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Evaluation of the Effects of Everolimus-Eluting and Paclitaxel-Eluting Stents on Target Lesions With Jailed Side Branches: 2-Year Results From the SPIRIT III Randomized Trial

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Objective: To evaluate whether an everolimus-eluting stent (EES) with thinner stent struts and polymer results in less periprocedural myonecrosis and adverse outcomes. **Background:** Higher periprocedural myocardial infarction (MI) rates have been reported with the TAXUS® EXPRESS² paclitaxel-eluting stent (PES) compared to the bare metal EXPRESS²® stent due to more frequent side branch compromise, presumably attributable to the thickness of the stent/polymer on the PES. **Methods:** In the SPIRIT III trial, we identified 113 patients in the XIENCE V® EES group and 63 patients in the TAXUS EXPRESS² PES group who met the criteria of having a lesion with a jailed side branch (<2 mm diameter, and <50% stenosis). Two-year clinical outcomes were evaluated. **Results:** A periprocedural increase in Creatine Kinase-MB >1× upper normal level occurred in 9.0% of EES compared to 29.7% of PES patients with jailed side branches, $P = 0.01$. Through 2 years, major adverse cardiac events (MACE; cardiac death, MI, or target lesion revascularization [TLR]) occurred in 6.8% of EES and 19.0% of PES jailed side branch patients ($P = 0.03$), with numerically lower rates of MI (2.9% vs. 10.3%, $P = 0.07$) and TLR (3.9% vs. 10.3%, $P = 0.17$) in the EES group, with comparable rates of cardiac death (1.9% vs. 1.7%, $P = 1.00$). **Conclusions:** In this post-hoc analysis of the SPIRIT III RCT, patients undergoing stenting of target lesions with jailed side branches with the thin strut and polymer XIENCE V EES compared to the thicker strut TAXUS PES had lower rates of MACE through 2 years due to fewer MIs and TLRs.

Key words: drug-eluting stent; biomarker; myonecrosis

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INTRODUCTION

Impairment of flow, or complete obstruction, of a branch originating within a stented segment has been associated with periprocedural myocardial infarction (MI) and thus contributes to higher rates of adverse outcomes [1–4]. Higher periprocedural MI rates have been reported with the first generation TAXUS® EXPRESS^2 paclitaxel-eluting stent (PES) compared to the bare metal EXPRESS$^{2®}$ stent due to more frequent side branch compromise. The mechanism remains uncertain but is presumably attributable to the thickness of the stent/polymer on the PES [5]. Whether side branches "jailed" by a thin stent/polymer second generation DES result in similar rates of periprocedural MI and adverse outcomes as seen with PES is uncertain.

The large-scale SPIRIT III randomized controlled clinical trial compared clinical and angiographic outcomes from use of a TAXUS PES to that of a thin-strut XIENCE V® everolimus-eluting stent (EES) [6]. The evaluation of both 1-year and 2-year primary outcomes have indicated that the newer generation of DES, the EES, was associated with fewer clinical events than the first generation of DES, the PES [6,7]. Whether this benefit extended to all subgroups of patients enrolled in the study, including those with jailed side branches within stented segments, however, remains uncertain. The goal of this post-hoc study was to assess the impact of jailed side branches on clinical outcomes and periprocedural myonecrosis within each of the stent treatment groups.

