EuroIntervention

Side branch occlusion with everolimus-eluting and paclitaxel-eluting stents: three-year results from the SPIRIT III randomised trial

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KEYWORDS

Everolimus-eluting stent, paclitaxel-eluting stent, side branch occlusion, non-Q-wave myocardial infarction

Abstract

Aims and methods: The rates of side branch occlusion and subsequent periprocedural MI during everolimuseluting stent (EES) and paclitaxel-eluting stent (PES) placement were examined in the randomised SPIRIT III trial. Periprocedural myocardial infarction (MI) following drug-eluting stent placement is associated with long-term adverse outcomes. Occlusion of side branches may be an important factor contributing to periprocedural MIs. Consecutive procedural angiograms of patients randomly assigned to EES (n=669) or PES (n=333) were analysed by an independent angiographic core laboratory. Side branch occlusion was defined as Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 or 1. Clinical outcomes through three years were compared by stent type and presence of side branch occlusion.

Conclusions: A total of 2,048 side branches were evaluated (EES N=1,345 side branches in 688 stented lesions, PES N=703 side branches in 346 stented lesions). Patients with compared to those without transient or final side branch occlusion had significantly higher non-Q-wave MI (NQMI) rates in-hospital (9.0% vs. 0.5%, p<0.0001). By multivariable analysis side branch occlusion was an independent predictor of NQMI (OR 4.45; 95% CI [1.82, 10.85]). Transient or final side branch occlusion occurred less frequently in patients receiving EES compared to PES (2.8% vs. 5.2%, p=0.009), contributing to the numerically lower rates of in-hospital NQMI with EES arm compared to PES (0.7% vs. 2.3%, p=0.05). Patients treated with EES rather than PES were less likely to develop side branch occlusion during stent placement, contributing to lower rates of periprocedural MI with EES compared to PES.

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Abbreviations

EES	Everolimus-eluting stent
PES	Paclitaxel-eluting stent
MI	Myocardial infarction
TIMI	Thrombolysis In Myocardial Infarction
NQMI	Non-Q-Wave MI
DES	Drug-eluting stent
PCI	Percutaneous coronary intervention
CK-MB	Creatine kinase-MB
TLR	Target lesion revascularisation
MACE	Major adverse cardiac events

Introduction

Myocardial infarction (MI) occurring after placement of drug-eluting stents (DES) has been associated with unfavourable late clinical outcomes[1-5]. Patients with moderately or severely elevated cardiac enzymes after percutaneous coronary intervention (PCI) have an increased risk of late mortality[6-8]. Although several baseline and procedural factors may contribute to the development of MI, understanding the mechanism of MI may provide insight into prevention, and side branch occlusion has been implicated as one possible contributing factor[9-11]. Side branch occlusion has been described as occurring more often in patients treated with coronary stents than atherectomy or balloon angioplasty due to shifting of atherosclerotic plaque into the side branches, as well as the mechanical straightening of the target vessel[12,13]. The frequency and clinical outcomes associated with side branch occlusion after DES placement have not been extensively studied.

First generation DES have thicker stent struts[14,15] compared to second generation DES such as the XIENCE V® everolimus-eluting stents (EES)[16]. Recent randomised clinical trials have demonstrated the clinical benefit of EES compared to treatment with PES[16,17]. The SPIRIT III randomised trial assessed the early and late clinical outcomes in 1,002 patients treated with EES vs. PES. The purpose of this analysis was to compare the rates of side branch occlusion after EES and PES implantation in SPIRIT III, and to assess whether side branch occlusion contributes to differences in clinical outcomes.

Methods

The SPIRIT III trial design has been described in detail previously[17,18]. In brief, SPIRIT III was a multicentre, prospective, single blinded, controlled trial that compared the safety and efficacy of EES (XIENCE V®; Abbott Vascular, Santa Clara, CA, USA) vs. PES (TAXUS® Express2®; Boston Scientific, Natick, MA, USA) in patients with up to two *de novo* coronary artery lesions. A total of 1,002 patients were randomised 2:1 into the EES group and the PES group at 65 US sites.

