Catheterization and Cardiovascular Interventions 76:60–66 (2010)

An Everolimus-Eluting Stent Versus a Paclitaxel-Eluting Stent in Small Vessel Coronary Artery Disease: A Pooled Analysis from the SPIRIT II and SPIRIT III Trials

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Objectives: To evaluate the safety and efficacy of the XIENCE V everolimus-eluting stent compared to the TAXUS paclitaxel-eluting stent in small vessels. **Backgroud:** The XIENCE V everolimus-eluting stent (EES) has been shown to improve angiographic and clinical outcomes after percutaneous myocardial revascularization, but its performance in small coronary arteries has not been investigated. **Methods:** In this pooled analysis, we studied a cohort of 541 patients with small coronary vessels (reference diameter <2.765 mm) by using patient and lesion level data from the SPIRIT II and SPIRIT III studies. TAXUS Express (73% of lesions) and TAXUS Liberté (27% of lesions) paclitaxel-eluting stents (PES) were used as controls in SPIRIT II. In SPIRIT III, Taxus Express^2 PES was the control. **Results:** Mean angiographic in-stent and in-segment late loss was significantly less in the EES group compared with the PES group, (0.15 ± 0.37 mm vs. 0.30 ± 0.44 mm; $P = 0.011$ for in-stent; 0.10 ± 0.38 mm vs. 0.21 ± 0.34 mm; $P = 0.034$ for in-segment). EES also resulted in a significant reduction in composite major adverse cardiac events at 1 year (19/366 [5.2%] vs. 17/159 [10.7%]; $P = 0.037$), due to fewer non-Q-wave myocardial infarctions and target lesion revascularizations. At 1 year, the rate of non-Q-wave myocardial infarction was significantly lower in the EES group compared with that of the PES group (6/366 [1.6%] vs. 8/159 [5.0%]; $P = 0.037$). **Conclusions:** In patients with small vessel coronary arteries, the XIENCE V EES was superior to the TAXUS PES.

Key words: drug-eluting stents; coronary arteries; small vessels; lumen loss

INTRODUCTION

In-stent restenosis (ISR) has been strikingly reduced by drug-eluting stents (DES). However, specific patient and lesion characteristics may still confer an increased risk of ISR even after DES implantation. Previous studies have shown that vessel size, type of DES, and final angiographic results are strong independent predictors of angiographic and clinical restenosis [1]. Of note, DES type has been demonstrated to have a particular impact on ISR in small coronary vessels, with sirolimus-eluting stents (SES) showing a significantly higher effectiveness as compared to paclitaxel-eluting stents (PES) [1,2]. However, analysis of in-stent late

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Conflict of interest: Dr. Antonio Bartorelli reports serving as a consultant for and receiving speaker's honoraria from Abbott Vascular; Wes Pierson and Drs. Karine Miquel-Hébert and Shui Yu are employees of Abbott Vascular; Dr. Gregg Stone is a member of the Abbott Vascular and Boston Scientific advisory boards. Dr. Patrick W. Serruys has nothing to report.

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Received 30 December 2009; Revision accepted 2 January 2010

DOI 10.1002/ccd.22452
Published online 26 May 2010 in Wiley InterScience (www.interscience.wiley.com)

loss and binary ISR in the SIRIUS trial demonstrated no significant difference between lowest and highest tertiles of target-vessel size, whereas in-segment analysis, which included 5 mm vessel margin proximal and distal to the deployed SES, showed an increase in late loss and ISR in the smallest tertile [3]. These findings suggest that, together with uniform and adequate delivery of an effective antiproliferative drug, newer drug-delivery platforms with a reduced potential for injury beyond the stent margins may have a positive impact particularly in smaller caliber vessels.

Everolimus, a derivative of rapamycin, inhibits cell cycle progression and smooth muscle proliferation [4]. The drug is eluted from a biocompatible polymer that is mounted on a thin-strut, low-profile cobalt-chromium stent. Preclinical studies have shown more rapid endothelialization with this stent compared to SES and PES [5]. Following favorable results with this device in the SPIRIT FIRST randomized study [6], the SPIRIT II study [7] was performed in Europe, India, and New Zealand and the SPIRIT III study [8] was performed in the United States to evaluate the XIENCE V everolimus-eluting stent (EES) in comparison to a widely used polymer-based PES in patients with coronary artery disease. The SPIRIT II and SPIRIT III studies had similar inclusion and exclusion criteria. Therefore, we performed a pooled analysis using individual patient data up to 1-year follow-up from these two trials to compare the safety and efficacy of the XIENCE V EES and the TAXUS PES in small coronary arteries.

