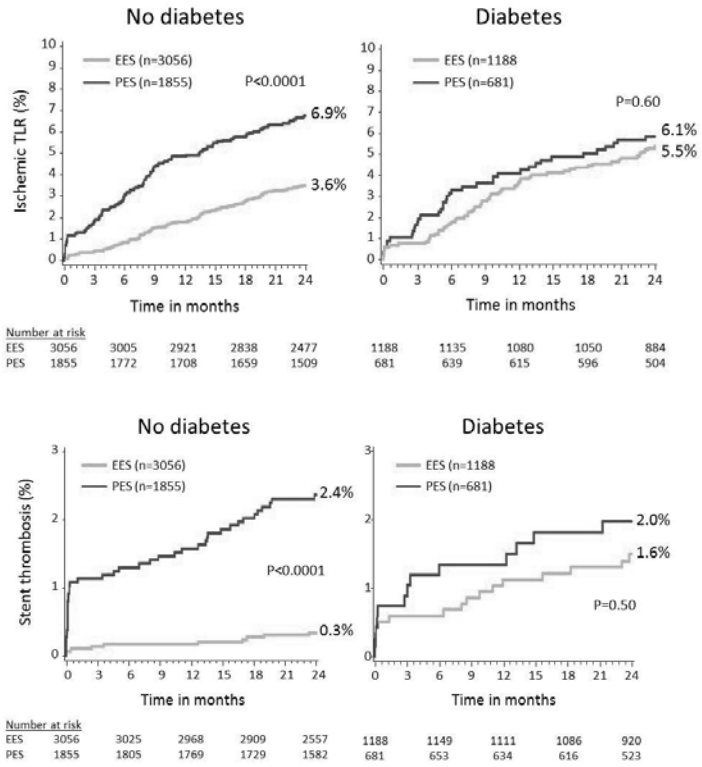


Figure 1 Time-to-event curves for major adverse cardiac events (cardiac death, myocardial infarction [MI], or ischemia-driven target lesion revascularization [TLR]; top left), cardiac death (top right); MI (middle left), ischemia-driven TLR (middle right), and stent thrombosis according to the Academic Research Consortium definition of definite or probable (bottom). EES indicates everolimus-eluting stents; PES, paclitaxel-eluting stents.

ischemia-driven TLR, and MACE, whereas in patients with diabetes mellitus, there were no significant differences in clinical outcomes at 2 years between the stent types; and (3) that an additional interaction was identified among patients with diabetes mellitus so that the 2-year rate of ischemia-driven TLR was reduced with EES compared with PES in those not requiring insulin, whereas the opposite trend was observed in those who were treated with insulin.

With 1869 randomized diabetic patients (larger than the SPIRIT II, SPIRIT III, and COMPARE trials individually) and 4911 randomized nondiabetic patients, the present analysis is of sufficient magnitude to examine the outcomes of patients with diabetes mellitus randomized to EES versus PES and to examine whether significant interactions exist between the presence of diabetes mellitus and clinical outcomes according to randomly assigned stent type. Highly

Table 4. Two-year event rates according to randomized stent type and diabetic status

	Patients without diabetes (n=4,911)			Patients with diabetes (n=1,869)		
	EES (n=3,056)	PES (n=1,855)	*p*	EES (n=1,188)	PES (n=681)	*p*
Death	1.9% (56)	3.1% (54)	0.01	3.9% (45)	2.9% (19)	0.27
- Cardiac	0.8% (25)	1.4% (24)	0.10	2.1% (24)	2.0% (13)	0.88
- Non-cardiac	1.0% (31)	1.7% (30)	0.06	1.9% (21)	0.9% (6)	0.13
MI	2.5% (74)	5.8% (105)	<0.0001	4.2% (48)	4.9% (32)	0.49
- Q-wave	0.1% (3)	1.3% (24)	<0.0001	0.5% (6)	0.7% (4)	0.79
- Non-Q-wave	2.4% (71)	4.6% (84)	<0.0001	3.7% (42)	4.4% (29)	0.43
Ischemic TLR	3.6% (105)	6.9% (123)	<0.0001	5.5% (62)	6.1% (39)	0.60
Ischemic TVR	5.7% (166)	8.5% (153)	<0.0001	8.3% (94)	9.8% (63)	0.29
Stent thrombosis*	0.3% (10)	2.4% (43)	<0.0001	1.6% (18)	2.0% (13)	0.50
- Definite	0.3% (8)	1.6% (29)	<0.0001	1.1% (12)	1.5% (10)	0.36
- Probable	0.1% (2)	0.9% (16)	<0.0001	0.5% (6)	0.5% (3)	0.85
MACE	6.2% (185)	11.4% (206)	<0.0001	10.1% (115)	10.3% (67)	0.86

Event rates are shown as Kaplan-Meier estimates, % (number of events). EES denotes everolimus-eluting stent; PES denotes paclitaxel-eluting stent; MI denotes myocardial infarction denotes; TLR denotes ischemia-driven target lesion revascularization; TVR denotes ischemia-drive target vessel revascularization; MACE denotes major adverse cardiovascular events (cardiac death, MI, or ischemia-driven TLR). * According to the Academic Research Consortium (ARC) definition.

Table 5. Adjusted odds ratios for the effect of randomized stent type on 2-year event rates according to diabetic status

	Patients without diabetes		Patients with diabetes	
2-Year Adverse Event	EES vs. PES OR [95% CI]	*p*	EES vs. PES OR [95% CI]	*p*
Cardiac death	0.66 [0.38, 1.17]	0.15	1.08 [0.54, 2.13]	0.83
MI	0.44 [0.32, 0.60]	<0.0001	0.87 [0.55, 1.40]	0.58
Ischemia-driven TLR	0.50 [0.39, 0.66]	<0.0001	0.90 [0.59, 1.37]	0.63
Stent thrombosis*	0.15 [0.07, 0.30]	<0.0001	0.80 [0.39, 1.67]	0.56
MACE	0.53 [0.43, 0.65]	<0.0001	0.94 [0.68, 1.30]	0.71

EES denotes everolimus-eluting stent; PES denotes paclitaxel-eluting stent; OR [95%CI] denotes odds ratio with 95% confidence interval. MI denotes myocardial infarction denotes; TLR denotes ischemia-driven target lesion revascularization; MACE denotes major adverse cardiovascular events (cardiac death, MI, or ischemia-driven TLR).
*According to the Academic Research Consortium (ARC) definite or probable definition.

statistically significant interactions were demonstrated between diabetes mellitus and stent type for the 2-year clinical end points of MI, stent thrombosis, TLR, and MACE. In patients without diabetes mellitus, significant improvements in nearly all measured safety and efficacy end points were present after treatment with EES compared with PES. Perhaps most striking is the observation that in patients without diabetes mellitus, stent thrombosis to 2 years occurred

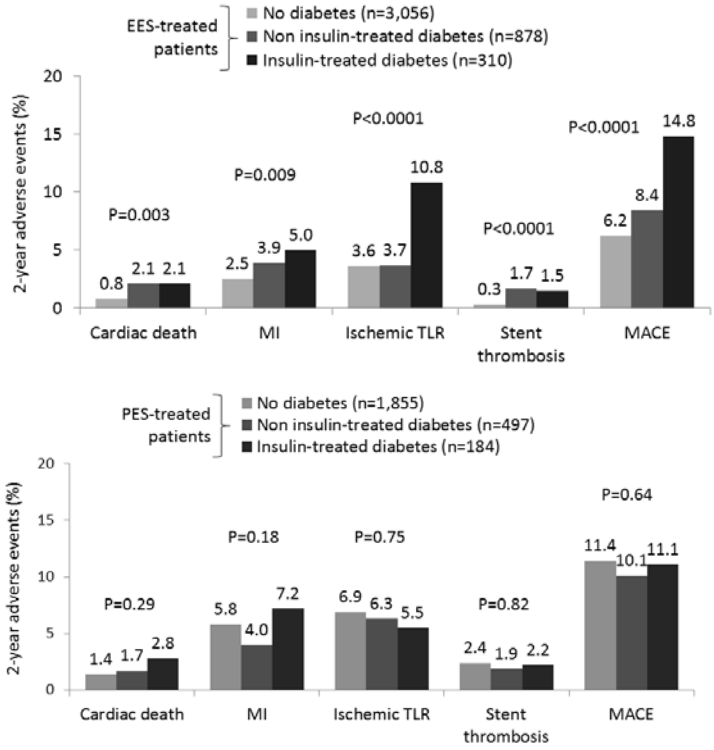


Figure 2 Two-year rates of adverse events according to diabetic status (no vs non–insulin-treated vs insulin-treated diabetes mellitus) in patients randomized to everolimus-eluting stents (EES; top) and paclitaxel-eluting stents (PES; bottom). TLR indicates target lesion revascularization; MACE, major adverse cardiac events.