Enrolment was restricted to patients with stable or unstable angina or inducible ischaemia. Key inclusion criteria included a maximum of two *de novo* native coronary artery lesions, each in a different epicardial vessel, reference vessel diameter (RVD) of ≥2.5 mm and ≤3.75 mm, lesion length ≤28 mm by visual estimation, % diameter stenosis (%DS) of ≥50% and <100%, Thrombolysis In Myocardial Infarction (TIMI) flow of ≥1, and non-target vessel percutaneous intervention in non-target vessel planned ≥90 days prior to or >9 months after the index procedure. Major clinical exclusion criteria included PCI in the target vessel prior to or planned within nine months of the index procedure, or in a non-target vessel within 90 days prior to or planned within nine months of index procedure; acute or recent myocardial infarction (MI), left ventricular ejection fraction <30%, recent major bleeding, serum creatinine >2.5 mg/dL or dialysis.

Key angiographic exclusion criteria included aorto-ostial location, left main location, excessive tortuosity, extreme angulation (≥90°), heavy calcification, target vessel containing thrombus, or other significant lesions (>40% DS) in the target vessel or side branch for which intervention was required within nine months. If two target lesions were treated, then each of these lesions had to meet all angiographic inclusion/exclusion criteria.

Following confirmation of angiographic eligibility, telephone randomisation was performed, stratified by the presence of diabetes, planned dual vessel treatment, and study site. Protocol specified angiographic follow-up was performed at 240 days in 436 patients, as previously described[18]. Clinical follow-up was performed at one month, six months, nine months, one year and then annually through five years.

Stent delivery system

The XIENCE V stent is formulated from L-605 cobalt chromium alloy with a stent strut thickness of 81 µm and with a thin (7.8 µm), non-adhesive, durable, biocompatible fluorinated copolymer coat consisting of two layers, a primer layer and a drug matrix layer containing everolimus at a concentration of 100 µg/cm^2, which is eluted over a 3-month period. EES were available in 2.5, 3.0, and 3.5 mm diameters, and in 8, 18, and 28 mm lengths. The TAXUS Express^2 stent is manufactured using 316 L stainless steel with a stent strut thickness of 132 µm and a 19.6 µm Translute™ polymer carrier coating loaded with 1 µg/mm^2 paclitaxel in a slow release formulation. The full range of US-manufactured PES was available, ranging from 2.5 to 3.5 mm in diameter and from 8 to 32 mm in length.

Interventional procedure

Pre-dilatation of the target lesion with standard balloon angioplasty was mandatory. The stent was implanted to cover a minimum of 3 mm of healthy vessel on either side of the lesion. Post-dilatation within the boundaries of the stent was left to the discretion of the investigator. If an additional stent was required for bailout purposes, a stent from the same treatment arm was utilised.

Medication administration

Subjects who were not on chronic antiplatelet or aspirin therapy were required to receive a loading dose of aspirin ≥300 mg before the procedure and clopidogrel bisulfate ≥300 mg no later than one hour after the procedure. All patients were to be maintained on

75 mg clopidogrel bisulfate daily for a minimum of six months and ≥80 mg of aspirin daily throughout the length of the trial (five years) following the index procedure. Other medications were prescribed as per standard of care.

Clinical follow-up and endpoint definition

Clinical follow-up was scheduled at 30 days, 180 days, 240 days, 270 days, and 365 days, with subsequent telephone follow-up yearly through five years. The primary clinical endpoint of the SPIRIT III trial was target vessel failure (TVF), consisting of the composite of cardiac death, MI, or ischaemia-driven target vessel revascularisation (TVR) at nine months. Secondary endpoints included major adverse cardiac events (MACE), defined as the composite of cardiac death, MI, or ischaemia-driven target lesion revascularisation (TLR), as well as the individual components of TVF and MACE, and stent thrombosis. Myocardial infarction was defined as either the development of new pathologic Q-waves 0.4 seconds or longer in duration in two or more contiguous leads or as the elevation of creatine kinase (CK) levels to ≥2 times the upper limit of normal, with elevated CK-MB in the absence of new pathological Q-waves. Stent thrombosis was prospectively defined by protocol as an acute coronary syndrome with angiographic evidence of thrombus within or adjacent to a previously treated target lesion, or in the absence of angiography, any unexplained death or acute MI with ST-segment elevation or new Q-waves in the distribution of the target lesion occurring within 30 days of post procedure. Definite or probable stent thrombosis was also adjudicated in a *post hoc* analysis using the Academic Research Consortium (ARC) definition[19].