METHODS

The authors of this manuscript have certified that they comply with the principles of ethical authorship and publishing [9]. The data used for the pooled analysis described in this article were drawn from two Abbott Vascular-sponsored studies, funded by Abbott Vascular.

The Everolimus-Eluting STENT

The XIENCE V EES (Abbott Vascular, Santa Clara, CA) is a low-profile (81 μm strut thickness), balloon-expandable coronary stent made of L-605 cobalt-chromium alloy. Everolimus is blended in a nonadhesive, durable, and biocompatible fluorinated copolymer and the thin (7.6 μm) everolimus-polymer matrix is applied to the stent surface.

The Paclitaxel-Eluting STENT

The TAXUS EXPRESS2 or TAXUS Liberté PES (Boston Scientific, Natick, MA) (148 μm strut thickness) is a balloon-expandable stainless steel coronary stent coated with translute paclitaxel-containing polymer (16 μm thickness) in a slow-release formulation.

Patients and Design

Details of the SPIRIT II and SPIRIT III trials have been previously described [7,8]. In brief, SPIRIT II was a prospective, randomized, single-blind, clinical study performed at 28 centers in Europe, India, and New Zealand in which 300 patients were randomized in a 3:1 ratio to receive the polymer-based XIENCE V EES or the polymer-based TAXUS EXPRESS2 or TAXUS Liberté PES. SPIRIT III was a prospective, multicenter, randomized, single-blind, clinical study performed at 65 sites in the United States in which 1002 patients were randomized in a 2:1 ratio to receive the XIENCE V EES or the TAXUS EXPRESS2 PES. For both studies, patients were eligible for enrollment if they were older than 18 years and had evidence of myocardial ischemia. The patient could have a maximum of two de novo native coronary artery lesions, which had to be located in different major epicardial vessels. The de novo target lesion(s) had to have a reference vessel diameter between 2.5 mm and 3.75 mm for SPIRIT III (up to 4.25 mm for SPIRIT II) by visual estimation, a target lesion length $\leq$28 mm, a visually estimated stenosis of the luminal diameter between 50 and 99%, and a thrombolysis in myocardial infarction flow grade of 1 or more. Patients were excluded if they had a known diagnosis of acute myocardial infarction 3 days prior to the index procedure, a left ventricular ejection fraction $<$30%, or were awaiting a heart transplant. Additionally, patients having target lesion(s) with an aorto-ostial or left main location, a lesion located within 2 mm of the origin of the left anterior descending or left circumflex coronary arteries, heavy calcification, or a visible thrombus within the target vessel were also excluded from the studies. All patients enrolled into the studies were maintained on 75 mg of clopidogrel daily for a minimum of 6 months and $\geq$ 75 mg of aspirin daily for a minimum of 1 year following the procedure. A pooled, patient-level analysis of the combined SPIRIT II and SPIRIT III data was independently performed by the Cardiovascular Research Foundation (New York, NY), an affiliate of Columbia University College of Physicians and Surgeons. This analysis included 1,302 patients, 892 in the XIENCE V EES arm and 410 in the TAXUS PES arm. For the purpose of this analysis, we report only patients with a reference vessel diameter (RVD) $<$2.765 mm who had only one vessel treated. This value was the median of the RVD for single vessel treated patients. Both studies

TABLE I. Baseline Clinical and Angiographic Characteristics of the Small Vessel Patients Randomized to Receive the Everolimus-Eluting Stent (EES) and the Paclitaxel-Eluting Stent (PES)

	EES group 376 patients 376 lesions	PES group 165 patients 165 lesions	*P*-value
Age, years (mean±SD)	63.4 ± 10.5	62.2 ± 10.3	0.247
Male patients (%)	63.8	58.8	0.290
Current smoking (%)	21.5	20.9	0.908
Hypertension requiring medication (%)	76.1	77.0	0.913
Hypercholesterolemia requiring medication (%)	73.3	77.5	0.330
Diabetes mellitus (%)	29.3	32.5	0.475
Stable angina (%)	55.0	50.9	0.397
Unstable angina (%)	21.5	27.0	0.182
Previous MI (%)	22.1	20.4	0.731
Target Vessel			
Left anterior descending (%)	43.6	52.1	0.075
Circumflex or Ramus (%)	33.0	30.3	0.551
Right coronary artery (%)	23.1	17.6	0.172
Left main (%)	0.3	0.0	1.000
Target Lesion			
Lesion length, mm (mean±SD)	13.7 ± 5.5	13.4 ± 4.9	0.471
RVD, mm (mean±SD)	2.41 ± 0.25	2.40 ± 0.24	0.557
MLD, mm (mean±SD)	0.74 ± 0.32	0.79 ± 0.34	0.104
%DS, (mean±SD)	68.9 ± 12.8	66.9 ± 13.3	0.110

MI, myocardial infarction; RVD, reference vessel diameter; MLD, minimal lumen diameter; %DS, percent diameter stenosis.

conform to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee and were approved by the Medical Ethics Committees of each enrolling institution. All patients provided written informed consent.

