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Clinical and Angiographic Outcomes With an Everolimus-Eluting Stent in Large Coronary Arteries: The SPIRIT III 4.0 mm Registry

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Objective: This study evaluates the safety and efficacy of the XIENCE V® 4.0 mm stent for the treatment of de novo native coronary artery lesions. Background: In the SPIRIT III trial, the XIENCE V® everolimus-eluting stent (EES), compared with the TAXUS EXPRESS[2] paclitaxel-eluting stent (PES) in 2.5–3.75 mm diameter coronary arteries, resulted in reduced angiographic late loss (LL), noninferior rates of target vessel failure (TVF), and fewer major adverse cardiac events (MACE). Methods: The SPIRIT III 4.0 mm registry was a concurrent arm of the SPIRIT III trial consisting of 69 nonrandomized patients with lesions ≤28 mm in length and reference vessel diameter 3.75–4.25 mm treated with a 4.0 mm EES. The primary endpoint was 8-month in-segment LL compared with the randomized PES arm. Results: In-segment LL was 0.17 ± 0.38 mm in the 4.0 mm EES registry compared with 0.28 ± 0.48 mm in the PES arm ($P < 0.0001$ for noninferiority). The 1-year rates of ischemia-driven TVF (cardiac death, myocardial infarction [MI], or target vessel revascularization) and MACE (cardiac death, MI, or target lesion revascularization [TLR]) were numerically, but not statistically, lower in the 4.0 mm EES patients compared with the randomized PES patients (5.9 vs. 11.3%, $P = 0.27$ and 5.9 vs. 10.3%, $P = 0.36$, respectively). There was no difference in 8-month LL or 1-year TVF or MACE between the 4.0 mm EES and randomized EES patients. Conclusions: In large coronary arteries, the 4.0 mm EES results in low rates of LL at 8 months and adverse clinical events at 1 year. © 2009 Wiley-Liss, Inc.

Key words: coronary disease; drug-eluting stents; paclitaxel; late loss

INTRODUCTION

Paclitaxel and sirolimus drug-eluting stents (DES) result in less angiographic late loss (LL), fewer major adverse cardiac events (MACE), and improved event-free survival compared with their bare metal counterparts when implanted in 2.5–3.5 mm diameter coronary arteries [1-3]. In the SPIRIT FIRST and SPIRIT II trials, the XIENCE V® everolimus-eluting coronary stent (EES) was shown to have less in-stent LL and angiographic restenosis compared with the ML VISION® bare metal stent (BMS) [4] and the TAXUS® EXPRESS[2]® paclitaxel-eluting stent (PES) [5]. In the large-scale SPIRIT III randomized controlled trial, the EES compared with the PES in 2.5–3.75 mm diameter vessels resulted in reduced 8-month angiographic LL, noninferior rates of target vessel failure (TVF) at 9 months, and fewer MACE at 1 year of follow-up [6].

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For both BMS and DES, reference vessel diameter (RVD) has an inverse relationship to angiographic restenosis and late target lesion revascularization (TLR) [2,3,7]. However, there is limited data for the safety and efficacy of DES in the treatment of de novo lesions in coronary arteries greater than 3.5 mm diameter.

Concurrent with enrollment in the SPIRIT III randomized trial, patients with lesions $\leq$28 mm in length and RVD of 3.75–4.25 mm were enrolled in a nonrandomized study arm and were treated with the 4.0 mm diameter EES. This study reports the results from the 4.0 mm SPIRIT III registry.

METHODS

Protocol Entry Criteria and Randomization

The design of the SPIRIT III trial has been previously described [6]. In brief, SPIRIT III was a prospective, multicenter, randomized, single-blind, controlled clinical trial in which 1,002 patients with either one or two de novo native coronary artery lesions (maximum one lesion per epicardial coronary artery) were randomized in a 2:1 ratio to receive the EES (XIENCE V, Abbott Vascular, Santa Clara, CA) or the PES (TAXUS EXPRESS^2, Boston Scientific, Natick, MA). The SPIRIT III 4.0 registry was a concurrent arm of nonrandomized patients with stenoses in native coronary arteries with a RVD of $\geq$3.75 mm and $\leq$4.25 mm and lesion length $\leq$28 mm, which were treated with a 4.0 mm diameter EES.