Angiographic methodology and endpoint definition

All baseline angiograms were reviewed at an independent core laboratory (Cardiovascular Research Foundation, New York, NY, USA) using standardised methodology. A detailed side branch analysis was performed of all side branches identified at the lesion site (stent location and 5 mm peri-stent area) at baseline, during the course of the intervention to capture any transient complications, and after final intervention. The quantitative angiographic analysis (MEDIS, Leiden, The Netherlands) included the reference size and total length of the side branch, the percent diameter stenosis of any side branch lesion and its length as well as the side branch TIMI flow at each time point. For the purpose of this *post hoc* analysis, side branch occlusion was defined as Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 or 1. Transient or final side branch occlusion was defined as side branch occlusion that occurred during the procedure, and either disappeared or persisted at the end of the procedure. Final side branch occlusion was defined as side branch occlusion that was only observed after the procedure.

Statistical analysis

All analyses are by intention-to-treat, utilising all patients randomised in the study, regardless of the treatment actually received. However, patients lost to follow-up in whom no event had occurred before the follow-up windows were not included in the denominator for calculations of binary endpoints. Categorical variables were compared by Fisher's exact test. Continuous variables are presented as mean ±1 standard deviation, and were compared by *t*-test. Time-to-event hazard curves were also constructed using Kaplan-Meier estimates and compared by log-rank test. A two-sided α=0.05 was used for all statistical tests to define significance.

For multivariable analyses, models were built using a stepwise (forward/backward) elimination procedure, with independent variables entered into the model at the 0.20 significance level and removed at the 0.10 level. A final model was selected and presented with selection criteria based on both statistical significance and clinical consideration. In addition, the adequacy of the fitted model was evaluated by Hosmer and Lemeshow goodness-of-fit test and C-statistic, which is the area under the Receiver Operating Characteristic (ROC) curve. Variables entered included stent treatment type, angiographic group, age, gender, current tobacco use, any diabetes, diabetes requiring medication, hypertension, hypercholesterolaemia, prior cardiac interventions, prior MI, number of diseased vessels, number of treated vessels, HbA1c (%), total cholesterol (>200 mg/dl), high-density lipoprotein (HDL) cholesterol (≤60 mg/dl), triglycerides (>150 mg/dl), number of stents implanted, total length of all stents, 2.5 mm stent implanted, bailout stent usage, IIb/IIIa inhibitor use, duration on clopidogrel or ticlopidine, and on clopidogrel or ticlopidine at 1095 days, and side branch occlusion. Separately, an analysis was performed in patients with side branch occlusion which, in addition to the variables listed above, excluded side branch occlusion and included pre-procedure side branch RVD and total side branch length to determine their effect on in-hospital CK-MB levels. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc, Cary, NC, USA).

Results

Study population and baseline characteristics

A total of 669 patients were treated with EES and 333 patients were treated with PES (Figure 1). In the EES arm, 606 (90.6%) patients had side branches and of them, 6.1% (37 patients) experienced side branch occlusion. By comparison, in the PES arm,

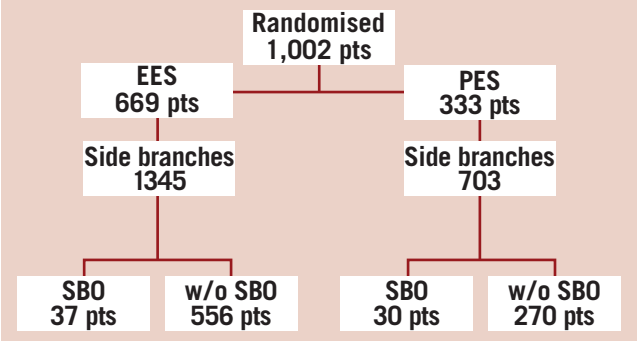

Figure 1. SPIRIT III RCT: flowchart of patient enrolment.

304 (91.3%) patients had side branches and of them, 9.9% (30 patients) experienced side branch occlusion. A total of 2,048 side branches were evaluated, including 1,345 side branches in 688 EES stented lesions (median 2.0 side branches per EES stented lesion) and 703 side branches in 346 PES stented lesions (median 2.0 side branches per PES stented lesion).

Baseline characteristics for patients with side branches in both the EES and the PES arms were comparable except for unstable angina which was significantly higher in the PES group (Table 1, p=0.02). There were no significant differences in the average number of side branches per patient (2.2±1.2 for EES vs. 2.3±1.2 for PES, p=0.28) or number of side branches per lesion (2.0±1.0 for EES vs. 2.0±1.0 for PES, p=0.24) between the two arms (Table 2). Average side branch diameters in both arms (1.60±0.49 mm for EES vs. 1.63±0.53 mm for PES, p=0.20) were comparable as was the total length of the side branch (97.4±63.7 EES vs. 104.9±69.0 PES, p=0.09). The baseline side branch % diameter stenosis was 19.7% for the EES arm and 19.6% for the PES arm, p=0.95. No significant difference was observed for preprocedural side branch occlusion in both of the EES and the PES arms (0.8% for EES vs. 0.3% for PES, p=0.24) (Figure 2). There was no significant difference in compliance of DAPT (dual antiplatelet therapy) per protocol between the EES and the PES arms through three years.