METHODS

The SPIRIT III trial design has been described previously [6]. In brief, the SPIRIT III trial is a multicenter, prospective, single-blinded, controlled trial that compares the safety and efficacy of the EES (XIENCE V; Abbott Vascular, Santa Clara, CA) vs. the PES (TAXUS EXPRESS^2; Boston Scientific, Natick, MA) in patients with up to two *de novo* coronary artery lesions. A total of 1,002 patients were randomized 2:1 into the EES group and the PES group in 65 US sites. A post-hoc analysis for patients with and without jailed side branches in the SPIRIT III trial was performed based on angiographic analysis of the index procedure with angiographic follow-up at 8 months and clinical outcomes up to 2 years. Patients with a side branch <2 mm in diameter and with an ostial stenosis $<50\%$ were enrolled and characterized as having a jailed side branch. In the SPIRIT III RCT, 113 patients in the EES group and 63 patients in the PES group who met the criteria of having a jailed side branch were identified at the time of the index procedure and confirmed by the angiographic core lab. Periprocedural was defined as hospitalization less than or equal to 7 days post index procedure. The CK-MB analysis has been performed for single vessel/single lesion. In cases where multiple CK-MB measurements were made, the highest value was used for analysis.

Stent Delivery System

The XIENCE V stent is formulated from an L-605 cobalt chromium alloy with a polymer coat consisting of two layers, a primer layer and a drug matrix layer. The drug matrix layer elutes 100 $\mu g\ cm^{-2}$ of everolimus 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 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.

Protocol Inclusion/Exclusion Criteria and Randomization

Enrollment was restricted to patients ≥ 18 years of age with stable or unstable angina or inducible ischemia. Key inclusion criteria included a maximum of two *de novo* native coronary artery lesions, each in a different epicardial vessel, RVD of ≥ 2.5 mm and ≤ 3.75 mm, lesion length ≤ 28 mm by visual estimation, % diameter stenosis (%DS) of $\geq 50\%$ and $<100\%$, TIMI flow of ≥ 1, and nontarget vessel percutaneous intervention in nontarget vessel planned ≥ 90 days prior to or >9 months after the index procedure. Major clinical exclusion criteria included percutaneous coronary intervention (PCI) in the target vessel prior to or planned within 9 months of the index procedure, or in a nontarget vessel within 90 days prior or planned within 9 months of index procedure; acute or recent MI, left ventricular ejection fraction $<30\%$; use of chronic anticoagulation or immunosuppressive therapy; known autoimmune disease, renal insufficiency, recent major bleed, hemorrhagic diathesis or objection to blood transfusions; contraindications or allergy to any of the study medications, components of the study stents, or iodinated contrast that could not be premedicated; elective surgery planned within 9 months after the procedure necessitating antiplatelet agent discontinuation; platelet count $<100{,}000$ cells mm^{-3} or $>700{,}000$ cells mm^{-3}, white blood cell count $<3{,}000$ cells mm^{-3}, serum creatinine >2.5 mg dL^{-1} or dialysis, or liver disease; stroke or transient ischemic attack within 6 months; comorbid conditions limiting life expectancy to less than 1 year or that could affect protocol compliance; and participation

in another investigational study that has not yet reached its primary endpoint.

Key angiographic exclusion criteria included aorto-ostial location, left main location, excessive tortuosity, extreme angulation ($\geq$90°), heavy calcification, target vessel containing thrombus, other significant lesions (>40% DS) in the target vessel or side branch for which intervention was required within 9 months. If two target lesions were treated, each of these lesions had to meet all angiographic inclusion/exclusion criteria.

Following confirmation of angiographic eligibility, telephone randomization was performed in randomly alternating blocks of three and six patients using an automated voice response system, stratified by the presence of diabetes, planned dual vessel treatment, and study site. Although the operators were by necessity unblinded during the stent implant procedure, the patient and staff involved in follow-up assessments remained blinded through the follow-up period, with a standardized follow-up interview script used to reduce bias. Protocol specified angiographic follow-up was performed at 240 ($\pm$28) days in 436 patients, as previously described [6]. Clinical follow-up was performed at 1 month, 6 months, 9 months, 1 year, and then yearly through 5 years.

Interventional Procedure

Predilatation 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. Postdilatation 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 utilized.