Enrollment was restricted to patients $\geq$18 years of age with stable or unstable angina or inducible ischemia. 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 myocardial infarction (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 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. The study was approved by the institutional review board at each participating center, and consecutive, eligible patients signed informed, written consent.

By visual assessment, all study lesions had a diameter stenosis of $\geq$50% and $<$100%, with a lesion length $\leq$28 mm. In the randomized study arms, all lesions had a visually estimated RVD of 2.5–3.75 mm, and in the nonrandomized 4.0 mm registry, all lesions had an estimated RVD of 3.75–4.25 mm. Angiographic exclusion criteria included ostial or left main lesions; bifurcation lesions with either the side branch $>$50% stenosed or $>$2 mm in diameter or requiring predilatation; excessive proximal tortuosity, lesion angulation $\geq$90% or heavy calcification, or thrombus; lesion located within a bypass graft conduit; the presence of untreated lesions with $>$40% stenosis within the target vessel or likelihood that additional PCI would be required within 9 months.

Following confirmation of eligibility, telephone randomization to EES vs. PES was performed for patients with 2.5–3.75 mm RVD lesions as previously described [6], whereas those with 3.75–4.25 mm RVD lesions were registered and consecutively treated with EES. Protocol specified angiographic follow-up was performed at 240 ($\pm$28) days in 486 patients in the randomized study arms [6], and was planned for all of the 4.0 mm registry patients.

Medication Administration and Clinical Follow-Up

Procedural anticoagulation was achieved with either unfractionated heparin or bivalirudin as per standard of care, with glycoprotein IIb/IIIa inhibitors used per operator discretion. Patients who were not on chronic antiplatelet or aspirin therapy were required to receive aspirin $\geq$300 mg preprocedure and a loading dose of 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$80 mg of aspirin daily throughout the length of the trial (5 years) following the index procedure. Other medications were prescribed as per standard of care. Clinical follow-up was scheduled at 30 ($\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.

Data Management

Independent study monitors verified 100% of case report form data on-site. An independent committee blinded to treatment allocation adjudicated all MACE after review of original source documentation. A

second clinical events committee blinded to randomization or registry enrollment performed a post hoc adjudication of stent thrombosis using the Academic Research Consortium (ARC) definitions [8]. Independent core angiographic laboratory analyses were performed and clinical outcomes using validated methods as previously described [9]. A Data Safety and Monitoring Committee periodically reviewed blinded safety data, each time recommending the study continue without modification.

Angiographic Endpoints and Definitions

The primary objective of the 4.0 mm registry was to demonstrate that in-segment LL at 240 days for the 4.0 mm EES is noninferior to the PES cohort from the randomized SPIRIT III trial. As a secondary analysis, the results of the 4.0 mm EES registry were also compared with the randomized EES cohort. In-stent LL was defined as the difference within the stent in minimal lumen diameter (MLD) assessed immediately after the procedure compared with the MLD at 240-day angiographic follow-up, whereas in-segment LL extends the measures 5 mm proximal and distal to the stent [9]. Additional secondary angiographic endpoints included a comparison of in-stent LL at 240 days, in-segment and in-stent percent diameter stenosis at 240 days (%DS = 100*(1 − (MLD/RVD)), and in-segment angiographic binary restenosis rate (ABR = % of patients with %DS $\geq$ 50%) at 240 days between the 4.0 mm group and the randomized groups. To avoid interlesion clustering of restenosis in patients receiving stents for multiple lesions (which would have required correction with multilevel generalized estimating equations), the protocol specified that for patients in whom two lesions were treated, a single lesion (analysis lesion) would be randomly selected by computer for analysis of LL. All lesions were included in the analyses for all other angiographic endpoints.