Statistical Analysis

All analyses were performed in the intent-to-treat population, consisting of all patients randomized in the study, regardless of the treatment actually received. However, patients lost to follow-up in whom no event had occurred prior to the follow-up window were not included in the denominator for calculations of binary end points. Survival curves using all available follow-up data were also constructed for time to event variables using Kaplan-Meier estimates and compared by log-rank test. For binary variables, such as target vessel revascularization (TVR), target vessel failure (TVF) and major adverse cardiac events (MACE), counts and percentages were calculated. We defined MACE as the composite of cardiac death, myocardial infarction and ischemia-driven target lesion revascularization (TLR) either by CABG or PCI. Fisher's exact test was used to compare binary variables between the two treatment arms. For continuous variables, such as in-segment late loss, means and standard deviations were calculated. Two sided *t*-test was used to compare continuous variables between the two treatment arms. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Patient Characteristics

Of the entire SPIRIT II and SPIRIT III patient population, 541 (42%) were patients with a single vessel treated and a RVD <2.765 mm and were included in this pooled analysis. In this cohort, 376 received an EES and 165 received a PES. Baseline characteristics of the patients were comparable between the two arms (Table I). Lesion characteristics, as measured by quantitative coronary angiography, were also similar (Table I). The average RVD in the EES and PES groups was 2.41 mm ± 0.25 mm vs. 2.40 mm ± 0.24 mm, respectively.

Postprocedural Results and Angiographic Outcomes

As shown in Table II, postprocedure angiographic measures were not significantly different between the two groups except for a greater post-procedure in-stent percent diameter stenosis in the EES arm. Angiographic outcome measures at follow-up, performed at 6 months in SPIRIT II and at 8 months in SPIRIT III in 266 patients in the EES group and 95 patients in the PES group, respectively, are presented in Table II. The mean in-stent and in-segment late loss was 0.15 mm ± 0.37 mm vs. 0.30 ± 0.44 mm ($P = 0.011$) and 0.10 mm ± 0.38 mm vs. 0.21 mm ± 0.34 mm ($P = 0.034$) in the EES and PES groups, respectively. No significant difference was observed in binary in-stent restenosis with the EES as compared to the PES (Table II).

TABLE II. Postprocedural and Follow-Up[a] Angiographic Outcomes in the Small Vessel Patients Randomized to Receive Everolimus-Eluting Stent (EES) or Paclitaxel-Eluting Stent (PES)

	EES group	PES group	*P*-value
Postprocedural angiographic results			
	266 patients	95 patients	
	266 lesions	95 lesions	
RVD, mm (mean±SD)	2.49 ± 0.34	2.49 ± 0.33	0.925
In-stent MLD, mm (mean±SD)	2.40 ± 0.30	2.46 ± 0.30	0.102
In-stent %DS, (mean±SD)	4.12 ± 10.59	1.02 ± 13.00	0.038
Angiographic follow-up results[a]	266 patients	95 patients	
	266 lesions	95 lesions	
RVD, mm (mean±SD)	2.50 ± 0.35	2.49 ± 0.36	0.846
In-stent MLD, mm (mean±SD)	2.25 ± 0.44	2.18 ± 0.54	0.278
In-stent %DS, (mean±SD)	9.66 ± 16.04	12.51 ± 20.92	0.300
In-stent late loss, mm (mean±SD)	0.15 ± 0.37	0.30 ± 0.44	0.011
In-segment late loss, mm (mean±SD)	0.10 ± 0.38	0.21 ± 0.34	0.034
In-stent binary restenosis rate, %	2.3	5.7	0.232
In-segment binary restenosis rate, %	4.7	5.7	0.753

[a]Performed at 6 months in SPIRIT II and at 8 months in SPIRIT III.