Medication Administration

Subjects who were not on chronic antiplatelet or aspirin therapy were required to receive a loading dose of aspirin $\geq$300 mg before the procedure and clopidogrel bisulfate $\geq$300 mg no later than 1 hr after the procedure. All patients were to be maintained on 75 mg clopidogrel bisulfate daily for a minimum of 6 months and $\geq$80 mg of aspirin daily throughout the length of the trial (5 years) following the index procedure. Other medications were prescribed as per standard of care.

Clinical Follow-Up and Endpoints

Clinical follow-up was scheduled at 30 ($\pm$7) days, 180 ($\pm$14) days, 240 ($\pm$28) days, 270 ($\pm$14) days, and 365 ($\pm$28) days, with subsequent telephone follow-up yearly ($\pm$28 days) through 5 years.

The primary clinical endpoint of the SPIRIT III trial was TVF, consisting of the composite of cardiac death, MI, or ischemia-driven TVR by either percutaneous coronary intervention or bypass graft surgery. Secondary endpoints included MACE, defined as the composite of cardiac death, MI, or ischemia-driven TLR, as well as the individual components of TVF and MACE, and stent thrombosis. 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 postprocedure. Definite or probable stent thrombosis was also adjudicated in a post-hoc analysis using the Academic Research Consortium (ARC) definitions [8].

Statistical Methods

All analyses are by intention-to-treat, utilizing all patients randomized 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 $\pm$ 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 $\alpha = 0.05$ was used for all statistical tests to define significance. All statistical analyses were performed by SAS version 9.1.3 (SAS Institute, Cary, NC).

RESULTS

Of the 1,002 patients enrolled in the study, 606 EES patients and 304 PES patients had side branches. Total sides branches in EES patients were 1,345 compared to 703 in the PES patients. There were no significant differences in the average number of side branches per patient (2.2 $\pm$ 1.2 for EES vs. 2.3 $\pm$ 1.2 for PES, $P = 0.28$) or number of lesions per patient (1.2 $\pm$ 0.4 for EES vs. 1.2 $\pm$ 0.4 for PES, $P = 0.83$) in both arms. Average side branch diameters in both arms (1.60 $\pm$ 0.49 mm for EES vs. 1.63 $\pm$ 0.53 mm for PES, $P = 0.20$) were comparable. The baseline side branch % diameter stenosis were 19.7% for the EES arm and 19.6% for the PES arm, $P = 0.95$. Of the 1,002 patients enrolled in the study, 113 EES (11.3%) and 63 PES (6.3%) patients were identified who satisfied the criteria for a jailed side branch by the treatment stent. The baseline demographics of those with and without a jailed side branch for EES and PES patients are shown