in only 0.3% of patients with EES compared with 2.4% of patients with PES (*P*=0.0001). Conversely, no significant differences were observed at 2 years in the rates of any clinical outcomes (either efficacy or safety) after EES versus PES treatment in patients with medically treated diabetes mellitus, including stent thrombosis. The difference in the relative rates of TLR according to stent type and diabetic status is consistent with the angio-graphic substudy findings from the SPIRIT III study, in which the median difference in in-segment late loss at 8 months in favor of EES compared with PES was 0.15 mm in patients without diabetes mellitus but only 0.06 mm in patients with diabetes mellitus.[12] Moreover, prior studies with PES have shown comparable angiographic and clinical rates of restenosis in patients with and without diabetes mellitus.[7] These data may reflect the different mechanisms of action through which paclitaxel and rapamycin analogs reduce restenosis. By disrupting microtubular function, paclitaxel interferes with multiple pathways of restenosis (including smooth muscle cell proliferation and migration, extracellular matrix production, and

Table 6. Two-year event rates among patients with diabetes according to randomized stent type and insulin treatment

2-Year Events	EES (n=1188)	PES (n=681)	*p*
Cardiac death			
- Insulin-treated	2.1% (6)	2.8% (5)	0.59
- Non-insulin-treated	2.1% (18)	1.7% (8)	0.58
MI			
- Insulin-treated	5.0% (15)	7.2% (13)	0.32
- Non-insulin-treated	3.9% (33)	4.0% (19)	0.93
Ischemia-driven TLR			
- Insulin-treated	10.8% (31)	5.5% (10)	0.08
- Non-insulin-treated	3.7% (31)	6.3% (29)	0.04
Stent thrombosis*			
- Insulin-treated	1.5% (4)	2.2% (4)	0.44
- Non-insulin-treated	1.7% (14)	1.9% (9)	0.75
MACE			
- Insulin-treated	14.8% (43)	11.1% (20)	0.34
- Non-insulin-treated	8.4% (72)	10.1% (47)	0.39

Event rates are shown as Kaplan-Meier estimates, % (number of events). EES denotes everolimus-eluting stent; PES denotes paclitaxel-eluting stent; MI denotes myocardial infarction denotes; TLR denotes ischemia-driven target lesion revascularization; TVR denotes ischemia-drive target vessel revascularization; MACE denotes major adverse cardiovascular events (cardiac death, MI, or ischemia-driven TLR).

*According to the Academic Research Consortium (ARC) definition.

cell-to-cell signaling); thus, its effects appear to be relatively independent of the diabetic state.[17] In contrast, the mechanism of rapamycin is limited to interfering with cellular mitosis, a process tightly regulated by glycosylation-dependent enzymes.[18] Even more unexpected than the observed differences in TLR were the significant interactions present for the relative risks of MI and stent thrombosis between EES and PES according to the presence of diabetes mellitus. Although the increase in restenosis observed in diabetic compared with nondiabetic patients with EES (but not PES) may in part have contributed to its greater rate of MI in this cohort,[19] this mechanism is unlikely to completely explain the loss of the safety benefit for EES in the diabetic group. Further studies are required to elucidate the mechanisms underlying the higher rates of MI and stent thrombosis in diabetic patients treated with EES but not PES. Among patients treated with EES, an apparent gradient of effect was observed so that the 2-year rates of most adverse events were lowest in nondiabetic patients, intermediate in non–insulin-treated diabetic patients, and highest in insulin treated diabetic patients. Conversely, in patients treated with PES, no

such relationships were apparent, and measures of both safety and efficacy occurred with similar frequency regardless of diabetic status or treatment. Furthermore, among medically treated diabetic patients, although the relative risk of safety end points (cardiac death, MI, and stent thrombosis) did not vary significantly between stent type according to insulin treatment, a significant interaction was observed between insulin use and stent type on the 2-year risk of ischemia-driven TLR. Treatment with EES (versus PES) was associated with a significant reduction in TLR among non–insulin-treated diabetic patients, whereas a nonstatistically significant trend toward an increase in TLR with EES was observed in diabetic patients treated with insulin (*P*interaction=0.01). Further investigation is required to determine whether this observation may be explained by either inherent differences between the insulin-deficient versus -resistant state on the antirestenotic effects of rapamycin analogs or a direct inhibitory effect of insulin on the vascular response to rapamycin analog–eluting stents. Also of note is the observation that the 2-year rates of cardiac death, MI, and stent thrombosis were numerically but non significantly lower after EES versus PES implantation in patients with insulin treated diabetes mellitus, despite the directionally opposite increase in TLR. Larger studies are required to determine whether these directionally opposite trends in safety and efficacy reflect true differences between the stent types in insulin-treated diabetic patients or are due to chance. Several limitations of the present study should be considered.

As a post hoc analysis from 4 pooled, randomized trials, the results should be considered hypothesis generating. In particular, although with 1869 patients the present study is the largest randomized DES study to date in patients with diabetes mellitus, the sample size remains inadequate to exclude small differences between the 2 stent types in the diabetic cohort (whether favoring PES or EES). Given the observed event rates, a very large randomized trial (>5000 patients) restricted to patients with diabetes mellitus would be required to determine whether meaningful differences in safety outcomes between EES and PES exist in this cohort. Conversely, the clinical outcomes observed in the nondiabetic group demonstrating statistical superiority in numerous safety and efficacy end points with EES compared with PES are consistent with the primary results from each of the individual trials and do not require replication. Moreover, although the present study was adequately powered for interaction testing between stent type and diabetes mellitus versus no diabetes mellitus, sufficient power to uncover all significant interactions in the diabetic cohort according to insulin treatment may not have been present. As expected in analyses of subgroups, small differences in baseline characteristics in the

randomized stent groups were present, although the results regarding clinical outcomes were not altered by multivariable adjustment. Similarly, the results of the present study were consistent for both PES platforms (TAXUS Express and TAXUS Liberte´) for the end points analyzed. The present analysis was restricted to data available at 2 years after stent implantation. Longer-term follow-up is necessary to determine whether meaningful differences between the stent types in diabetic patients will emerge over time. Finally, the present study results specifically apply only to the comparison of PES with EES (and not necessarily to other rapamycin analog– eluting stents). In this regard, a previously reported metaanalysis of 5 modest-sized randomized trials of sirolimus-eluting stents versus PES in diabetic patients suggested a reduction in angiographic and clinical restenosis with sirolimus-eluting stents, although with comparable rates of cardiac death, MI, and stent thrombosis.[20] This study, however, did not include stratified subgroup diabetic data from other large trials in which there were no significant differences in the repeat revascularization rates between these 2 stents.[6,8] Our study also showed a reduction in TLR with EES compared with PES in non–insulin-treated diabetic patients. Larger studies are thus warranted to determine whether the findings from the present analysis in diabetic patients are generalizable to all stents eluting rapamycin analogs, especially in those treated with insulin. Because the EES is currently the most commonly used stent in the United States and Europe, the clinical implications of the present study require careful consideration. In patients without diabetes mellitus who undergo percutaneous coronary intervention, treatment with EES compared with PES provides considerable benefit with respect to freedom from death, MI, stent thrombosis, and recurrent ischemia necessitating repeat TLR procedures. Thus, EES should clearly be preferred over PES in nondiabetic patients. In patients with diabetes mellitus, 2-year outcomes in the present study did not vary substantially after treatment with EES compared with PES, suggesting clinical equipoise between the devices. For those using EES routinely in patients with and without diabetes mellitus, the current analysis does not require a change in practice, especially because the present study suggests that EES compared with PES may reduce ischemia-driven TLR in non–insulin-treated diabetic patients. Further studies are required to determine the optimal stent choice for patients with insulin-treated diabetes mellitus.

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DISCLOSURES

Dr Stone reports having served as a consultant for Boston Scientific, Abbott Vascular, and Medtronic. Dr Kereiakes reports having served as a consultant for and having received grants and/or research support from Boston Scientific and Abbott Vascular. Dr Smits reports having served as a consultant for Boston Scientific, St. Jude, Blue Medical, and Abbott Vascular and having received lecture honoraria from Abbott Vascular. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Patients with diabetes mellitus are at high risk for major adverse cardiac events after percutaneous coronary intervention. Drug-eluting compared with bare metal stents improve event-free survival in diabetic patients by decreasing ischemiadriven repeat revascularization procedures (target lesion revascularization). In large trials, everolimus-eluting stents have been shown to be safer and more effective than paclitaxel-eluting stents; whether this holds equally for diabetic patients has been debated. In the present large-scale study drawn from a pooled patient-level analysis of 4 randomized trials, patients without diabetes mellitus treated with everolimus-eluting stents compared with paclitaxel-eluting stents had significantly reduced 2-year rates of mortality, myocardial infarction, stent thrombosis, and ischemia-driven target lesion revascularization. In contrast, clinical outcomes with the 2 stents were not significantly different in patients with diabetes mellitus. Statistically significant interaction effects were present, suggesting that the difference in the relative effects of these 2 stents is conditioned by the diabetic state. Furthermore, non–insulin-treated diabetic patients had reduced rates of ischemia-driven target lesion revascularization with everolimus-eluting stents, whereas insulin-treated patients tended to have reduced rates of ischemia-driven target lesion revascularization with paclitaxel-eluting stents. These data thus demonstrate that the diabetic state, specifically insulin treatment, may substantially affect the clinical outcomes of patients treated with everolimus-eluting stents and paclitaxel-eluting stents. Further studies are required to understand the mechanisms underlying these findings so that more effective therapies can be developed for high-risk patients with diabetes mellitus.