Clinical Endpoints and Definitions

The secondary clinical endpoint of the SPIRIT III 4.0 mm registry was ischemia-driven TVF at 270 days, 1, 2, 3, 4, and 5 years, consisting of the composite of cardiac death, MI, or ischemia-driven target vessel revascularization (TVR) by either PCI or bypass graft surgery. TVR (or lesion) was considered to be ischemia-driven if associated with a positive functional study, a target vessel (or lesion) diameter stenosis $\geq$50% by core laboratory quantitative analysis with ischemic symptoms, or a target vessel (or lesion) diameter stenosis $\geq$70% with or without documented ischemia. MACE was defined as the composite of cardiac death, MI, or ischemia-driven TLR. MI was defined as either the development of new pathologic Q-waves ($\geq$0.4 sec in duration in $\geq$2 contiguous leads) or an elevation of creatine phosphokinase levels to >2.0 times normal levels with positive creatine phosphokinase-MB. Stent thrombosis was prospectively defined per 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 stent thrombosis, ST-segment elevation, or new Q-waves in the distribution of the target lesion occurring within 30 days postprocedure. Definite or probable stent thrombosis was also adjudicated in a post hoc analysis using the ARC definitions [8].

Statistical Methods

Sample size calculations for the 4.0 mm registry were based on noninferiority for the primary endpoint of in-segment LL at 8 months in the EES 4.0 mm registry patients comparing to the PES group from the randomized trial. Hypothesis testing for primary endpoint of in-segment LL will be performed using analysis lesion. Hypothesis testing for major secondary endpoint and all of the ad hoc analyses will be performed using all target lesions. Analysis lesion is defined as the target lesion for subjects with single de novo lesion and a randomly selected lesion for subjects with two de novo lesions. If the randomized lesion cannot be treated for any reason, the other target lesion, by default, becomes the analysis lesion.

Assuming a mean LL of 0.24 (SD, 0.47) mm for both the PES and the EES 4.0 mm stent groups and 169 analysis lesions from the PES group, an one-sided alpha of 0.05, and a noninferiority margin of 0.195 mm, a sample size of 80 EES 4.0 mm patients (allowing for 10% dropout) afforded 90% power to demonstrate noninferiority for in-segment LL using analysis lesion. Sequential superiority testing was prespecified if noninferiority for LL was met.

Interim Analysis for the 4.0 mm Registry

Of the planned 80 patients, 69 were enrolled at 30 sites in the 4.0 mm registry. An interim analysis was prospectively planned for the 69 enrolled patients after the completion of their scheduled follow-up and after unblinding of the randomized SPIRIT III clinical trial. At the interim analysis, 69 patients (~62 evaluable patients with 90% follow-up rate) in the 4.0 mm registry were to be compared

TABLE I. Baseline Demographics

	EES 4.0 mm registry ($N = 69$) ($M = 69$)	EES 2.5–3.75 mm randomized ($N = 669$) ($M = 772$)	PES 2.5–3.75 mm randomized ($N = 333$) ($M = 383$)
Age (years)	61.93 ± 11.20 (69)	63.23 ± 10.53 (669)	62.80 ± 10.24 (332)
Male	72.5% (50/69)	70.1% (469/669)	65.7% (218/332)
Diabetes mellitus	30.4% (21/69)	29.6% (198/669)	27.9% (92/330)
Requiring insulin	8.7% (6/69)	7.8% (52/669)	5.5% (18/330)
Current smoker	27.9% (19/68)	23.4% (154/659)	22.5% (73/324)
Hypertension requiring medication	65.2% (45/69)	76.2% (510/669)	74.0% (245/331)
Hypercholesterolemia requiring medication	77.9% (53/68)	74.2% (489/659)	71.5% (233/326)
Stable angina	47.8% (32/67)	53.3% (350/657)	47.7% (156/327)
Unstable angina	19.4% (13/67)	18.7% (123/657)	25.1% (82/327)
Prior myocardial infarction	17.4% (12/69)	19.9% (130/652)	18.0% (59/327)
Target coronary artery			
Left anterior descending	26.1% (18/69)	41.3% (317/768)	42.9% (164/382)
Left circumflex or ramus	17.4% (12/69)	27.6% (212/768)	28.3% (108/382)
Right coronary artery	56.5% (39/69)	31.0% (238/768)	28.5% (109/382)
Left main coronary artery	0.0% (0/69)	0.1% (1/768)	0.3% (1/382)
Preprocedure			
Reference vessel diameter (mm)	3.53 ± 0.36 (69)	2.77 ± 0.45 (767)	2.76 ± 0.46 (382)
Minimal luminal diameter (mm)	1.01 ± 0.49 (69)	0.82 ± 0.41 (767)	0.83 ± 0.40 (382)
Diameter stenosis (%)	71.4 ± 13.38 (69)	70.0 ± 13.3 (767)	69.4 ± 13.6 (382)
Lesion length (mm)	15.4 ± 6.2 (69)	14.7 ± 5.6 (767)	14.7 ± 5.7 (379)