TABLE I. Baseline Demographics and Lesion Characteristics

	No jailed side branches			Jailed side branches		
	EES ($N = 552$); ($M = 624$)	PES ($N = 268$); ($M = 302$)	P-value	EES ($N = 113$); ($M = 141$)	PES ($N = 63$); ($M = 80$)	P-value
Patient level analysis						
Age (years)	63.41 ± 10.63 (552)	63.05 ± 10.19 (268)	0.64	62.30 ± 10.19 (113)	61.80 ± 10.54 (63)	0.76
Male	68.8% (380/552)	65.7% (176/268)	0.38	75.2% (85/113)	65.1% (41/63)	0.17
Current smoker	22.6% (123/545)	23.0% (60/261)	0.93	27.9% (31/111)	21.0% (13/62)	0.37
Hypertension requiring medication	75.0% (414/552)	73.5% (197/268)	0.67	81.4% (92/113)	75.8% (47/62)	0.44
Hypercholesterolemia requiring medication	74.1% (403/544)	71.9% (189/263)	0.50	73.9% (82/111)	71.0% (44/62)	0.72
Stable angina	54.0% (293/543)	45.7% (121/265)	0.03	49.1% (54/110)	57.4% (35/61)	0.34
Unstable angina	18.2% (99/543)	26.8% (71/265)	0.006	21.8% (24/110)	16.4% (10/61)	0.43
Prior myocardial infarction	20.0% (107/536)	19.2% (51/265)	0.85	20.5% (23/112)	12.9% (8/62)	0.30
Lesion level analysis (target coronary artery)						
Left anterior descending	37.5% (234/624)	40.4% (122/302)	0.43	58.2% (82/141)	52.5% (42/80)	0.48
Circumflex or ramus	27.9% (174/624)	27.8% (84/302)	1.00	25.5% (36/141)	30.0% (24/80)	0.53
Right coronary artery	34.5% (215/624)	31.5% (95/302)	0.37	16.3% (23/141)	17.5% (14/80)	0.85
Left main	0.2% (1/624)	0.3% (1/302)	0.55	0.0% (0/141)	0.0% (0/80)	NA
Preprocedure						
Reference vessel diameter (mm)	2.76 ± 0.46 (624)	2.74 ± 0.46 (302)	0.55	2.81 ± 0.44 (141)	2.84 ± 0.46 (80)	0.58
Minimal luminal diameter (mm)	0.81 ± 0.42 (624)	0.80 ± 0.39 (302)	0.73	0.90 ± 0.40 (141)	0.95 ± 0.43 (80)	0.38
Diameter stenosis (%)	70.53 ± 13.37 (624)	70.28 ± 13.36 (302)	0.79	67.20 ± 12.85 (141)	66.30 ± 14.22 (80)	0.64
Lesion length (mm)	14.72 ± 5.63 (624)	14.85 ± 5.73 (299)	0.74	14.55 ± 5.41 (141)	14.29 ± 5.61 (80)	0.73

Note: N is the total number of patients; M is the total number of lesions. Patients/lesions with missing or unknown information are excluded from the analysis.

TABLE II. Periprocedural[a] Elevation of CK-MB[b]

	No jailed side branches			Jailed side branches		
	EES ($N = 552$)	PES ($N = 268$)	P-value	EES ($N = 113$)	PES ($N = 63$)	P-value
Any CK-MB $>1 \times$ upper normal level	11.7% (44/376) 6)	19.5% (36/185)	0.02	9.0% (6/67)	29.7% (11/37)	0.01
CK-MB >1–$<3 \times$ upper normal level	8.5% (32/376)	11.9% (22/185)	0.22	6.0% (4/67)	16.2% (6/37)	0.16
CK-MB $\geq 3 \times$–$\leq 5 \times$ upper normal level	1.6% (6/376)	3.8% (7/185)	0.14	1.5% (1/67)	5.4% (2/37)	0.29
CK-MB $>5 \times$ upper normal level	1.6% (6/376)	3.8% (7/185)	0.14	1.5% (1/67)	8.1% (3/37)	0.13

Note: N is the total number of patients. Patients with missing or unknown information are excluded from the analysis.

[a]Periprocedural: In-hospital, defined as hospitalization less than or equal to 7 days post index procedure.

[b]The analysis has been performed for single vessel/single lesion. In cases where multiple CK-MB measurements were made, the highest value was used for analysis.

in Table I. There were no clinically meaningful differences in baseline demographics among the different subgroups. Preprocedural vessel and lesion characteristics were also similar for all of the subgroups with the exception of the study-mandated presence or absence of a jailed side branch within the stented target lesion(s).

Occlusion of a jailed side branch during the index procedure occurred in 3/99 (3.0%) of EES, and 4/58 (6.9%) of PES, $P = 0.43$. A periprocedural increase in CK-MB $>1\times$ upper normal level (UNL) occurred in 11.7% of EES and 19.5% of PES patients without jailed side branches, $P = 0.02$; and 9.0% of EES and 29.7% of PES patients with jailed side branches, $P = 0.01$. The periprocedural rise in CK-MB was similar for EES patients with and without jailed side branches (9.0% vs. 11.7%, $P = 0.68$), but trended higher for PES patients with jailed side branches compared to those without jailed side branches (29.7% vs. 19.5%, $P = 0.19$). The extent of periprocedural biomarker elevation with and without jailed side branches for those with single lesion and vessel treatment EES and PES is shown in Table II. Among patients with a jailed side branch, the elevation of CK-MB three to five times more than UNL was 3.6-fold lower in EES patients than in PES patients (1.5% vs. 5.4%, $P = 0.29$). Additionally, the rate of CK-MB more than five times UNL was 5.4-fold lower in EES patients than in PES patients (1.5% vs. 8.1%, $P = 0.13$). The lower rates of CK-MB elevation for EES compared to PES were sustained through 2 years.