Table 1. SPIRIT III RCT: baseline demographics and angiographic characteristics for intent-to-treat population with side branches.

	XIENCE V 606 pts	TAXUS 304 pts	*p*-value
Age (years)	63.4±10.5	62.8±10.3	0.45
Male (%)	69.6	66.4	0.36
Hypertension (%)	75.9	73.6	0.46
Hypercholesterolaemia (%)	73.4	71.5	0.58
Diabetes mellitus (%)	30.7	27.2	0.28
Current smoker (%)	23.6	23.0	0.87
Prior MI (%)	19.3	18.7	0.93
Unstable angina (%)	18.8	25.8	0.02
Number of diseased Vessels			
1 vessel CAD	63.7	68.1	0.21
2 vessel CAD	27.1	23.0	0.20
3 vessel CAD	9.2	8.6	0.81
Number of lesions per patient	1.2±0.4	1.2±0.4	0.83
Number of stents per lesion	1.2±0.4	1.1±0.3	0.07
Lesion location			
LAD	42.4	44.6	0.51
LCX	26.6	26.7	1.00
RCA	30.9	28.4	0.43
LMCA	0.1	0.3	0.55
ACC/AHA lesion complexity			
A	7.5	6.6	0.62
B1	36.3	33.1	0.34
B2	36.8	42.1	0.11
C	19.4	18.2	0.68
Quantitative measures			
RVD (mm)	2.79±0.45	2.78±0.46	0.84
MLD (mm)	0.83±0.42	0.83±0.40	0.98
% DS	69.8±13.3	69.5±13.6	0.77
Lesion length (mm)	14.8±5.6	14.9±5.8	0.76

Table 2. SPIRIT III RCT ITT: procedure and baseline side branch characteristics.

	EES (N=669)	PES (N=333)	*p*-value
Total treated lesions (main vessel)	688	346	NA
Total lesion site side branches	1345	703	NA
No. side branches (per patient)	2.2±1.2	2.3±1.2	0.28
No. side branches (per lesion)	2.0±1.0	2.0±1.0	0.24
Baseline side branch analysis			
Reference diameter (mm)	1.60±0.49	1.63±0.53	0.20
Total side branch length	97.4±63.7	104.9±69.0	0.09
% diameter stenosis	19.68±17.22 (1345)	19.63±16.49	0.95
Lesion length	6.83±5.97	7.48±6.44	0.12
% Lesions with DS >50%	15.7 (108/688)	13.0 (45/345)	0.27
Lesion length for SB DS >50%	12.39±9.03	13.69±10.28	0.47
SB TIMI 0/1	0.8% (11/1342)	0.3% (2/701)	0.24
SB TIMI 2	0.9% (12/1342)	1.6% (11/701)	0.19
SB TIMI 3	98.3% (1319/1342)	98.1% (688/701)	0.86
Worst side branch analysis			
% Diameter stenosis	45.36±24.41	48.15±25.07	0.08
Any complications*	8.3% (57/686)	13.2% (45/342)	0.02
SB TIMI 0/1	2.8% (38/1339)	5.2% (36/695)	0.009
SB TIMI 2	1.6% (21/1339)	2.4% (17/695)	0.17
SB TIMI 3	95.6% (1280/1339)	92.4% (642/695)	0.004
Final side branch analysis			
% Diameter stenosis	30.11±25.24	31.72±26.70	0.19
Any complications*	7.9% (54/686)	11.4% (39/343)	0.08
SB TIMI 0/1	2.7% (36/1339)	4.3% (30/695)	0.06
SB TIMI 2	1.3% (18/1339)	2.2% (15/695)	0.20
SB TIMI 3	96.0% (1285/1339)	93.5% (650/695)	0.02

*Any complications: composite of TIMI <3; abrupt closure, any dissection, thrombus, distal embolisation

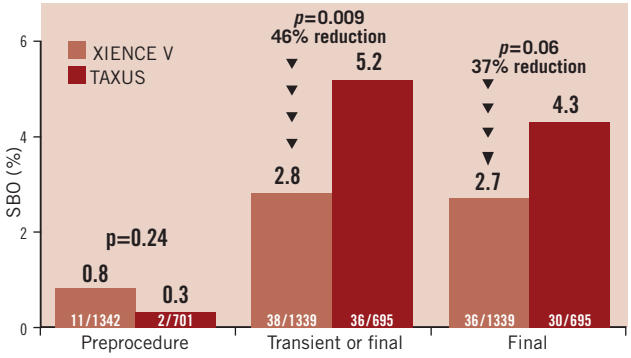

Figure 2. SPIRIT III – side branch occlusion frequency.