N is the total number of patients; *M* is the total number of lesions

with the PES angiographic subset patients. Sequential boundaries based on the Pocock alpha spending function [10] would be applied to the interim analysis of in-segment LL. With 62 evaluable patients and all other assumptions remaining the same as those specified for the sample size calculation of the 4.0 mm registry, the power of the interim analysis was 84% using a nominal alpha of 0.0377 for the interim analysis.

Categorical variables were compared by Fisher's exact test. Continuous variables are presented as mean ±1 standard deviation and were compared by *t*-test. 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. Survival curves using available follow-up data were also constructed for time-to-event variables using Kaplan-Meier estimates and compared by log-rank test. A two-sided $\alpha = 0.05$ was used for superiority testing. All statistical analyses were performed by SAS version 9.1.3 (SAS Institute, Cary, NC).

Role of the Funding Source

The trial was sponsored and funded by Abbott Vascular. The sponsors were involved in study design and in data collection, analysis, and interpretation, along with the principal investigator and steering committees [6]. The corresponding author had full access to all the data in the study. The manuscript was prepared by the corresponding author and revised by all co-authors. The authors controlled the decision to submit the paper for publication.

RESULTS

Patients and Enrollment

Between June 22, 2005 and March 15, 2006, 69 patients were enrolled in the 4.0 mm EES registry, 669 patients were enrolled in the randomized EES arm, and 333 patients were enrolled in the randomized PES arm. Baseline demographics were similar between the three groups. By design, the mean RVD and the preprocedure MLD were larger in the 4.0 mm EES registry arm in comparison with both the randomized EES and PES arms, although the percent diameter stenosis and lesion length were similar between the three groups (Table I).

Procedural and Angiographic Results

Procedural success, number of stents per lesion, and maximum balloon inflation pressure were similar among all three groups (Table II). As expected in larger vessels, acute gain was greater in the 4.0 mm cohort compared