Chapter 4.2

The Clinical Impact of the Second Generation Everolimus-eluting stent Compared to the First Generation Drug-Eluting Stents in Diabetes Mellitus Patients: Insights from a nation-wide coronary intervention register.

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JACC *submitted*

ABSTRACT

Objectives:
To study the second-generation everolimus-eluting stent (EES) as compared to first-generation sirolimus-eluting (SES) and paclitaxel-eluting stents (PES) in diabetes mellitus (DM) patients.

Background*:*
There is limited data available comparing EES with SES, while studies comparing EES to PES are not powered for low-frequency endpoints.

Methods:
All DM patients treated with EES, PES or SES from January 18th 2007 till July 29th 2011 from the Swedish Coronary Angiography and Angioplasty Register (SCAAR) were included. EES was compared to SES or PES for clinically-driven detected restenosis, definite stent thrombosis (ST) and all-cause mortality.

Results:
In 4751 PCI-treated DM patients 8.134 stents were implanted (EES = 3928, PES = 2836, SES = 1370). The EES was associated with significantly lower all-cause mortality than SES and PES (EES vs. SES Hazard ratio (HR) 2.02; 95% Confidence Interval (CI) [1.03-3.98]; EES vs. PES HR, 1.69; 95% CI [1.06-2.72]). EES was also associated with significantly lower ST rates than SES while only a trend was observed in PES (EES vs. SES HR 2.87 95% CI [1.08-7.61]; EES vs. PES HR 1.74 CI [0.82-3.71]). No differences in restenosis rates were observed between EES and SES or PES (EES vs. SES HR 1.26; 95% CI[0.77-2.08]; EES vs. PES HR 1.05; 95% CI[0.71-1.55]).

Conclusions:
The EES is associated with significantly lower mortality rates when compared to SES and PES in all-comer DM patients, and with low rates of ST. No differences in restenosis rates were observed with EES as compared to SES and PES.

KEY WORDS:

Everolimus-eluting stent, Sirolimus-eluting stent, Paclitaxel-eluting stent, Diabetes Mellitus, Stent Thrombosis, Restenosis, all-cause mortality, SCAAR

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INTRODUCTION

The introduction of the first generation sirolimus- and paclitaxel -eluting stents (SES and PES) has led to markedly reduced restenosis rates and reduced need for target lesion revascularisation compared to bare metal stents, in diabetics as well as non-diabetic patients.[1-5] However diabetes mellitus (DM) remains associated with increased risk of in-stent restenosis, target lesion revascularisation, and target vessel revascularisation in patients undergoing percutaneous coronary interventions (PCI).[6] The second generation everolimus-eluting stent (EES), has recently been found to be superior to the first-generation PES for reduction of target lesion revascularisation, target vessel revascularisation and ST in two large randomised trials, however these significant improvements in safety and efficacy endpoints were limited to the non-diabetic subgroup of patients, as no differences in treatment effect between these two stents were observed in DM patients in both trials.[7,8] These findings were further confirmed by a large patient-level pooled analysis from four randomised clinical trials comparing EES to PES.[9] Furthermore, when stratified for insulin vs. non-insulin treatment, a statistically significant interaction emerged, suggesting a difference in the relative treatment effects of these two devices. Whether these results hold true in larger all-comer population is unknown. There is a paucity of data on differences in clinical outcomes between EES and SES in DM setting, as the only data available derives from relatively small series of patients and therefore are not adequately powered to detect low frequency endpoints.[10] Different issues regarding the impact of metal alloy, strut thickness, polymer biocompatibility and especially the effect of eluted active principle in patients with DM remain still unanswered. For this reason we compared the safety and

efficacy of the second generation EES as compared to the most studied first generation DES, represented by the SES and PES in diabetic patients using the data from the Swedish Coronary Angiography and Angioplasty Register (SCAAR).[11]

METHODS

Study sample

For the present analysis we analyzed all PCI-treated DM patients from the SCAAR database between January 2007 (date when the first EES stent was implanted in a DM patient in Sweden) and July 30th 2011, that were treated with one of the following stents: EES, PES, or SES. The EES was compared individually with PES and SES for the 1-year incidence of clinically driven, angiography visualised in-stent restenosis, stent thrombosis and all-cause mortality.

The SCAAR has been previously described.[11,12] Briefly, this registry holds data on consecutive patients from all 29 centres that perform coronary angiography and percutaneous coronary intervention (PCI) in Sweden. The registry is sponsored by the Swedish Health Authorities and is independent of commercial funding. The technology is developed and administered by the Uppsala Clinical Research Centre. Since 2001, SCAAR has been web-based, with recording of data online through a Web-interface in the catheterization laboratory; data are transferred in an encrypted format to a central server at the Uppsala Clinical Research Centre. All patients undergoing a coronary angiography or a PCI procedure nation-wide are included. Since May 2005 all information with respect to restenosis and stent thrombosis of previously treated patients that return in the catheterisation lab for subsequent coronary angiography or PCI is entered in the SCAAR as well as the indication of such procedures. The web-based system provides each centre with immediate and continuous feedback on processes and quality-of-care measures. Monitoring and verification of registry data are periodically performed in all hospitals since 2001 by comparing 50 entered variables in 20 randomly selected interventions per hospital and year with the patients' hospital records.

Study endpoints

The SCAAR register includes follow-up data for every implanted stent device permitting device-oriented as well as patient-oriented endpoint analysis. For the current study the analysis on restenosis and ST are performed at device level while mortality is analysed at patient level. The same definition for restenosis

as defined by the SCAAR steering committee were used. The SCAAR definitions of restenosis is defined as a stenosis assessed by angiographic visual estimation (>50%) or by fractional flow reserve value (FFR) of < 0.80 in a previously stented segments identified by coronary angiography for any clinical indication in any of the 29 centres in Sweden.[11,12] The clinical relevance of restenotic lesions was detected by symptoms, routine non-invasive functional testing (exercise test, myocardial scintigraphy) and/or invasive functional evaluation by fractional flow reserve. The clinically driven detected restenosis, the efficacy endpoint in this study, differs from the classical target lesion revascularisation endpoints used in other large studies. The target lesion revascularisation combines revascularizations performed due to restenosis as well as ST and therefore may introduce biases, especially for high risk populations treated with first generation DES, where the ST can generate a consistent percentage of the target lesion revascularisation events. To avoid biases that can arise by pooling efficacy and safety endpoints, in our analysis we reported restenosis and ST separately.

Stent thrombosis was defined in SCAAR as an angiographic occlusion or a non-occlusive thrombus in a previously implanted stent with an acute clinical presentation[13], definition that resembles highly the ACR definition of definite ST.[14]

All-cause mortality data were obtained from the National Population Death Registry. The merging of the registries was performed by the Epidemiologic Centre of the Swedish National Board of Health and Welfare and approved by the local ethical committee at the Uppsala University.

Statistical analysis

The baseline clinical and angiographic characteristics were compared by means of the χ^2 test for categorical variables and the *t* test for the continuous variables. Stent groups were compared using survival analyses. The Kaplan-Meier estimator was used to compute cumulative hazards and Cox proportional hazards regression to estimate hazard ratios. Differences between stent groups in baseline characteristics were adjusted by using propensity score methods. Two different propensity scores were created, both defined as the conditional probability of having a Everolimus-eluting stent, one in a populations of stents with only Everolimus or Paclitaxel-eluting stents and the other in a population with only Everolimus or Sirolimus-eluting stents. The following variables were forced into logistic regression models: previous myocardial infarction, coronary artery bypass grafting (CABG) or PCI; gender; hypertension; hyperlipidemia; smoking; prior aspirin, clopidogrel or warfarine use; anticoagulant use;

glycoprotein IIb/IIIa inhibitor use; number of vessel disease; graft; restenosis; chronic occlusion; indication for PCI; complete revascularisation; bifurcation lesion; type of lesion and hospital. These propensity scores were entered in Cox proportional hazards models together with the type of stent drug and the year of PCI procedure to calculate the adjusted hazard ratio for ST and restenosis. In a similar way two additional propensity scores were created and used in the outcome analysis of all-cause mortality including the following variables: previous myocardial infarction, CABG or PCI; gender; hypertension; hyperlipidemia; smoking; number of vessel disease; indication for PCI; complete revascularisation; bifurcation lesion; hospital.

The same endpoints were evaluated in medically treated DM as stratified for insulin treatment. Statistical interaction between insulin treatment and stent type was examined by introducing these variables as interaction terms in the Cox proportional hazard models.

All statistical analyses were performed with SPSS version 19 (Chicago, IL)

RESULTS

A total of 4751 DM patients were treated with PCI and were included in the present study. These patients received 8.134 drug eluting stents; respectively 3928 EES (average 2.23±1.25 stent per patient), 2836 PES (average 2.03±1.11 stent per patient), 1370 SES (average 2.34±1.34 stent per patient). Baseline characteristics of the groups are shown in Table 1. Although, baseline clinical and angiographic results were in general well balanced some significant differences were detected.