Angiographic follow-up was available in 80.8% of eligible EES and 71.4% of eligible PES patients with jailed side branches. At 8 months in-segment late loss

TABLE III. Jailed Side Branches Group: Clinical Outcomes Through 1-Year[a] and 2-Year[a] Follow-Up

	1-Year follow-up			2-Year follow-up		
	EES ($N = 113$)	PES ($N = 63$)	P-value	EES ($N = 113$)	PES ($N = 63$)	P-value
Major adverse cardiac event	6.4% (7/109)	13.1% (8/61)	0.16	6.8% (7/103)	19.0% (11/58)	0.03
Target vessel failure	9.2% (10/109)	14.8% (9/61)	0.31	10.7% (11/103)	20.7% (12/58)	0.10
All Death	3.6% (4/111)	1.6% (1/61)	0.66	4.7% (5/106)	3.4% (2/59)	1.00
Cardiac Death	1.8% (2/111)	1.6% (1/61)	1.00	1.9% (2/106)	1.7% (1/59)	1.00
Non Cardiac Death	1.8% (2/111)	0.0% (0/61)	0.54	2.8% (3/106)	1.7% (1/59)	1.00
Myocardial infarction	2.8% (3/109)	8.2% (5/61)	0.14	2.9% (3/103)	10.3% (6/58)	0.07
Q wave	0.9% (1/109)	1.6% (1/61)	1.00	1.0% (1/103)	3.4% (2/58)	0.30
Non-Q wave	1.8% (2/109)	6.6% (4/61)	0.19	1.9% (2/103)	6.9% (4/58)	0.19
Target lesion revascularization (TLR)	3.7% (4/109)	4.9% (3/61)	0.70	3.9% (4/103)	10.3% (6/58)	0.17
TLR—Coronary artery bypass graft surgery	0.0% (0/109)	0.0% (0/61)	NA	0.0% (0/103)	3.4% (2/58)	0.13
TLR—Percutaneous coronary intervention	3.7% (4/109)	4.9% (3/61)	0.70	3.9% (4/103)	6.9% (4/58)	0.46
Target vessel revascularization (TVR), nontarget lesion	3.7% (4/109)	8.2% (5/61)	0.29	4.9% (5/103)	10.3% (6/58)	0.21
TVR—Coronary artery bypass graft surgery	1.8% (2/109)	1.6% (1/61)	1.00	1.9% (2/103)	3.4% (2/58)	0.62
TVR—Percutaneous coronary intervention	1.8% (2/109)	6.6% (4/61)	0.19	2.9% (3/103)	6.9% (4/58)	0.25

Note: N is the total number of patients. Patients with missing or unknown information are excluded from the analysis.
[a]Including ±28 days window.

TABLE IV. No Jailed Side Branches Group: Clinical Outcomes Through 1-Year[a] and 2-Year[a] Follow-Up