TABLE II. Procedural Results and Angiographic Outcomes

	EES 4.0 mm registry ($N = 69$) ($M = 69$)	EES 2.5–3.75 mm randomized ($N = 669$) ($M = 772$)	PES 2.5–3.75 mm randomized ($N = 333$) ($M = 383$)
Clinical device success	98.5% (67/68)	98.3% (750/763)	98.7% (374/379)
Clinical procedure success	94.2% (65/69)	98.5% (651/661)	97.3% (322/331)
Number of stents per lesion	1.2 ± 0.5 (69)	1.2 ± 0.4 (768)	1.1 ± 0.3 (382)
Total stent length per lesion (mm)	22.9 ± 6.0 (69)	21.6 ± 6.2 (763)	20.6 ± 6.1 (376)
Mean balloon pressure (atm.)	14.9 ± 2.9 (69)	14.8 ± 2.9 (772)	15.1 ± 2.6 (382)
IIb/IIIa inhibitor usage	31.9% (22/69)	27.5% (184/669)	24.7% (82/332)
Postprocedure			
Reference vessel diameter (mm)[a]	3.60 ± 0.36 (69)	2.84 ± 0.45 (766)	2.84 ± 0.46 (379)
In-segment minimal luminal diameter (mm)	3.07 ± 0.43 (69)	2.37 ± 0.45 (766)	2.36 ± 0.45 (379)
In-stent minimal luminal diameter (mm)	3.46 ± 0.38 (69)	2.71 ± 0.43 (763)	2.74 ± 0.41 (379)
In-segment diameter stenosis (%)	13.4 ± 8.1 (69)	13.5 ± 7.6 (765)	14.4 ± 7.1 (379)
In-stent diameter stenosis (%)[b]	2.1 ± 10.3 (69)	0.3 ± 8.9 (762)	−0.2 ± 9.9 (379)
In-segment acute gain (mm)	2.07 ± 0.57 (49)	1.56 ± 0.53 (343)	1.57 ± 0.49 (158)
In-stent acute gain (mm)	2.47 ± 0.53 (49)	1.92 ± 0.49 (342)	1.94 ± 0.45 (158)
240-day angiographic follow-up			
Reference vessel diameter (mm)[a]	3.55 ± 0.41 (49)	2.77 ± 0.43 (344)	2.78 ± 0.42 (158)
In-segment minimal luminal diameter (mm)	2.91 ± 0.51 (49)	2.22 ± 0.53 (344)	2.12 ± 0.60 (158)
In-stent minimal luminal diameter (mm)	3.36 ± 0.46 (49)	2.56 ± 0.53 (343)	2.45 ± 0.65 (158)
In-segment diameter stenosis (%)[b]	17.9 ± 10.8 (49)	18.8 ± 14.4 (344)	22.8 ± 16.4 (158)
In-stent diameter stenosis (%)[b]	4.8 ± 13.2 (49)	5.9± 16.4 (343)	10.3 ± 21.4 (158)
In-segment late loss (mm, analysis lesions[c])	0.17 ± 0.38 (49)	0.14 ± 0.41 (301)	0.28 ± 0.48 (134)
In-segment late loss (mm, all lesions[d])	0.17 ± 0.38 (49)	0.14 ± 0.39 (343)	0.26 ± 0.46 (158)
In-stent late loss (mm, all lesions)	0.12 ± 0.34 (49)	0.16 ± 0.41 (342)	0.30 ± 0.53 (158)
In-segment binary restenosis	2.0% (1/49)	4.7% (16/344)	8.9% (14/158)
In-stent binary restenosis	0.0% (0/49)	2.3% (8/343)	5.7% (9/158)

N is the total number of patients; *M* is the total number of lesions.

Clinical device success was defined as successful delivery and deployment of the first inserted study stent (in overlapping stent setting a successful delivery and deployment of the first and second study stent) at the intended target lesion and successful withdrawal of the stent delivery system with attainment of final residual stenosis of <50% of the target lesion by QCA (by visual estimation if QCA unavailable). Bailout subjects will be included as device success only if the above criteria for clinical device are met.

Clinical procedure success was defined as successful delivery and deployment of the study stent or stents at the intended target lesion and successful withdrawal of the stent delivery system with attainment of final residual stenosis of <50% of the target lesion by QCA (by visual estimation if QCA unavailable) and/or using any adjunctive device without the occurrence of major adverse cardiac event (MACE) during the hospital stay with a maximum of first 7 days postindex procedure. In dual lesion setting both lesions must meet clinical procedure success.

[a]User-defined method is used to calculate reference vessel diameter.

[b]Interpolated method used to calculate % diameter stenosis.

[c]Analysis lesion is defined as the target lesion for subjects with single de novo lesion and a randomly selected lesion for subjects with two de novo lesions. If the randomized lesion cannot be treated for any reason, the other target lesion, by default, becomes the analysis lesion.

[d]All lesions are all target lesions for subjects with single and two de novo lesions.

with the randomized groups (Table II). An interim analysis was performed for the 69 enrolled patients. The clinical follow-up rate for these 69 patients was 97%. Angiographic follow-up was performed for 49 patients, representing a follow-up rate of 71%, which is in accordance with the angiographic follow-up rates reported previously [2,3], and in the SPIRIT III randomized trial (77%). The angiographic results from the EES 4.0 mm arm were compared to the angiographic follow-up at 8 months for 158 lesions in the randomized PES cohort and 342 lesions in the randomized EES cohort. The primary endpoint of in-segment LL, per analysis-lesion analysis, was significantly reduced by 39% in the 4.0 mm EES registry cohort compared with the randomized PES cohort (0.17 ± 0.38 mm vs. 0.28 ± 0.48 mm respectively, $P < 0.0001$ for noninferiority). In-stent LL was also less in the 4.0 mm EES cohort compared with the randomized PES cohort (0.12 ± 0.34 vs. 0.30 ± 0.53, respectively, $P = 0.005$), per all-lesion analysis. Both in-segment and in-stent LL were comparable between the 4.0 mm EES registry arm and the randomized EES cohort. In-segment binary angiographic restenosis at 240 days occurred in only one patient receiving a 4.0 mm EES (2.0%).