Clinical outcomes

Clinical outcome data are presented in Table 2.

The EES was associated with significantly lower rates of all-cause mortality compared to SES or PES after adjustment for propensity scores (EES vs. SES HR 2.02, 95%CI[1.03-3.98]; EES vs. PES HR 1.69; 95% CI[1.06-2.72]). After stratifying for insulin dependence a trend to lower mortality rates with EES was maintained irrespective of insulin treatment, but reached significance only for the EES and SES comparison in the insulin treated group (Table 2).

No differences were seen in restenosis rates when comparing EES to SES or PES even after stratifying for insulin treatment (Figure 1). A trend towards better outcomes with EES was observed when compared to SES in non-insulin treated diabetes mellitus patients, while no differences were observed in

Table 1. Baseline clinical and angiographic characteristics

	Everolimus	Paclitaxel	Sirolimus	P-value
Number of stents (n)	3928	2836	1370	
Patient Background				
Age (±SD)	66.7±10.1	67.4±9.865	65.9±9.8	<0.001
Female (%)	29.8	30.3	32.0	0.31
Never smoked (%)	36.0	41.5	39.0	<0.001
Hypertension treated (%)	82.3	79.5	77.7	0.001
Hyperlipidaemia	77.9	76.9	78.8	0.04
Previous MI (%)	46.1	46.4	44.2	0.50
Previous PCI (%)	41.3	44.9	46.4	<0.001
Previous CABG	17.8	18.5	18.2	0.74
Diabetes (%)	100	100	100	<0.001
- Insulin treatment	47.2	52.3	49.5	
- No insulin treatment	52.4	47.7	50.2	
GP IIbIIIa (%)	9.5	11.9	7.9	<0.001
Indication for index procedure				<0.001
Stable angina (%)	33.9	35.4	35.8	
Unstable anigina (%)	53.8	50.6	54.7	
STEMI (%)	10.0	11.5	8.1	
Other (%)	2.3	2.6	1.3	
Treated vessel and lesion type				0.001
LM (%)	3.3	4.1	2.8	
LAD (%)	42.8	39.9	42.6	
LCX (%)	22.9	24.4	24.2	
RCA (%)	26.2	26.3	25.2	
Vein graft (%)	4.8	5.3	5.3	
1-VD (%)	28.3	28.6	34.3	<0.001
2-VD (%)	33.7	32.9	33.4	
3-VD (%)	28.2	26.6	25.5	
Left main (%)	7.6	9.4	4.4	
Type A-B1 lesion (%)	40.9	38.0	33.5	<0.001
Type B2-C lesion (%)	59.1	62.0	66.5	
De novo (%)	89.8	86.6	80.7	<0.001
In stent restenosis (%)	10.2	13.4	19.3	<0.001
CTO (%)	4.9	4.3	6.1	0.08
Stent length (mm, SD)	19.4±7.4	19.4±6.9	18.6±7.2	<0.001
Stent diameter (mm, SD)	2.91±0.47	2.87±0.42	2.98±0.54	<0.001
Mean number of stents	2.23±1.25	2.03±1.11	2.34±1.34	<0.001

Anticoagulant use				
Heparin	74.1	84.2	59.0	<0.001
LMWH	7.4	3.6	9.3	<0.001
Bivalirudin	17.6	11.4	30.9	<0.001
Antiplatelet prior to PCI				
Aspirin	96.2	96.4	95.8	0.74
Clopidogrel	88.2	85.5	85.7	0.002
Warfarin	1.2	1.8	1.2	0.03

CTO = chronic total occlusion; GP IIbIIIa = glycoprotein IIbIIIa inhibitor; LAD = left anterior descending; LCX = left circumflex artery; LM = left main; LMWH = low molecular weight heparin; PCI = percutaneous coronary intervention; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction * 1st generation

Table 2. Adjusted hazard ratios for restenosis, stent thrombosis and all-cause mortality

Stent type	Nr of stents	Restenosis Nr	Adjusted hazard ratio (95% CI)	Stent Thrombosis Nr	Adjusted hazard ratio (95% CI)	Nr of patients	Deaths Nr	Adjusted hazard ratio (95% CI)
All diabetics								
Everolimus	3928	113	1.0	27	1.0	1915	82	1.0
Paclitaxel	2836	96	1.05 (0.71-1.55)	34	1.74 (0.82-3.71)	1386	76	1.69 (1.06-2.72)
Everolimus	3928	113	1.0	27	1.0	1915	82	1.0
Serolimus	1370	64	1.26 (0.77-2.08)	18	2.87 (1.08-7.61)	717	35	2.02 (1.03-3.98)
Insulin-treated								
Everolimus	1855	73	1.0	17	1.0	880	49	1.0
Paclitaxel	1484	68	1.21 (0.74-1.98)	30	2.37 (0.97-5.81)	703	50	1.99 (0.82-4.86)
Everolimus	1855	73	1.0	17	1.0	880	49	1.0
Serolimus	678	36	0.95 (0.48-1.88)	12	2.67 (0.76-9.44)	357	24	1.98 (1.07-3.68)
Non-insulin treated								
Everolimus	2060	40	1.0	10	1.0	1028	33	1.0
Paclitaxel	1352	28	0.81 (0.41-1.59)	4	0.69 (0.13-3.67)	683	26	1.44 (0.67-3.11)
Everolimus	2060	40	1.0	10	1.0	1028	33	1.0
Serolimus	688	26	1.76 (0.82-3.77)	6	3.41 (0.70-16.57)	357	11	2.22 (0.75-6.61)

95%CI = 95% confidence interval.

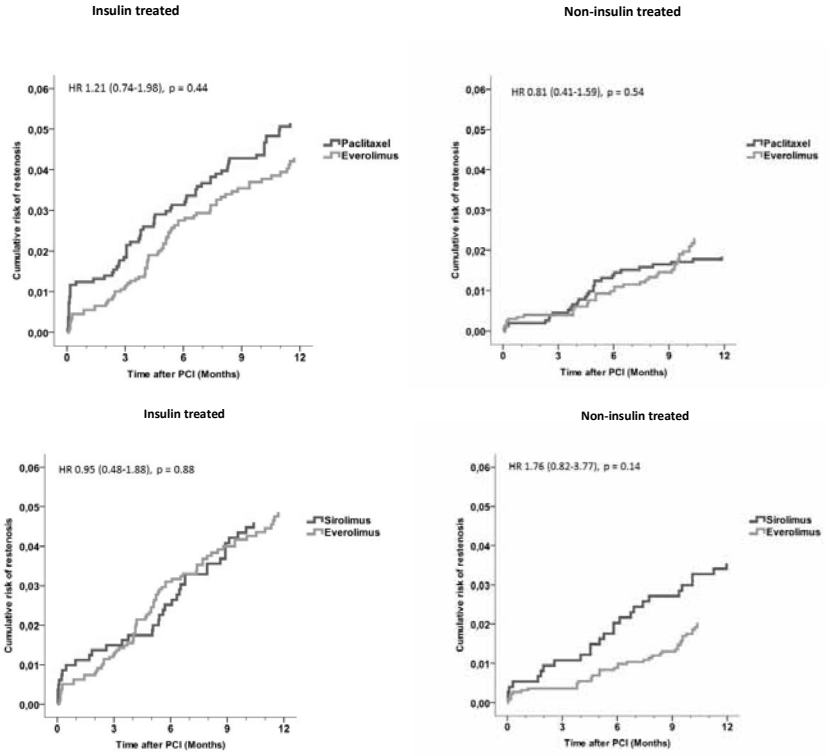

Figure 1 Time to event Kaplan-Meier curves of propensity score adjusted in-stent restenosis. Data stratified to insulin treated (left) and non-insulin treated (right).

insulin dependent DM patients. In the EES to PES comparison no differences were observed between groups, however a small trend for better outcomes with EES was observed in insulin treated DM while the opposite trend was observed in non-insulin treated DM. A significant interaction between stent type and insulin dependence was found for restenosis outcomes for EES vs. PES ($p<0.001$) and EES vs. SES ($p=0.001$).

For all diabetics, rates of ST were numerically higher for both PES and SES as compared to EES, with a significantly higher risk for SES (Table 2). For the insulin-treated subgroup, stent thrombosis rates were not significantly different among stents, albeit numerically higher for both PES and SES compared to EES. Among the non-insulin treated diabetics a trend towards higher stent thrombosis rates was found for SES compared to EES, whereas the opposite was found for PES. For cumulative 1-year rate of stent thrombosis (Figure 2) a significant interaction between stent type and insulin treatment was found for EES vs. PES ($p<0.001$), but not EES vs. SES ($p=0.31$).