	1-Year follow-up			2-Year follow-up		
	EES ($N = 552$)	PES ($N = 268$)	P-value	EES ($N = 552$)	PES ($N = 268$)	P-value
Major adverse cardiac event	5.7% (31/541)	9.7% (25/257)	0.05	7.7% (41/530)	12.6% (31/246)	0.03
Target vessel failure	8.3% (45/541)	10.9% (28/257)	0.24	11.3% (60/530)	15.4% (38/246)	0.13
All death	0.7% (4/541)	1.2% (3/258)	0.69	1.5% (8/532)	2.4% (6/249)	0.39
Cardiac death	0.6% (3/541)	0.8% (2/258)	0.66	0.9% (5/532)	1.2% (3/249)	0.72
NonCardiac death	0.2% (1/541)	0.4% (1/258)	0.54	0.6% (3/532)	1.2% (3/249)	0.39
Myocardial infarction	2.8% (15/541)	3.1% (8/257)	0.82	3.4% (18/530)	4.9% (12/246)	0.32
Q wave	0.2% (1/541)	0.0% (0/257)	1.00	0.4% (2/530)	0.0% (0/246)	1.00
Non-Q wave	2.6% (14/541)	3.1% (8/257)	0.65	3.0% (16/530)	4.9% (12/246)	0.22
Target lesion revascularization (TLR)	3.1% (17/541)	5.8% (15/257)	0.08	4.5% (24/530)	6.9% (17/246)	0.17
TLR—Coronary artery bypass graft surgery	0.2% (1/541)	0.0% (0/257)	1.00	0.4% (2/530)	0.0% (0/246)	1.00
TLR—Percutaneous coronary intervention	3.0% (16/541)	5.8% (15/257)	0.08	4.2% (22/530)	6.9% (17/246)	0.11
Target vessel revascularization (TVR), nontarget lesion	3.0% (16/541)	3.9% (10/257)	0.52	4.9% (26/530)	5.7% (14/246)	0.73
TVR—Coronary artery bypass graft surgery	0.4% (2/541)	0.4% (1/257)	1.00	0.8% (4/530)	0.8% (2/246)	1.00
TVR—Percutaneous coronary intervention	2.6% (14/541)	3.5% (9/257)	0.50	4.2% (22/530)	4.9% (12/246)	0.71

Note: N is the total number of patients. Patients with missing or unknown information are excluded from the analysis.
[a]Including ±28 days window.

was 0.14 ± 0.28 mm for EES and 0.23 ± 0.42 mm for PES, $P = 0.32$. The clinical outcomes at one and two years for the EES and PES patients with and without a jailed side branch are shown in Tables III and IV. For patients with a jailed side branch, MACE (6.4% vs. 13.1%, $P = 0.16$), TVF (EES vs. PES, 9.2% vs. 14.8%, $P = 0.31$), and TLR (EES vs. PES, 3.7% vs. 4.9%, $P = 0.70$), at 1 year were numerically lower in the EES group compared to the PES group, but were not significantly different. In contrast to one year MACE rates, 2-year cumulative incidence rates of MACE for patients with a jailed side branch was significantly lower in the EES group, 6.3%, compared to the PES group, 18.1%, $P = 0.02$ (Fig. 1). The lower MACE rate was driven by lower rates of MI, 2.9% for EES vs. 10.3% for PES, $P = 0.07$, and TLR, 3.9% for EES, and 10.3% for PES, $P = 0.17$. The interaction effect between stents with and without jailed side branches for MACE at 2 years was not significant, $P = 0.23$. Rates of cardiac death were similar. Two year cumulative incidence rate of TVF for patients with a jailed side branch was numerically lower in EES, 10.0%, compared to PES group, 19.7%. $P = 0.08$. Overall, rates of clinical outcomes at one and two years were similar for EES patients with and without a jailed side branch. However, the rates of clinical events at 1 and 2 years for PES patients with a jailed side branch including overall MACE were numerically higher than those without a jailed side branch.