Clinical Outcomes

In the 4.0 mm EES registry, 68 of 69 patients had follow-up through 270 days, and 67 patients completed 1-year follow-up, four of whom had clinical events (Table

TABLE III. Clinical Outcomes Through 1-Year Follow-Up

	EES 4.0 mm registry ($N = 69$)	EES 2.5–3.75 mm randomized ($N = 669$)	PES 2.5–3.75 mm randomized ($N = 333$)
All-cause death	1.5% (1/68)	1.2% (8/655)	1.2% (4/321)
Cardiac death	1.5% (1/68)	0.8% (5/653)	0.9% (3/320)
Myocardial infarction	4.4% (3/68)	2.8% (18/653)	4.1% (13/320)
Q-wave	0.0% (0/68)	0.3% (2/653)	0.3% (1/320)
Non-Q-wave	4.4% (3/68)	2.5% (16/653)	3.8% (12/320)
Target vessel revascularization, all[a]	1.5% (1/68)	7.3% (48/655)	10.9% (35/321)
Ischemia-driven[b]	1.5% (1/68)	6.1% (40/655)	7.5% (24/321)
Nonischemia-driven[c]	0.0% (0/68)	2.3% (15/655)	5.6% (18/321)
Target lesion revascularization, all	1.5% (1/68)	4.7% (31/655)	9.7% (31/321)
Ischemia-driven	1.5% (1/68)	3.4% (22/655)	5.6% (18/321)
Nonischemia-driven	0.0% (0/68)	1.5% (10/655)	5.3% (17/321)
Target vessel revascularization, nontarget lesion	0.0% (0/68)	3.7% (24/655)	5.6% (18/321)
Ischemia-driven	0.0% (0/68)	3.1% (20/655)	4.4% (14/321)
Nonischemia-driven	0.0% (0/68)	0.8% (5/655)	1.2% (4/321)
Stent thrombosis, protocol definition	1.5% (1/67)	0.8% (5/647)	0.6% (2/317)
Acute (<1 day)	1.4% (1/69)	0.1% (1/669)	0.0% (0/330)
Subacute (1–30 days)	0.0% (0/69)	0.3% (2/667)	0.0% (0/330)
Late (30–393 days)	0.0% (0/67)	0.3% (2/646)	0.6% (2/317)
Stent thrombosis, ARC definite or probable	0.0% (0/68)	1.1% (7/652)	0.6% (2/319)
Definite	0.0% (0/68)	0.8% (5/652)	0.0% (0/319)
Probable	0.0% (0/68)	0.3% (2/652)	0.6% (2/319)
Major adverse cardiac events	5.9% (4/68)	6.0% (39/653)	10.3% (33/320)
Target vessel failure	5.9% (4/68)	8.6% (56/653)	11.3% (36/320)

N is the total number of patients.
[a]Target vessel revascularization, all includes TLR and TVR, nontarget lesion.
[b]Ischemia-driven target lesion revascularization, all includes ID-TLR and ID-TVR, nontarget lesion.
[c]Nonischemia-driven target lesion revascularization, all includes non-ID-TLR and non-ID-TVR, nontarget lesion.

III and Fig. 1). Three patients developed periprocedural non-Q-wave MIs, one as a result of acute stent thrombosis (representing the only case of stent thrombosis among 4.0 mm EES patients); no other MIs occurred during follow-up. One 4.0 mm EES patient died during follow-up on day 45 due to cardiac death. TVR was also required in only one patient, who previously experienced periprocedural non-Q-wave MI, during follow-up.

Ischemia-driven TVF at 1 year occurred for 5.9% of patients in the 4.0 mm EES cohort compared with 11.3% of randomized PES cohort ($P = 0.27$). Ischemia-driven MACE at 1 year was also numerically but not significantly lower in the 4.0 mm EES registry compared with the randomized PES cohort (5.9 vs. 10.3%, $P = 0.36$). The 1-year rates of TVF and MACE were comparable between the 4.0 mm EES and the randomized EES patients.