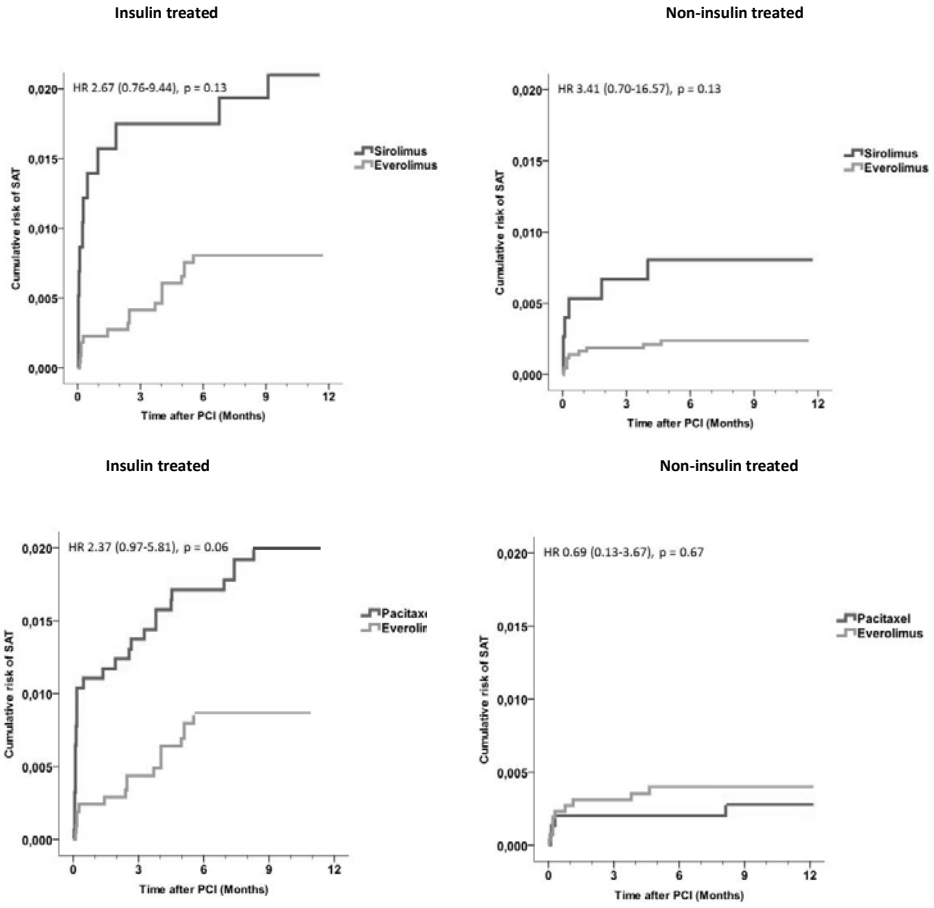

Figure 2 Time to event Kaplan-Meier curves of propensity score adjusted definite stent thrombosis. Data stratified to insulin treated (left) and non-insulin treated (right).

DISCUSSION

The major findings of the present analysis, the largest study up to date comparing the outcomes of first and second generation DES in DM, are 1) treatment with EES was associated with a significantly lower all-cause mortality when compared respectively to SES and PES, 2) that EES was associated with significantly lower rates of definite ST when compared to SES and a trend for lower ST when compared to PES, 3) no significant differences in restenosis rates were observed when comparing EES with PES and EES with SES in DM patients and finally 4) that there is a significant interaction for restenosis outcomes in EES and PES as well as EES and SES when stratified for non-insulin treated DM vs. insulin treated DM.

While the performance of EES and PES in DM has been extensively studied in large randomized trials as well as patient level pooled databases, there is a paucity of data when comparing the EES with SES in all-comer DM patients.[8,9,15,16] However all available studies comparing EES to SES or PES have been inadequately powered to provide answers on end-points such as all-cause mortality and ST, as well as providing insights on treatment effect differences on DM patients when further stratified according to insulin treatment. As dedicated randomised and adequately powered trials to study such low frequency events may represent significant organizatory or financial challenges, data from large national registers can be used to provide insights that can further guide our daily clinical practice and future research, as is the case here. Indeed this study reports for the first time a significant difference in all-cause mortality between EES as compared separately to SES and PES. Such a finding should mainly be attributed to the magnitude of this analysis that with its almost 5000 patients represents the largest study that has analysed the most used first generation SES and PES with a second generation drug eluting stent in a DM population. What is striking is that the mortality outcomes with EES as compared to SES or PES, in all DM patients, as well as in DM patients stratified for insulin dependence closely parallel the outcomes of definite ST. The reduction in mortality rates with EES may be attributed to the lower rates of definite ST, which as shown in previous studies has a strong correlation with death or myocardial infarction.[17]

The EES was associated with a significantly lower rate of ST when compared to SES in the total DM population. The same trend was observed also after stratifying for insulin treatment. The second generation EES has emerged as a very promising stent with low rates of ST, as concluded from several large prospective randomised trials with moderate risk or all-comer patients, but this is the first time that such a finding was observed specifically in a large cohort of DM patients[7,8]. The pathophysiological mechanism(s) underlying the marked reduction in ST following EES implantation, although speculative, may relate to specific design features of this stent. The combination of thin, fracture-resistant struts, the low dose of everolimus, and the thromboresistant non-inflammatory proprieties of the fluorinated polymer may contribute to the lower rates of early ST with EES.[18,19] Another possible mechanism may be a more rapid and complete stent re-endothelialisation as observed in pre-clinical animal models.[19] However such advantages offered from EES as compared to PES in non-diabetics are less pronounced in DM patients as shown also from the present analysis.[20] Interestingly, a significant reduction on definite ST with EES as compared to PES was observed also in the insulin treated DM patients,

while an opposite trend was observed in non-insulin treated DM. Although such findings can be due to chance, it is also known that insulin treated DM represents the most severe form of this condition, which often has a longer duration and therefore can be expected to be associated with a more severe form of coronary disease. This could be the reason why the rates of ST with PES (as shown in Figure 2) in the insulin treated IDDM patients were higher in this subgroup, similarly as observed in other high risk populations.[21] However, it cannot be excluded that different treatment effects of EES as compared to PES may be present in DM patients when stratified for insulin dependence, therefore more evidence is needed to clarify this issue.

Another important finding is that this study, despite its large size, could not detect any significant differences in restenosis rates between EES and PES as well as EES and SES. These results corroborate previous findings from other studies comparing EES to PES or SES in DM.[9,10,22] No difference in restenosis rates between EES and PES or EES and SES could be detected even when the analysis was performed in DM patients stratified for insulin dependence, however a significant interaction was detected for EES as compared to PES or SES. Indeed these findings reflect once more the severity and complexity of the coronary disease in DM patients. These patients are known to have increased oxidative stress and profound endothelial dysfunction, both factors which are believed to strongly impact intracellular signal transduction. As a result the cell growth and migration inhibition (anti-restenotic effect) exerted from both paclitaxel or rapamycin analogs is altered in these patients, resulting in a similarly affected efficacy for both rapamycin-analogs or paclitaxel eluting stents.[23,24] The imbalance in efficacy outcomes with EES as compared to PES, as indicated from the observed interaction when stratified for IDDM and NIDDM may also rely on the impact of the insulin resistance on the mechanism of action of the active principle eluted from these stents. While the mechanism of action of paclitaxel may be less influenced from the DM status, the rapamycin (and other rapamycin analogs) inhibition of mTOR may be affected by the insulin resistance as it is regulated from glycosilation-dependent enzymes.[25] However, as the intracellular signalling pathways in these patients are very complex and not entirely understood, this interpretation should be only regarded as a hypothesis which needs further investigation. A significant interaction was observed also in EES versus SES comparison in IDDM and NIDDM. Although both stents do elute a rapamycin-analog, the polymer and release kinetics of the SES and EES differ from each other in that sirolimus is released at a higher dose and for a longer period of time than everolimus.[26] The SES specific release kinetics may offer some advantages in protection from restenosis in DM patients, which

magnitude seems to parallel the DM severity. However, although this release kinetics of SES may in a way counterbalance the design related disadvantages such as thicker stent struts and polymer layer, and in term of efficacy lead to similar outcomes as EES, it may render this device more vulnerable to ST, as indeed observedIn the light of this findings the newer, recently introduced, modern design, rapamycin-analogs or paclitaxel–eluting stents with durable, bioabsorbable or polymer-free platforms may theoretically represent valid alternatives on regards of both safety and efficacy in percutaneous treatment of DM patients, and therefore need to be studied in large and dedicated randomised trials.

This study has several limitations. This analysis represents a retrospective register study, therefore due to lack of randomisation, differences may arise on baseline characteristics, however adjustments for baseline differences were implemented using propensity score analysis, for each individual stent comparison incorporating 22 baseline variables. In this study the analysis of device performance was performed on the device level and therefore can differ slightly from endpoints used in other trials. Indeed the clinically driven restenosis detection, the efficacy endpoint in this study, differs from the classical TVR/TLR endpoint, however, in our opinion, it offers an more accurate evaluation of device efficacy than the classical endpoints, as explained in the method section.

This analysis incorporates only patients included in SCAAR, these results represent only the Swedish population and the standard of care, however Sweden has adopted the ESC guidelines and therefore we do believe that they can be extrapolated to the rest of the western world.