TABLE III. Clinical Outcomes at 1 Year in the Small Vessel Patients Randomized to Receive Everolimus-Eluting Stent (EES) or Paclitaxel-Eluting Stent (PES)

	EES group	PES group	*P*-value
Cardiac Death	3/366 (0.8%)	1/159 (0.6%)	1.000
Myocardial Infarction	7/366 (1.9%)	8/159 (5.0%)	0.082
Q-wave	1/366 (0.3%)	0/159 (0.0%)	1.000
Non-Q-wave	6/366 (1.6%)	8/159 (5.0%)	0.037
Target lesion revascularization[a]	11/366 (3.0%)	10/159 (6.3%)	0.091
Target vessel revascularization, non-target lesion[a]	11/366 (3.0%)	4/159 (2.5%)	1.000
Bleeding complication	9/362 (2.5%)	11/158 (7.0%)	0.023
Vascular complication	6/362 (1.7%)	9/158 (5.7%)	0.019
Hierarchical major adverse cardiac events	19/366 (5.2%)	17/159 (10.7%)	0.037
Hierarchical target vessel failure	29/366 (7.9%)	18/159 (11.3%)	0.244
Stent Thrombosis (ARC, definite + probable)			
Acute (<1 day)	0/376 (0.0%)	0/165 (0.0%)	NA
Subacute (1 to 30 days)	0/375 (0.0%)	1/165 (0.6%)	0.306
Late (>30 days)	1/362 (0.3%)	2/159 (1.3%)	0.222

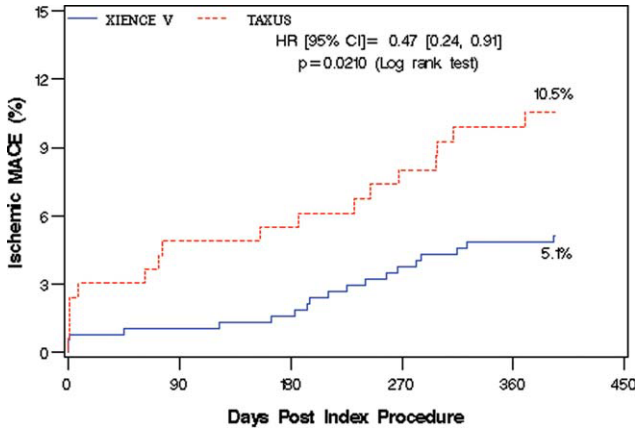
[a]All treated with percutaneous coronary intervention, or treated with coronary artery bypass graft.

Clinical Outcomes

The use of the EES compared to the PES resulted in a significant reduction in the composite endpoint of MACE at 1 year (5.2% vs. 10.7%; $P = 0.037$) (Table III). There were no significant differences between the two groups in the 1-year rates of cardiac death, TVR, and TVF. However, a trend was present toward a reduction in TLR with the EES as compared to the PES (Table III). In the EES patients, a trend toward a lower incidence of non-Q-wave myocardial infarction was also observed in-hospital and at 30 days (0.8% vs. 2.4%; $P = 0.208$ and 0.8% vs. 3.0%; $P = 0.061$, respectively). At 1 year, the use of the EES resulted in a significantly lower rate of non-Q-wave myocardial infarction compared to the use of PES (1.6% vs. 5.0%; $P = 0.037$) and of bleeding complications (2.5% vs. 7.0%; $P = 0.023$) and vascular complications (1.7% vs. 5.7%; $P = 0.019$). No significant difference between the 2 devices was found in the incidence of stent thrombosis, either early (≤30 days) or late (>30 days), when analyzed by the Academic Research Consortium definitions [10]. As shown in Fig. 1, the difference between the curves for MACE became apparent in the early postprocedural period due to fewer non-Q-wave myocardial infarctions with the EES. The MACE curves then diverged significantly ($P = 0.021$) between 6 and 12 months due to a lower rate of non-Q-wave myocardial infarction and TLR in the EES group.

DISCUSSION

This retrospective, patient-level pooled analysis conducted in patients with small diameter coronary arteries enrolled in the SPIRIT II and SPIRIT III trials



No. at risk	0	90	180	270	360	393
XIENCE V Everolimus-eluting stent (EES)	376	367	364	352	347	346
TAXUS Paditaxel-eluting stent (PES)	165	154	153	146	143	141

Fig. 1. Kaplan-Meier survival curve for major adverse cardiac events (MACE) among small vessel patients randomized to receive the XIENCE V everolimus-eluting stent and the TAXUS paclitaxel-eluting stent.

demonstrated that an EES compared to a widely used PES resulted in a significantly lower in-stent and in-segment late loss. The 12-month rate of MACE was also significantly reduced in patients treated with the EES. The difference in long-term outcome was attributable to fewer non-Q-wave myocardial infarctions and TLR procedures in the EES group. As shown by previous studies [11,12], SPIRIT II and SPIRIT III trials pooled results indicated that the 1-year MACE rates in patients with larger vessel size ($\geq$2.765 mm) were lower compared to the MACE rates observed in patients with smaller vessel size ($<$2.765 mm) (4.2% vs. 5.2% in the EES patients and 4.7% vs. 10.7% in the PES patients). A similar difference was also present in the TVF rate (5.6% vs. 7.9% in the EES patients and 5.9% vs. 11.3% in the PES patients).