Rates of stent thrombosis by study protocol definition and by ARC definition through 2 years for the EES and PES groups with and without a jailed side

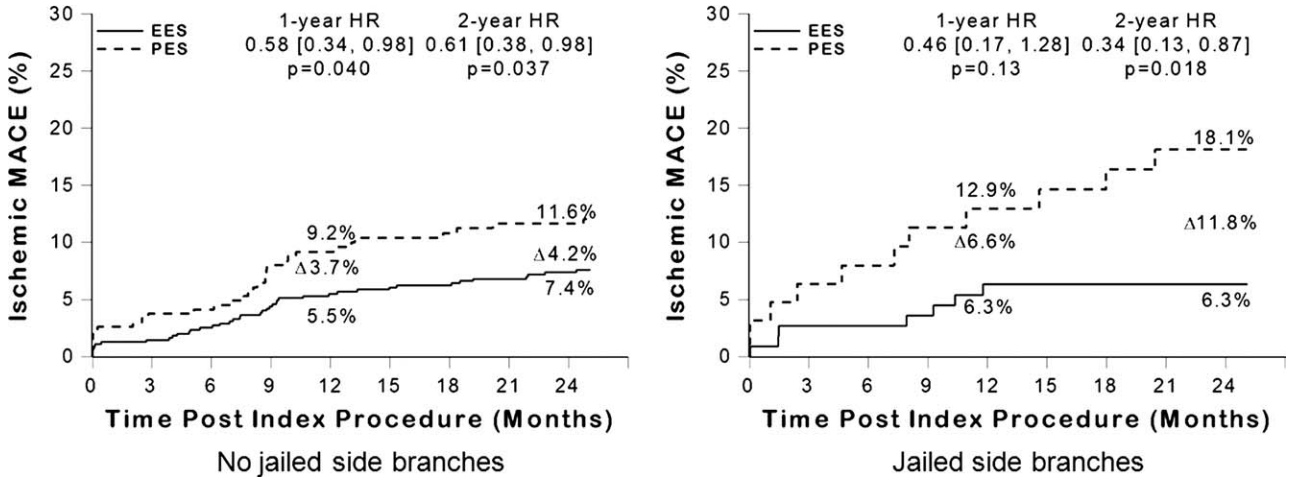

Fig. 1. Cumulative incidence rates of ischemic major adverse cardiac events (MACE) for EES and PES patients with and without jailed side branches implanted through 2 years.

TABLE V. Stent Thrombosis Through 2 Years[a]

	No jailed side branches			Jailed side branches		
	EES ($N = 552$)	PES ($N = 268$)	*P*-value	EES ($N = 113$)	PES ($N = 63$)	*P*-value
			Stent thrombosis			
Protocol definition	1.0% (5/522)	1.2% (3/243)	0.71	1.0% (1/101)	3.5% (2/57)	0.30
Acute (<1 day)	0.2% (1/552)	0.0% (0/266)	1.00	0.0% (0/113)	0.0% (0/63)	NA
Subacute (1–30 days)	0.4% (2/550)	0.0% (0/266)	1.00	0.0% (0/113)	0.0% (0/63)	NA
Late (31–393 days)	0.2% (1/536)	0.4% (1/254)	0.54	0.9% (1/107)	1.7% (1/60)	1.00
Very late (394–758 days)	0.2% (1/521)	0.8% (2/243)	0.24	0.0% (0/101)	1.8% (1/56)	0.36
ARC definition						
Definite	1.0% (5/523)	0.8% (2/242)	1.00	1.0% (1/102)	0.0% (0/57)	1.00
Probable	0.2% (1/523)	0.4% (1/242)	0.53	1.0% (1/102)	3.5% (2/57)	0.29
Definite/probable	1.1% (6/523)	1.2% (3/242)	1.00	2.0% (2/102)	3.5% (2/57)	0.62

Note: *N* is the total number of patients. Patients with missing or unknown information are excluded from the analysis.
[a]Including ±28 days window.

branch are shown in Table V. Rates of stent thrombosis by either criterion were similar for both the EES and PES groups with and without a jailed side branch for all of the time intervals examined (Table V).