Angiographic and clinical outcomes

During the interventional procedure, there was no significant difference in the worst mean side branch %DS by device at baseline (EES 45.4% vs. PES 48.2%, p=0.08) or after final

intervention (EES 30.1% vs. PES 31.7%, p=0.19) (Table 2). There was a 46% lower frequency of transient or final (p=0.009) and a 37% lower frequency of final (p=0.06) side branch occlusion with EES compared to PES (Figure 2).

Rates of non-Q-wave MI (NQMI) were significantly higher in-hospital and were sustained at all subsequent time points (30 days, one year, two years and three years) in patients with vs. without side branch occlusion (Figure 3). Among patients with side branch occlusion, the size and length of the side branch did not correlate with in-hospital CK-MB release (data not shown).

The higher MACE rates out to three years for patients with versus without side branch occlusion were mainly driven by the higher NQMI rates. Side branch occlusion was not associated with cardiac death, QMI or TLR at any time point, (Table 3).

Three-year clinical outcomes are shown in Table 4. A total of 90.6% of patients treated with EES and 91.3% of patients treated with PES had lesion site side branches. NQMI was a major component contributing to the occurrence of MACE in both the EES and the PES arms (Table 5), and the periprocedural NQMI rate was

Table 3. SPIRIT III RCT ITT: clinical outcomes through three years for patients with or without side branch occlusion.

	With SBO (N=67)	Without SBO (N=836)	*p*-value
In-hospital events (%)*			
Cardiac death	0.0% (0/67)	0.0% (0/835)	NA
QMI	0.0% (0/67)	0.0% (0/835)	NA
NQMI	9.0% (6/67)	0.5% (4/835)	<0.0001
TLR	0.0% (0/67)	0.1% (1/835)	1.00
MACE	9.0% (6/67)	0.6% (5/835)	<0.0001
30-day events (%) **			
Cardiac death	0.0% (0/67)	0.0% (0/833)	NA
QMI	0.0% (0/67)	0.0% (0/833)	NA
NQMI	9.0% (6/67)	0.8% (7/833)	0.0002
TLR	0.0% (0/67)	0.5% (4/833)	1.00
MACE	9.0% (6/67)	1.2% (10/833)	0.0006
1-year events (%) ***			
Cardiac death	0.0% (0/66)	0.9% (7/812)	1.00
QMI	0.0% (0/66)	0.4% (3/812)	1.00
NQMI	10.6% (7/66)	2.2% (18/812)	0.002
TLR	7.6% (5/66)	4.2% (34/812)	0.21
MACE	16.7% (11/66)	6.9% (56/812)	0.01
2-year events (%) ***			
Cardiac death	0.0% (0/65)	1.3% (10/789)	1.00
QMI	0.0% (0/65)	0.6% (5/789)	1.00
NQMI	13.8% (9/65)	2.8% (22/789)	0.0003
TLR	10.8% (7/65)	5.7% (45/789)	0.11
MACE	21.5% (14/65)	9.3% (73/789)	0.004
3-year events (%) ***			
Cardiac death	0.0% (0/65)	1.8% (14/777)	0.62
QMI	0.0% (0/65)	0.6% (5/777)	1.00
NQMI	13.8% (9/65)	3.3% (26/777)	0.0008
TLR	10.8% (7/65)	6.8% (53/777)	0.21
MACE	21.5% (14/65)	11.3% (88/777)	0.03

*In-hospital is defined as hospitalisation less than or equal to 7 days post index procedure; **Including ±7 days window; ***Including ±28 days window; SBO: side branch occlusion

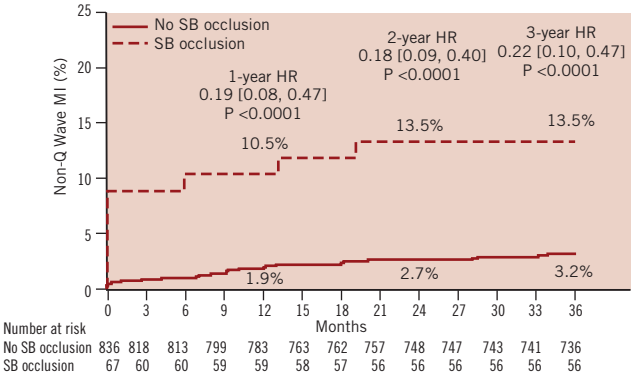

Figure 3. Non-Q-wave MI rates in patients with or without side branch occlusion.