In conclusion, this analysis, the largest to date to study the impact of second generation EES in DM patients as compared to first generation PES and SES showed significantly lower rates of all-cause mortality for EES; an effect that may mainly rely on the safety improvements with this device, as no differences in efficacy outcomes were observed between these stents. Further data from large clinical trials, are needed to clarify if either rapamycin-analogs or paclitaxel, eluted from modern stent designs, should become the eluting principle agent of choice in DM patients.

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Chapter 5

Summary, conclusions and clinical perspective

SUMMARY OF THE THESIS

Nowadays, as PCI has become the treatment modality of choice for patients with coronary heart disease and millions of patients worldwide are treated with PCI each year, device short and long term differences in treatment outcomes do have important implications for global health. Thanks to improvements in device design and performance, new techniques and treatment strategies, major achievements has been possible even in patients with complex and severe coronary disease. This thesis reflects the results of our research with the second generation EES in all-comer patients as well as high risk patients presenting with MI or diabetes mellitus. The results, their clinical impact, and future implications will be discussed in detail below.

Chapter 2.

In the COMPARE trial the use of second-generation EES as compared with PES, was associated with a significant reduction in the risk of major adverse cardiac events at 1 year. The outcome of the primary endpoint was consistent across all but one subgroup: patients with diabetes mellitus. The superior outcome with EES was a result of reduction in the rate of non-fatal MI, a safety component of the primary endpoint, and reduction in repeat revascularisation of the target vessel, while the rates of all-cause or cardiac mortality did not differ between the two groups. The significantly lower rate of MI with EES was already apparent at 30 days and was attributable to a significantly lower rate of early ST as there was no significant difference between the groups in the rate of periprocedural MI.

In the second paper we have shown that the substantial clinical benefit of the EES stent over the PES with regard to measures of both safety and efficacy is maintained at 2 years in real-life practice. We observed an increasing benefit in terms of safety and efficacy between one and two years. The benefit associated to EES usage, at 2 years, was driven by reductions in both MI and TVR. A further reduction in ST was observed between 1-2 years resulting in a reduction of cumulative ST at 2 years. As was the case at one year also at two years no differences were observed in the outcomes of the primary endpoint between EES and PES in the diabetic population. Further research was therefore required to understand the lack of benefit of EES over PES in this setting, or if larger populations should be studied to detect underlying differences in this subset of patients.

Importantly the safety of the EES is maintained also in the subgroup of patients presenting with MI as shown in the third paper of this chapter. In this

study the use of the second generation EES in percutaneous coronary intervention for acute myocardial infarction, as compared to PES, was associated with a significant reduction in the risk of both primary and secondary endpoint. These event-free survival improvements with EES were driven by a reduction in repeat TVR/TLR as well as non-fatal MI, a safety component of the primary and secondary endpoint, while no apparent differences were observed in rates of all-cause and cardiac mortality. In respect to the primary as well as secondary endpoints the curves separate already early, effect that grows in magnitude through the 2-year follow-up period.

Another notable finding of this study is that the use of EES was associated with a significant reduction in ST, when compared to PES. We also note that EES, in terms of safety performs at least as safe as BMS when used in MI setting, when historically compared.

The treatment effect is maintained also for the STEMI and NSTEMI subgroups with respect to the primary and secondary endpoints, including their component endpoints and ST.

The impact of the previous findings results in the following clinical impact and perspectives: (1) based on the finding of COMPARE and SPIRIT IV first generation PES is mainly not used any more worldwide, while the use of PES with modern designs in DM is being studied, (2) COMPARE, was historically important as for the first time it showed that with the second generation EES, efficacy improvements could be matched also by safety improvements, even in all-comer populations, opening new bright horizons for percutaneous treatment in patients with complex coronary disease, (3) in setting of AMI, the long held concerns on safety of DES are no more grounded with the new generations of DES and particularly with the second-generation EES, and therefore the widespread use of DES for treatment of AMI should be guided by cost-effectively trials, (4) that the outcomes of the major cardiovascular events and ST in MI patients treated with EES are not different than those of the all-comer population, and therefore the MI patients on a long term device outcome perspective should not be considered as high risk. Together with what discussed in point 3) treatment with modern generation DES offers new perspectives for new strategy approaches on regard to the percutaneous intervention treatment as well as antiplatelet therapy of MI patients.

Chapter 3

The SPIRIT IV and COMPARE trials, discussed together in the first paper, have demonstrated that large-scale studies in complex patients and lesions are required to elicit important clinical differences between devices.

Based on the results of these two trials, the belief that had previously been held by some that clinically relevant differences between DES of various designs do not exist (the so called DES class effect) has clearly been discredited. Greater mechanistic insights into how the design properties of the EES translate into improved safety and effectiveness compared with earlier designs will no doubt spur development of even safer and more effective devices. These trials have also shown that low angiographic late loss (resulting in greater efficacy) as well as improved safety may be simultaneously achieved in a single DES platform. Both trials showed strikingly similar relative risk reductions in thrombotic events with EES compared with PES at 30-day and one-year follow-up, with the majority of the stent thromboses occurring during the first 30 days. Until recently, the interventional community has been focused on very late stent thrombosis (after one year) given the ongoing propensity of first-generation DES to occlude acutely after one year when compared with BMS. However, early stent thrombosis accounts for the majority of stent thrombosis events during follow-up. This is even more evident in complex populations as shown in the COMPARE trail. It becomes therefore evident that in order to reduce the ST outcomes with new devices, the technological improvements should focus not only on reduction of very late ST, but most importantly, in the reduction of early ST as is the case with EES.

The second paper, a result of a collaboration with the New York based Cardiovascular Research Foundation and Columbia University as well as with the University of Cincinnati, Ohio and Erasmus Medical Centre affiliated to the Erasmus Universiteit Rotteradm, The Netherlands, with its 6785 patients represented the largest study comparing ST rates between a first and second-generation DES at the moment is was performed, and was powered enough to study time frame outcomes (landscape analyses) as well as identify predictors of ST. The major finding of this analysis was that EES markedly reduced the 2-year rates of ST compared to PES, with significant difference in ST frequency present at every time interval examined through the 2-year follow-up period. By multivariable analysis, stent type (PES compared to EES) was found to be an independent predictor of 2-year ST. Younger age, diabetes mellitus, multivessel treatment and lesion length were also predictive factors for ST.

Importantly the reduction in ST was accompanied by a reduction in the composite occurrence of cardiac death or MI.

The premise that EES-treated patients, due to the improved safety profile compared to the first generation DES, may require shorter durations of DAPT is also supported by the findings of the current analyses. Indeed interruption of DAPT at any time point after the first month did not influence the rate of ST at two years in the EES cohort. After excluding events within the first 6 months, no difference was observed with regard to ST rates in the EES cohort regardless of DAPT compliance, suggesting that permanent DAPT interruption beyond 6 months following EES implantation may be safe. In contradistinction, we found that discontinuation of DAPT following PES deployment any time before 24 months (but especially between 1 and 6 months) was associated with increased rates of ST.

Such findings remain hypothesis generating but shorter duration of DAPT, which may be associated with lower bleeding risks and therefore lower mortality, are being intensively studied in different prospective randomised clinical trails worldwide.

Chapter 4

The first paper represents the larges patient level pooled database ever analysed to date, evaluates the relative safety and efficacy of different DES types stratified by the presence of diabetes mellitus, showed the following important findings: (1) that a significant interaction was present between diabetic status and treatment with EES compared with PES on the relative risk of 2-year clinical outcomes, reflecting measures of both safety and efficacy; (2) that in patients without diabetes mellitus, treatment with EES compared with PES reduced the 2-year rates of death, MI, stent thrombosis, ischemia-driven TLR, and MACE, whereas in patients with diabetes mellitus, there were no significant differences in clinical outcomes at 2 years between the stent types; and (3) that an additional interaction was identified among patients with diabetes mellitus so that the 2-year rate of ischemia-driven TLR was reduced with EES compared with PES in those not requiring insulin, whereas the opposite trend was observed in those who were treated with insulin.

The second paper represents the largest retrospective register analysis which focuses only on treatment differences with first and second generation DES in patients with medically treated diabetes mellitus, was performed using the data of the Swedish Coronary Angiography and Angioplasty Register (SCAAR) thanks to the cooperation with the Department of Medical Sciences Uppsala University , Department of Cardiology, Lund University, and the Cardiology Department, Heart and Lung Institute of the Sahlgrenska University Hospital, Göteborg, Sweden.

The outcomes of this study, representing all-comer patients DM patients treated with PCI in Sweden, showed that: (1) treatment with EES was associated with a significant lower rates of all-cause mortality when compared respectively to SES and PES, (2) that there is a significant lower rate of definitive ST with EES as compared to SES and, although significance was not reached, the same important trend was observed also when compared to PES, (3) that no significant differences in restenosis rates were observed when comparing EES with PES and EES with SES in DM patients and finally, (4) that there is a significant interaction for restenosis outcomes in EES and PES as well as EES and SES when stratified for NIDDM vs. IDDM.