DISCUSSION

This post hoc analysis of the randomized comparison of EES to PES evaluated the impact of jailing a small side branch within a stented target lesion on clinical outcomes and periprocedural myonecrosis through two years. We observed that use of a PES was associated with an increase in rates of periprocedural CK-MB elevation, which was most prevalent in those patients with a jailed side branch. In contrast, rates of periprocedural CK-MB elevation were similar in those patients receiving an EES regardless of the presence or absence of a jailed side branch. Moreover, the rates of periprocedural CK-MB elevation were lower in those with an EES compared to a PES in those with and without a jailed side branch. The clinical outcomes at 1 and 2 years were similar in the EES treated patients with and without a jailed side branch, but were numerically higher in the PES treated patients with a jailed side branch compared to those without a jailed side branch. These observations confirm previous studies demonstrating a relative increase in the incidence of periprocedural elevation of biomarkers with PES use, and demonstrate the absence of this phenomenon with a second generation DES, an EES.

The association of a periprocedural rise in cardiac biomarkers after PCI and subsequent potential adverse clinical outcomes has been the subject of considerable interest and debate [9–13]. An ischemic event during or after a PCI resulting in a clinically recognizable myocardial infarction has a clearly demonstrated adverse effect on subsequent morbidity and mortality [14]. However, an asymptomatic rise in cardiac

biomarkers may occur after up to 20% of PCI procedures, and the clinical consequences of this periprocedural biomarker elevation are less clear [15]. At least one study found an association between any elevation of CK-MB >1x UNL and mortality at 1 year [4,16,17]. However, the association of adverse late clinical outcomes including death are strongest in those with the largest periprocedural rise in biomarkers, i.e., >5× UNL [11,12,18]. Fortunately, these marked elevations of biomarkers are infrequent after PCI, and were observed in only 2.6% of patients in this study.

The periprocedural rise in biomarkers after PCI may be influenced by several factors. Jailing small side branches during a stent procedure is not uncommon. Several studies have demonstrated a small but significant incidence of side branch transient or persistent occlusion after stent procedures [1,19]. The extent of myonecrosis after this event is dependent on both the territory of myocardium at jeopardy, and the duration and extent of occlusion. Other factors are also important, including the extent and severity of atherosclerosis within the target vessel as well as the jailed side branch itself. A detailed analysis of these factors would be useful in better understanding the relative increase in myonecrosis seen with PES compared to EES but is beyond the scope of this study.

The reasons for the increase in myonecrosis after PES use compared to EES use, particularly in those with jailed side branches, are uncertain. Potential explanations include physical flow obstruction and/or thrombogenicity near or within the jailed side branch [20]. There are physical differences in profile of the two stents. The PES has a strut thickness of 132 microns, and a polymer thickness of 19.6 μm, while the EES has a strut thickness of 81 μm and a polymer thickness of 7.8 μm [21–23]. This relatively larger vascular footprint of the PES would potentially create a physical barrier to flow to the jailed side branch, resulting in ischemia and/or occlusion. A recent study observing higher rates of branch vessel occlusion after PES compared to a thinner profile zotarolimus-eluting stent supports stent profile as an important determinant of periprocedural myonecrosis [22]. Differences also exist in the polymer coatings of the two stents. Whether these differences translate into different effects on thrombogenicity including the likelihood of local platelet adhesion and aggregation remains to be determined. However, the clinician should be reassured by these data that rates of TLR with EES are similar whether a side branch is jailed or not.

There are potential limitations of this sub-study that merit discussion. This was a post-hoc analysis of 2-year outcomes. As such, reporting and selection biases may have occurred. However, the clinical follow-up was excellent and similar for both stent types. Quantitative coronary angiography and intra-coronary ultrasound were not performed at the time of a clinical event routinely or at 2 years. Thus, correlation of angiographic findings and outcomes at the time of clinical events was not possible. Finally, the SPIRIT III study was not powered to evaluate rare clinical events. Further larger clinical studies such as SPIRIT IV, which is powered to evaluate rare clinical outcomes, such as composite of cardiac death or target vessel-MI, will be necessary to confirm the presented data.

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