Table 4. SPIRIT III ITT: 3-year clinical outcomes.

	XIENCE V (N=669)	TAXUS (N=333)	*p*-value
In-hospital events* (%)			
Cardiac death	0.0% (0/669)	0.0% (0/330)	NA
QMI	0.0% (0/669)	0.0% (0/330)	NA
NQMI	0.7% (5/669)	2.4% (8/330)	0.04
TLR	0.1% (1/669)	0.0% (0/330)	1.00
MACE	0.9% (6/669)	2.4% (8/330)	0.08
30-day events** (%)			
Cardiac death	0.0% (0/667)	0.0% (0/330)	NA
QMI	0.0% (0/667)	0.0% (0/330)	NA
NQMI	1.0% (7/667)	2.7% (9/330)	0.06
TLR	0.4% (3/667)	0.3% (1/330)	1.00
MACE	1.3% (9/667)	3.0% (10/330)	0.08
1-year events*** (%)			
Cardiac death	0.8% (5/655)	0.9% (3/319)	0.72
QMI	0.3% (2/655)	0.3% (1/319)	1.00
NQMI	2.4% (16/655)	3.8% (12/319)	0.31
TLR	3.4% (22/655)	5.6% (18/319)	0.12
MACE	6.0% (39/655)	10.3% (33/319)	0.02
2-year events*** (%)			
Cardiac death	1.1% (7/637)	1.6% (5/309)	0.54
QMI	0.5% (3/637)	0.6% (2/309)	0.66
NQMI	2.8% (18/637)	5.2% (16/309)	0.09
TLR	4.9% (31/637)	7.8% (24/309)	0.08
MACE	8.0% (51/637)	14.2% (44/309)	0.004
3-year events*** (%)			
Cardiac death	1.6% (10/629)	2.0% (6/305)	0.79
QMI	0.5% (3/629)	0.7% (2/305)	0.66
NQMI	3.3% (21/629)	5.9% (18/305)	0.08
TLR	5.7% (36/629)	9.2% (28/305)	0.05
MACE	9.7% (61/629)	16.4% (50/305)	0.004

*In-hospital is defined as hospitalisation less than or equal to 7 days post index procedure; **Including ±7 days window; ***Including ±28 days window

Table 5. SPIRIT III ITT: 3-year clinical outcomes for patients with side branches.

	XIENCE V (N=606)	TAXUS (N=304)	*p*-value
In-hospital events * (%)			
Cardiac death	0.0% (0/606)	0.0% (0/302)	NA
QMI	0.0% (0/606)	0.0% (0/302)	NA
NQMI	0.7% (4/606)	2.3% (7/302)	0.05
TLR	0.2% (1/606)	0.0% (0/302)	1.00
MACE	0.8% (5/606)	2.3% (7/302)	0.12
30-day events ** (%)			
Cardiac death	0.0% (0/604)	0.0% (0/302)	NA
QMI	0.0% (0/604)	0.0% (0/302)	NA
NQMI	1.0% (6/604)	2.6% (8/302)	0.08
TLR	0.5% (3/604)	0.3% (1/302)	1.00
MACE	1.3% (8/604)	3.0% (9/302)	0.12
1-year events *** (%)			
Cardiac death	0.8% (5/593)	0.7% (2/291)	1.00
QMI	0.3% (2/593)	0.3% (1/291)	1.00
NQMI	2.5% (15/593)	3.8% (11/291)	0.30
TLR	3.7% (22/593)	5.8% (17/291)	0.16
MACE	6.4% (38/593)	10.3% (30/291)	0.04
2-year events *** (%)			
Cardiac death	1.0% (6/577)	1.4% (4/282)	0.74
QMI	0.5% (3/577)	0.7% (2/282)	0.67
NQMI	2.9% (17/577)	5.3% (15/282)	0.12
TLR	5.0% (29/577)	8.2% (23/282)	0.09
MACE	8.1% (47/577)	14.5% (41/282)	0.006
3-year events *** (%)			
Cardiac death	1.6% (9/569)	1.8% (5/278)	0.78
QMI	0.5% (3/569)	0.7% (2/278)	0.67
NQMI	3.3% (19/569)	6.1% (17/278)	0.07
TLR	5.8% (33/569)	9.7% (27/278)	0.05
MACE	9.8% (56/569)	16.9% (47/278)	0.005