DISCUSSION

The 4.0 mm EES registry arm of the SPIRIT III trial was designed to evaluate the safety and efficacy of the XIENCE V EES in large coronary arteries ranging from 3.75 to 4.25 mm in diameter. With angiographic follow-up at 8 months and clinical follow-up through 1 year, the results of this study demonstrate that the 4.0 mm EES is safe, and results in a low rate of LL, binary restenosis, and adverse cardiac events. Compared with PES in 2.5–3.75 mm vessels, the 4.0 mm EES results in significant trends toward less in-stent LL ($P = 0.005$) and MACE ($P = 0.02$), with nonsignificant trends toward less TLR, TVR, and TVF. However, the study was underpowered to demonstrate a significant difference in clinical endpoints between patients who received the 4.0 mm EES and the randomized PES.

Prior BMS studies have shown an inverse relationship between vessel diameter and angiographic binary restenosis, TLR and MACE [2,3,7]. This relationship has also held true in the pivotal randomized trials for PES and sirolimus-eluting stents (SES), in which PES and SES were compared to their BMS counterpart [1,3].

Data comparing the use and benefit of DES vs. BMS in larger diameter vessels are limited. In TAXUS IV, subgroup analysis demonstrated that the significant benefit of DES over BMS was principally present in vessels <3.0 mm in diameter [2]. In a single center, nonrandomized comparison, Steinberg et al. compared a cohort of 233 patients who underwent single vessel DES implantation in large (≥3.5 mm) coronary arteries with 233 propensity-matched patients treated with BMS in vessels with similar RVD. At 1 year, there was no significant