While pointing for the first time to important safety improvements, as represented from the lower rates of mortality with EES, this study concords with the previous one in that there is room for improvement, especially in efficacy outcomes in patients with diabetes mellitus and that other large size studies are required to study: (1) whether rapamycin-analogs or paclitaxel should become the eluting principle agent of choice in DM patients, (2) the impact of drug -elution profile and especially of the elution time, (3) the impact of the stent design focusing in the type of metal alloys, strut thickens and role of polymer.

New clinical trials and future perspectives

The research presented in this thesis has opened new horizons for the interventional cardiology. Indeed different hypothesis, generated on the base of the outcomes with EES from our own studies and from the results of the patient –level pooled database of SPIRIT II, III, IV and COMPARE trials, have now been transformed in new already ongoing clinical trials.

Based on the improved outcomes with EES in MI patients (STEMI and NSTEMI) in efficacy and specifically, safety endpoints, new treatment strategies in STEMI are being tested. The COMPARE -ACUTE is a prospective, randomised, multicentre trail that is comparing (for superiority) the clinical outcomes between two treatment strategies in almost 900 STEMI patients: a new revascularisation strategy, guided by fractional flow reserve measurements, for treatment of non-culprit arteries during the same procedure or hospitalisation versus the staged revascularisation based on evidence of ischemia on non invasive tests, which represents the actual strategy of choice, as recommended from the guidelines.

Another prospective, randomised, multicentre trial (DAPT-STEMI) is testing (for non-inferiority in terms of net (TIMI major bleeding included) clinical major cardiovascular events) the duration of DAPT after stenting with DES

in STEMI patients. In this trial approximately 1100 patients will be enrolled and the event-free patients at 6 months (approximately 1000) will be further randomised in single (aspirin alone) arm versus double antipaletelet therapy (aspirin and a P2Y12 inhibitor) arm and will be followed for 18 months after randomisation.

Furthermore results of the SPIRIT series of trials and COMPARE trials, allowed us to examine how the results of the randomized SYNTAX trial, a 1700-patient study of PES versus CABG in patients with left main and three-vessel coronary artery disease, might have been influenced if EES was used in place of PES. As result of this paper, published last year in the Netherlands Heart Journal together with the colleagues from the Academic Medical Centre affiliated to the University of Amsterdam, we concluded that the use of EES rather than PES in the SYNTAX trial might have led to a total reduction of 81 events in the PCI group, much more than the 20 needed events to declare noninferiority for PCI in this trial. This analysis, of course, is only a hypothesis-generating exercise; whether PCI with the EES is truly noninferior (or superior) to CABG in patients with complex coronary artery disease can only be determined by a dedicated large randomized controlled trial. Indeed such trial (The international Evaluation of XIENCE Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL)), a large-scale randomized trial of EES versus CABG for left main disease, which plans to randomise 2500 patients has started, and if positive will establish PCI as the treatment of choice for the most complex patients with coronary artery disease.

Conclusions

The present thesis has shown that

a) The second generation everolimus-eluting stent is associated with significant improvements in both efficacy and safety outcomes compared to the first generation paclitaxel-eluting stent in all-comer patients at one and two years, and proved for the first time that differences in the stent technology between different DES can lead to significant clinical benefits.
b) These results hold true at two years also in the subgroup of patients presenting with myocardial infractions, either STEMI or NSTEMI, and therefore have help to mitigate the long disbelieve in DES safety in this setting.
c) That by reducing ST in all time points up to two years, everolimus-eluting stents have set new standards in term of DES safety. This device favorable safety profile might open the way to shorter dual antiplatelet therapy regimens, which in turn might result in important clinical benefits, due to less bleeding complications.
d) That the better safety outcomes, of everolimus-eluting stent as compared to the most used first-generation DES might be extended also to the subgroup of patients with diabetes mellitus, while this is not yet the case for the efficacy endpoints, where further research is needed.
e) And finally the improvement on clinical outcomes with this device has opened the way to new clinical trials which outcomes may further shape the future of interventional cardiology.

Short summary of the thesis

Korte samenvatting van het proefschrift

Er is grote vooruitgang geboekt in de invasieve behandeling van patiënten met ernstig en complex coronarialijden dankzij verbeteringen in het ontwerp en de functie van stents, nieuwe invasieve technieken en behandelstrategieën.

Dit proefschrift beschrijft de resultaten van ons onderzoek met een tweede generatie EES in een 'all-comer' populatie met een groot aantal hoog risico patiënten.

Achtereenvolgens zullen de resultaten, de klinische relevantie en nieuwe ontwikkelingen worden besproken.

Hoofdstuk 2: In de COMPARE studie werd, door gebruik te maken van een tweede generatie EES in vergelijking met een PES, na 1 jaar follow-up een significante reductie van MACE gezien. Deze betere uitkomst bij het gebruik van EES was een gevolg van een reductie in de incidentie van niet-fataal myocardinfarct en een reductie in nieuwe revascularisatie van het behandelde vat. Tussen de beide groepen werd echter geen verschil gezien in cardiale sterfte.

De significante lagere incidentie van een niet-fataal myocardinfarct in de EES groep was al zichtbaar na een follow-up periode van 30 dagen, alsmede na een follow-up van 1 jaar.

In het tweede artikel laten we zien dat in de dagelijkse praktijk het klinische voordeel van EES ten opzichte van PES in zowel veiligheid als in effectiviteit ook na een follow-up periode van twee jaar blijft bestaan. Het voordeel van EES ten opzichte van PES neemt zelfs significant toe bij 2 jaar follow-up ten opzichte van 1 jaar. Het voordeel door het gebruik van EES, bij 2 jaar follow up was met name te danken aan de reductie in MI en TVR. Een verdere toename in de reductie van stent trombose na 2 jaar follow-up ten opzichte van 1 jaar follow-up leidde uiteindelijk tot een significante reductie van stent trombose op 2 jaar.

Eveneens wordt de veiligheid van de EES in de groep patiënten met een acuut myocardinfarct vastgesteld waarvan de resultaten in het derde artikel van dit hoofdstuk worden beschreven. In dit onderzoek tonen we aan dat er een lagere incidentie is van zowel het primaire als het secundaire eindpunt in patiënten met een myocardinfarct die werden behandeld met een EES in vergelijking met PES. Dit werd voornamelijk veroorzaakt door een afname van het aantal re-TVR/TLR en van het aantal niet-fatale myocardinfarcten, een veiligheidsmaat voor de primaire en secundaire eindpunten. Er was in beide groepen geen verschil aantoonbaar in cardiale en niet-cardiale mortaliteit.

Een andere belangrijke uitkomst van dit onderzoek is dat het gebruik van EES geassocieerd is met een reductie van het aantal stent tromboses in vergelijking met PES. De incidentie van stent trombose bij patiënten met een acuut myocardinfarct die behandeld worden met een EES is te vergelijken met historische data over de incidentie van stent trombose bij BMS. Het klinische voordeel in effectiviteit en veiligheid van EES ten opzichte van PES was zowel in de NSTEMI als in de STEMI patiënten aantoonbaar.

Hoofdstuk 3: De SPIRIT IV en COMPARE studie, beiden besproken in het eerste artikel, hebben laten zien dat groot opgezette onderzoeken in patiënten met complexe laesies nodig zijn om belangrijke klinische verschillen tussen coronaire stents aan te tonen.

Op basis van deze twee onderzoeken kan de tot voor kort geldende gedachte dat er geen werkelijke klinische verschillen zouden bestaan tussen de verschillende typen DES, of dat er sprake zou zijn van een zogenaamde DES klasse effect, worden ontkracht. In de toekomst zal een beter mechanistisch inzicht in hoe het ontwerp van EES leidt tot verbeterde veiligheid en effectiviteit ongetwijfeld leiden tot ontwikkeling van nog beter presterende coronaire stents. Ook hebben deze onderzoeken aangetoond dat het mogelijk is om in een type coronaire stent gelijktijdig zowel de veiligheid als ook de effectiviteit te verbeteren.

Beide onderzoeken hebben dezelfde mate van reductie in trombotische events met EES aangetoond vergeleken met PES na 30 dagen en 1 jaar follow-up, waarbij de meeste stent trombose werd gezien in de eerste 30 dagen. Tot voor kort was er onder interventiecardiologen en onderzoekers met name aandacht voor 'very-late' stent trombose (meer dan 1 jaar na implantatie). Met name eerste generatie drug-eluting stents toonden vrij veel stent trombose na 1 jaar in vergelijking met bare-metal stents. Vroege stent trombose vormt echter het grootste deel van de stent trombose events tijdens follow-up. Dit is nog meer uitgesproken in hoog risico patiënten met complexe laesies zoals in de COMPARE studie. Het is daarom belangrijk dat bij de toekomstige ontwikkeling van nieuwe devices niet alleen gefocust moet zijn op reductie van erg late stent trombose, maar belangrijker nog, met name gericht moet zijn op het reduceren van vroege stent trombose zoals in EES.