* In-hospital is defined as hospitalisation less than or equal to 7 days post index procedure; ** Including ±7 days window; *** Including ±28 days window.

significantly lower with EES vs. PES (0.7% vs. 2.3%, p=0.05). Other components of peri-procedural MACE, including cardiac death, Q-wave MI (QMI) and TLR were comparable between the EES and the PES arms (Table 5). Beyond the periprocedural time, NQMI rates were numerically less frequent in patients treated with EES vs. PES, and at 1, 2, and 3 years MACE was significantly lower with EES (9.8% for EES vs. 16.9% for PES, p=0.005) (Table 5).

Cumulative Kaplan-Meier (KM) analysis showed a significant reduction in MACE with EES compared to PES at 1 year (EES 5.7% vs. PES 9.9%, p=0.01), 2 years (EES 7.5% vs. PES 13.1%, p=0.003), and 3 years (EES 9.1% vs. PES 15.7%, p=0.003 (Figure 4).

Multivariable analysis (Table 6) revealed several factors predictive of side branch occlusion including multivessel disease, 2.5 mm stents, and treatment with PES. Side branch occlusion was an independent predictor of NQMI (OR 4.45; 95% CI [1.82, 10.85]) as

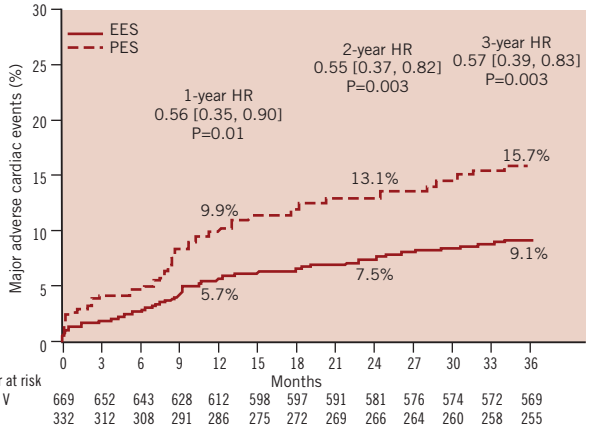

Figure 4. SPIRIT III RCT ITT: KM curve for MACE through three years.

well as MACE (OR 2.41; 95% CI [1.23, 4.71]). However, neither side branch RVD nor SB length, were predictors of in-hospital CK-MB levels among patients with side branch occlusion (data not shown).

Periprocedural levels of CK-MB are shown in Table 7. Overall rates in patients with side branch occlusion were numerically higher compared to patients without occlusion.

Discussion

In the present study the rates of NQMI, both periprocedural and during follow-up, were significantly higher in patients with side branch occlusion compared to those without occlusion. MACE rates in patients with side branch occlusion were also significantly higher at each time point driven chiefly by NQMI, as cardiac death and TLR rates were not significantly different between these two groups. Furthermore, patients treated with EES rather than PES were less likely to develop transient or final side branch occlusion during stent placement. The lower frequency of side branch occlusion with EES treatment contributed to significantly reduced rates of periprocedural MI and improved long-term outcomes compared to the PES group. At 1, 2 and 3 years, MACE rates in EES patients were significantly lower compared to PES patients, due to lower rates of NQMI and TLR. Furthermore, by three years, TLR rates in patients with side branches were significantly lower in the EES group compared to the PES group.

Coronary artery lesions often form near branch points, and generally, side branches with ostial stenoses are more susceptible to occlusion during stent placement in the target vessel[20,21]. A number of factors are thought to contribute to the development of side branch occlusion. Shifting of plaque from the main vessel to the side branch during the procedure (often termed the "snow-plow effect")[20], dissection of the main artery[22], and mechanical obstruction from stent placement[12] can all contribute to occlusion leading to higher rates of adverse events. One reason for the reduction in side branch occlusion after EES placement may be due to the thinner struts of the EES compared to the PES. Presumably, this may lead to reduced compromise of the side branch as well as less mechanical straightening of the

Table 6. Clinical and angiographic predictors.