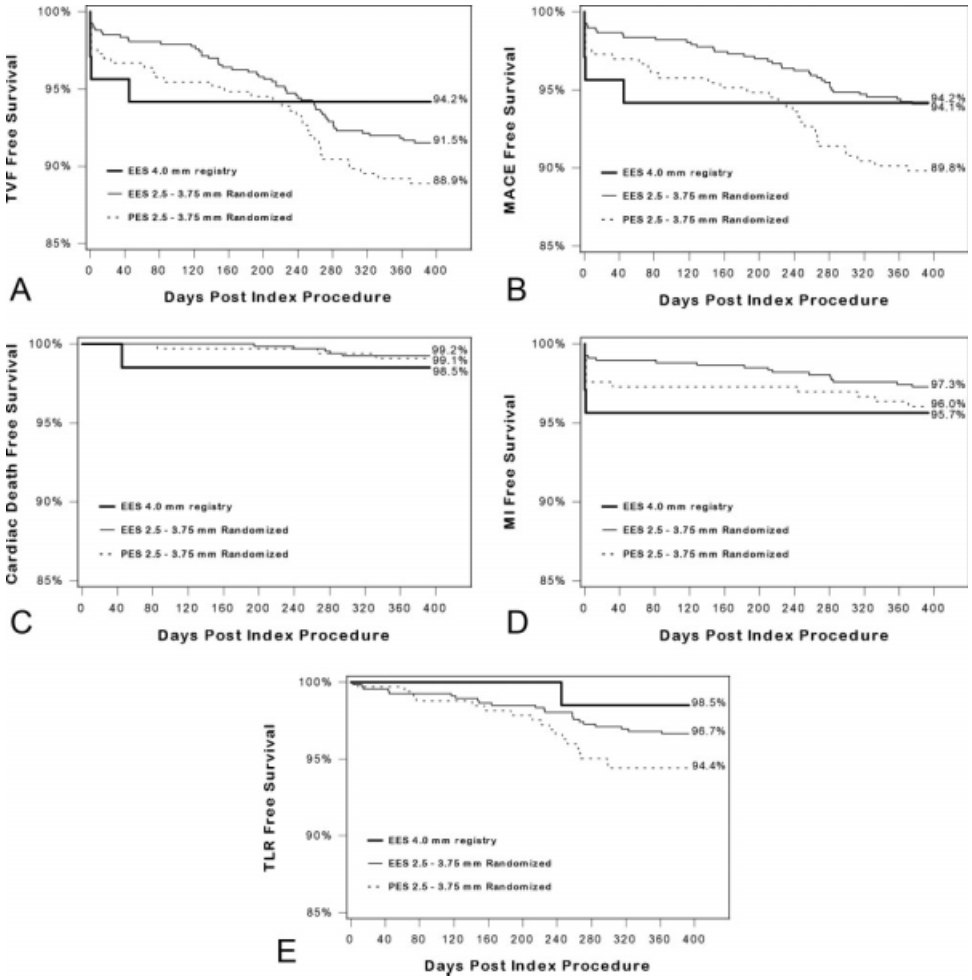

Fig. 1. Event-free survival in the EES 4.0 mm registry arm (*N* = 69), the EES 2.5–3.75 mm randomized arm (*N* = 669), and the PES 2.5–3.75 mm randomized arm (*N* = 333) A: Freedom from target vessel failure (TVF); B: Freedom from major adverse cardiac events (MACE); C: Freedom from cardiac death; D: Freedom from myocardial infarction; E: Freedom from target lesion revascularization (TLR).

benefit in the MACE rates between the DES and BMS groups (8.5 vs. 7.7%, respectively) [11]. However, in their study, the BMS arteries were treated with significantly larger diameter (mean 3.88 mm) and shorter length (mean 16.0 mm) stents than the DES group (mean 3.57 and 19.9 mm, respectively), both of which are predictors of lower rates of TLR and MACE [7].

Only one trial has randomized 4.0 mm DES and BMS. In the TAXUS V trial, 202 patients with single de novo coronary lesions with RVD of 3.75–4.25 mm were randomized to 4.0 mm TAXUS PES vs. EXPRESS BMS [12]. In-segment LL and binary restenosis were significantly reduced with the 4.0 mm PES compared with the BMS (0.22 ± 0.40 vs. 0.54 ± 0.57, $P < 0.001$ and 2.3 vs. 14.4%, $P = 0.005$, respectively). With follow-up reported through 9 months, a trend was present for reduced rates of MACE in the PES compared with the BMS arm (6.5 vs. 14.9%, $P = 0.07$). In a larger combined analysis from the randomized TAXUS IV and V trials, PES was shown to result in a >50% reduction in MACE compared to EXPRESS BMS in vessels ≥3.5–<4.0 mm in diameter and in vessels ≥4.0 mm in diameter [13]. The results of this study confirm the low rates of clinical and angiographic restenosis that can be achieved with DES in large coronary arteries. Moreover, only one stent thrombosis occurred with the 4.0 mm EES (and none with the 4.0 mm PES in TAXUS V), suggesting that the rate of DES thrombosis is low in large coronary arteries, though larger number of patients with longer term follow-up is required to ensure the low rate of infrequent adverse events such as stent thrombosis.

Several other limitations of this study are worth noting. The study was composed of a small cohort of nonrandomized patients with a single lesion treated with a 4.0 mm EES. The results of the 4.0 mm EES were

compared to smaller diameter randomized groups treated with either PES or EES stents. There was no direct comparison to the thin strut ML VISION bare metal counterpart, which in itself may have resulted in lower angiographic restenosis and clinical MACE rates compared to BMS with thicker stent struts. The 8-month angiographic follow-up rate was 71%, which was in accordance with the angiographic follow-up rates reported previously [2,3], and in the SPIRIT III randomized trial (77%). In addition, the clinical follow-up rate for these 69 patients was 97%. Given the high rate of clinical follow-up and the infrequent occurrence of TLR at 1 year, it is unlikely restenosis is more frequent than reported herein.

In conclusion, this study supports the safety and efficacy of the 4.0 mm EES in large coronary arteries. The use of EES in the SPIRIT III 4.0 mm registry arm resulted in significantly reduced angiographic LL and fewer MACEs at 1-year follow-up when compared with the use of PES in less than 3.75 mm vessels. Future randomized studies comparing the 4.0 mm EES directly to other large diameter DES or BMS would be desirable to further guide optimal treatment in patients with disease in large coronary vessels.

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