Het tweede artikel beschrijft de grootste studie -op het moment van verschijnen- die stent trombose incidentie vergelijkt tussen een eerste en tweede generatie DES. Deze studie had genoeg statistische 'power' om 'time frame outcomes' (landscape analyse) en voorspellers van stent trombose te bestu-

deren. De belangrijkste uitkomst was dat EES het risico op stent trombose duidelijk verminderd in vergelijking met PES. Dit verschil was significant in alle geanalyseerde tijdsintervallen in de 2 jaars follow-up. Bij multivariate analyse was het type stent (PES vergeleken met EES) een onafhankelijke voorspeller van stent trombose. Lagere leeftijd, diabetes mellitus, meervats behandeling en lengte van de behandelde laesie waren ook onafhankelijke voorspellers voor stent trombose. Belangrijk is te vermelden dat een reductie in stent trombose gepaard ging met een reductie in het gecombineerde eindpunt cardiale dood of myocardinfarct .

De gedachte dat patiënten die behandeld zijn met EES vanwege de toegenomen veiligheidsprofiel in vergelijking tot de eerste generatie DES mogelijk korter kunnen worden behandeld met DAPT wordt ondersteund door de uitkomsten van de huidige analyse. Het stoppen van DAPT op een willekeurig moment 1 maand na stent plaatsing had geen invloed op de incidentie van stent trombose tot 2 jaar follow-up in het EES cohort. Na exclusie van events in de eerste zes maanden werd er geen verschil gevonden in de incidentie van stent trombose onafhankelijk van de compliantie van DAPT. Dit suggereert dat patiënten die zijn behandeld met een EES mogelijk al na 6 maanden het gebruik van DAPT veilig kunnen staken.

Hoofdstuk 4: In het eerste hoofdstuk wordt een analyse beschreven uitgevoerd op een uit verschillende studies samengesteld patiëntenbestand, waarbij naar de relatieve veiligheid en effectiviteit van verschillende type DES is gekeken en de groep is gestratificeerd naar het hebben van diabetes (suikerziekte). De belangrijkste bevindingen in deze studie waren: 1) er is een significante interactie tussen het hebben van diabetes en de mate van veiligheid en effectiviteit van de stent op 2 jaar als er een vergelijking wordt gemaakt tussen EES en PES, 2) indien de patiënt geen diabetes heeft, reduceert behandeling met een EES de kans op dood, myocardinfarct, stenttrombose, de noodzaak tot reinterventie van het letsel en MACE op 2 jaar, vergeleken met PES, echter wanneer de patiënt wel diabetes heeft is er geen verschil in effectiviteit tussen de verschillende stent types op 2 jaar; 3) binnen de groep met diabetes verlaagd EES t.o.v. PES de 2-jaar kans op de noodzaak tot reinterventie van het letsel in die groep van diabeten die geen insuline nodig hebben, terwijl het omgekeerde het geval was voor die diabeten die wel insuline-afhankelijk waren. In het tweede hoofdstuk wordt een grote retrospectieve register analyse beschreven die kijkt naar mogelijk effectiviteits verschillen tussen eerste en tweede generatie DES bij patiënten die met medicijnen worden behandeld voor diabetes. Hierbij is gebruik gemaakt van gegevens uit het Swedish Coronary Angiography and Angioplasty Register (SCAAR). De resultaten van

deze studie die keek naar de totale groep patiënten met diabetes in Zweden die een dotterbehandeling ondergingen, toonden aan dat: 1) de behandeling met een EES was geassocieerd met een significant lager voorkomen van dood vergeleken met SES en PES; 2) de behandeling met EES een significant lager aantal stenttromboses opleverde vergeleken met SES, en dat eenzelfde trend werd gezien voor de vergelijking met PES, echter dat deze verschillen geen significantie bereikten; 3) er geen verschil in de kans op restenose was tussen de verschillende stent types (EES, PES en SES) bij deze diabeten.

Ofschoon er nu voor het eerst belangrijke veiligheidsverbeteringen zijn aangetoond voor het gebruik van EES bij patiënten met diabetes, bestaande uit een lager aantal overlijdens, sluit deze studie aan bij de bevindingen uit de eerdere analyse dat er nog voldoende ruimte is voor verbetering, met name wat betreft effectiviteit. Voor patiënten met diabetes mellitus zijn daarom grotere studies nodig om te kijken naar: 1) of rapamycin-analogen of paclitaxel het voorkeursmedicijn moet worden bij patiënten met diabetes, 2) de rol van het afgifteprofiel en met name de afgifte tijd, 3) de rol van het ontwerp van de stent, het type metaal, de stentdikte en de rol van het gebruikte polymeer.

NIEUWE STUDIES EN TOEKOMSTPERSPECTIEVEN

De studies die in dit proefschrift worden beschreven zetten nieuwe deuren open voor de interventiecardiologie. Reeds nu al zijn nieuwe hypothesen, ontstaan uit de ervaringen met EES uit onze eigen studies en uit de samengestelde database van de SPIRIT II, III, IV en COMPARE trials, omgezet in nieuwe reeds lopende onderzoeken. Gebaseerd op de betere uitkomsten met EES bij patiënten met acuut myocardinfarct (STEMI en non-STEMI) met betrekking tot effectiviteits -en vooral veiligheidseindpunten, worden er op dit moment al nieuwe strategieën voor de behandeling van STEMI getest. De COMPARE-ACUTE studie is een prospectief, gerandomiseerde, multicenter studie die de klinische uitkomsten tussen twee behandelstrategieën vergelijkt (superiority) in bijna 900 STEMI patiënten. In deze studie wordt een nieuwe revascularisatie strategie bij STEMI, opgeleide van fractional flow reserve, voor de behandeling van "non-culprit" vaten in dezelfde sessie versus gestadieerd en opgeleide van non-invasief gemeten ischemie, getest, hetgeen overeenkomt met de standaard guidelines behandeling. Een andere prospectieve, gerandomiseerde, multicenter studie (DAPT-STEMI) onderzoekt (gericht op non-inferiority m.b.t. netto klinisch majeure cardiovasculaire voorvallen, inclusief TIMI majeure bloedingen) de duur van DAPT na het gebruikt van een DES in patiënten met een

STEMI. In deze studie zullen ongeveer 1000 patienten worden geincludeerd en de mensen die geen ernstig voorval hebben gehad in de eerste 6 maanden na behandeling (ongeveer 1000) zullen worden gerandomiseerd naar enkele (alleen aspirine) versus duale antiplaatjestherapie (aspirine en P2Y12 remmer) en zij zullen gedurende 18 maanden worden vervolgd.

CONCLUSIES

Dit proefschrift heeft laten zien dat:

a. De tweede generatie everolimus-afgevende stents zijn geassocieerd met een significante verbetering in zowel effectiviteit en veiligheid vergeleken met de eerste generatie paclitaxel-afgevende stents op 1 en 2 jaar bij een gemengde groep patienten. Hiermee is voor de eerste keer aangetoond dat verschil in stenttechnologie binnen DES ook daadwerkelijk kunnen leiden tot verschil in klinische uitkomsten.
b. De resultaten bestendigen zich ook op 2 jaar voor de subgroep van patienten die zich presenteren met een myocardinfarct, of STEMI of NSTEMI, en helpen hiermee de zorg voor DES veiligheid in deze populatie weg te nemen.
c. Door het verlagen van de kans op stenttrombose tot 2 jaar, hebben de EES een nieuwe standaard gezet m.b.t. DES veiligheid. Dit gunstige profiel zet de deur open naar korte duale antiplaatjesremming, hetgeen op zijn beurt belangrijke klinische voordelen op kan leveren door het verlagen van bloedingscomplicaties.
d. De verbeterde veiligheid van de everolimus-afgevende stents vergeleken met de meest gebruikte eerste generatie DES zich mogelijk strekt tot de subgroep van patiënten met diabetes. Ofschoon dit nog niet het geval is voor de effectiviteitseindpunten, is hiervoor verder onderzoek noodzakelijk.
e. Als laatste, de verbetering in klinische uitkomsten met deze stent de deur heeft opengezet voor nieuwe klinische studies die de toekomst van de interventiecardiologie verder vorm kunnen geven.

Chapter 6

Acknowledgments

LIST OF PUBLICATIONS

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* Shared first authorship

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1) **Stent Thrombosis: Insights on Outcomes, Predictors and Impact of Dual Antiplatelet Therapy Interruption from the SPIRIT II, SPIRIT III, SPIRIT IV and COMPARE Trials**

   Elvin Kedhi, Gregg W. Stone, Dean J. Kereiakes, Patrick W. Serruys, Helen Parise, Martin Fahy, Charles A. Simonton, Krishnankutty Sudhir, Poornima Sood, Pieter C. Smits
   J Am Coll Cardiol

2) **Everolimus – eluting, Sirolimus – eluting and Paclitaxel - eluting stents of for treatment of Coronary Heart Disease in patients with Diabetes Mellitus: Insights from the SCAAR register**

   Elvin Kedhi[1], Marc E Gomes[3*], Bo Lagerqvist[2], J.Gustav Smith[3], Elmir Omerovic[4], Stefan James[2], Jan Harnek[3], Göran K.Olivecrona[3]

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"*The most important career choice you'll make is who you marry*"
Sheryl Sandberg (COO Facebook)

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