Variable	Coding for binary variables	*p*-value	Odds ratio [95% CI]
Predictors of 3-year target vessel failure			
Number of vessels treated	Dual vs. single	0.0009	2.20 [1.38, 3.51]
Total cholesterol (>200 mg/dl)	Yes vs. No	0.006	1.85 [1.19, 2.88]
HbA1c (%)		0.003	1.23 [1.07, 1.40]
Model checking statistics			
Hosmer and Lemeshow goodness-of-fit test		0.27	
C-statistic (the area under the ROC curve): 0.64			
Predictors of 3-year MACE			
Side branch occlusion	Yes vs. No	0.01	2.41 [1.23, 4.71]
Total cholesterol (>200 mg/dl)	Yes vs. No	0.003	2.12 [1.30, 3.44]
Bailout stent usage	Yes vs. No	0.05	2.00 [1.01, 3.94]
Number of vessels treated	Dual vs. Single	0.01	1.99 [1.18, 3.38]
Gender	Female vs. Male	0.01	1.82 [1.15, 2.87]
HbA1c (%)		0.003	1.25 [1.08, 1.44]
Model checking statistics			
Hosmer and Lemeshow goodness-of-fit test		0.55	
C-statistic (the area under the ROC curve): 0.68			
Predictors of 3-year non-Q-Wave MI			
Side branch occlusion	Yes vs. No	0.001	4.45 [1.82, 10.85]
Number of vessels treated	Dual vs. Single	0.01	2.77 [1.27, 6.03]
HbA1c		0.01	1.32 [1.07, 1.63]
Model checking statistics			
Hosmer and Lemeshow goodness-of-fit test		0.37	
C-statistic (the area under the ROC curve): 0.68			
Predictors of side branch occlusion			
2.5 mm stent implanted	2.5 vs. No 2.5mm Stents	0.02	0.45 [0.23, 0.88]
Number of diseased vessels	Multiple vs. Single	0.03	1.87 [1.05, 3.34]
Treatment	EES vs. PES	0.02	0.55 [0.33, 0.92]
Model checking statistics			
Hosmer and Lemeshow goodness-of-fit test		0.35	
C-statistic (the area under the ROC curve): 0.66			

Table 7. CK-MB levels in patients with or without side branch occlusion.

	With side branch occlusion			Without side branch occlusion		
	EES (n=37)	PES (n=30)	*p*-value	EES (n=566)	PES (n=270)	*p*-value
Periprocedure						
CK-MB <3x UNL	81.3% (26/32)	57.7% (15/26)	0.08	97.1% (438/451)	94.8% (201/212)	0.18
CK-MB 3-5x UNL	6.3% (2/32)	15.4% (4/26)	0.39	1.8% (8/451)	2.8% (6/212)	0.39
CK-MB >5-8x UNL	3.1% (1/32)	19.2% (5/26)	0.08	0.9% (4/451)	0.9% (2/212)	1.00
CK-MB >8x UNL	9.4% (3/32)	7.7% (2/26)	1.00	0.2% (1/451)	1.4% (3/212)	0.10

target vessel resulting in fewer alterations to side branch morphology.

Elevated levels of cardiac biomarkers such as CK-MB have been associated with increased risk of cardiac adverse events[23-26]. Side branch occlusion after stent implantation is one of a number of factors that have been linked to increased levels of CK-MB[26,27]. In this study, levels of CK-MB were elevated in patients with side branch occlusion compared to those without occlusion. However, there did not appear to be a correlation between side branch length, diameter or %DS and CK-MB levels. By lowering rates of side branch occlusion, treatment with EES may result in a reduction in CK-MB levels which leads to overall lower rates of clinical adverse events.

By multivariable analysis, treatment with PES compared to EES was a predictor of side branch occlusion. Other factors contributing to side branch occlusion were the use of 2.5 mm stents and multivessel disease. Not surprisingly, side branch occlusion was a predictor of 3-year MACE and NQMI. Both the number of vessels treated and levels of HbA1c were also independent predictors of both MACE and NQMI at three years. Taken together, these data strongly suggest that treatment with EES results in fewer side branch occlusions, resulting in lower rates of immediate and sustained NQMI and MACE.

The major limitation of the present study is that the SPIRIT III trial included principally patients with stable coronary artery disease,

and excluded complex lesions such as chronic total occlusions, thrombotic lesions, true bifurcation lesions and saphenous vein grafts. The incidence of side branch occlusion would be expected to be higher in these situations, which might have led to even greater differences between the two stent platforms.

In summary, in the SPIRIT III randomised trial, EES-treated patients developed fewer instances of side branch occlusion during stent placement compared to PES-treated patients. The stent type rather than characteristics of the side branch predicted side branch occlusion. Less frequent side branch occlusion with EES contributed to lower rates of periprocedural MI and improved long-term outcomes compared to PES.

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