Several factors may be predictive of ISR even in the DES era. One of these factors is the reference diameter of the treated coronary vessel. Small vessel disease is a challenging area for the interventional cardiologist. Indeed, the therapeutic benefit of stent implantation in small coronary arteries is reduced due to the well-known higher risk of restenosis and MACE [13,14]. Moreover, many patients with small vessel disease have other factors such as diffuse disease and diabetes that increase the risk of ISR. Finally, an important percentage of DES implanted in small vessels fail to achieve a minimum stent area larger than 5 mm^2, a consistent predictor of DES failure [15,16]. Subset analyses of large randomized trials and registries and results of randomized studies specifically aimed at evaluating DES in small vessels have expanded our knowledge regarding this subgroup of patients [17–20]. Compared with large vessels, small vessels have a smaller postprocedural luminal area that is less able to accommodate more neointimal hyperplasia before ISR occurs and the ischemic threshold is reached [21]. Therefore, even slight differences in late loss are important in small vessels that, therefore, derive the greatest proportional benefit from DES implantation. However, despite remarkably low values for late lumen loss having been documented across all DES studies, there is still a relationship between vessel size and restenosis, with increased restenosis rates in small vessels. In the SIRIUS trial, angiographic restenosis increased from 1.9% in large vessels to 17.6% in vessels with a diameter less than 2.75 mm [3]. Similarly, in the TAXUS V trial the subset of small vessels showed an angiographic restenosis of 31.2% as compared to the 3.5% rate observed in large vessels [22]. In a prospective registry of 1,845 patients treated with SES or PES, Kastrati et al. demonstrated that vessels equal to or less than 2.6 mm in diameter had a significant increase in the odds of angiographic and clinical restenosis compared to a subgroup with larger reference diameters [1]. A combination of additional factors may play a role in DES failure in small coronary vessels, including arterial trauma outside the stented segment during pre-dilation and post-dilation, incomplete lesion coverage and insufficient antiproliferative efficacy of the drug being delivered. Indeed, in the study of Kastrati et al., the type of DES used was a strong independent predictor of restenosis only for small vessels, with PES having a significantly higher likelihood of angiographic restenosis and TLR compared to SES [1]. Similar findings providing evidence in favor of SES in patients with very small vessels treated with these two DES have been reported also by Rodriguez-Granillo et al. [2]. The ISAR-SMART 3 trial showed that PES is less effective than SES in reducing neointimal proliferation after implantation in 380 patients with small coronary vessels. In addition, this randomized trial demonstrated a considerable increase in the relative risk of angiographic restenosis with PES and a clear advantage of SES with respect to the need for TLR [23]. Finally, a subgroup analysis of the Sirtax trial that stratified clinical events at 2-year follow-up for vessel size demonstrated that SES was more effective in reducing MACE than PES [11]. This difference was mainly due to a 69% reduction in TLR.

It is interesting to note that EES patients included in this pooled analysis showed an in-stent binary restenosis rate (2.3%) that compares very favorably to those reported by previous studies with SES. These results

indicate that even slight differences in late loss may have an important effect in high-restenosis-risk groups such as patients with small vessel disease. There are some possible explanations for the better performance demonstrated by EES as compared to PES in the patients with small vessel coronary artery disease included in this pooled analysis. Disparities in the drug mechanism of action, drug-release kinetic, polymer composition and thickness, and pattern of drug distribution may have contributed to a different degree of neointimal proliferation suppression. With regards to the lower rate of in-hospital non-Q-wave myocardial infarction observed in the EES group, we can speculate that it may be attributable to a reduced risk of occluding small side branches due to the different characteristics of this stent [22]. Indeed, compared to the PES, the EES has a thinner polymer (7.6 μm vs. 16 μm), a lower total polymer plus stent strut thickness (81 μm vs. 148 μm) and no webbing effect [22]. These differences may play an even more relevant role in small vessels in which the risk of side branch occlusion and procedure-related myonecrosis caused by DES implantation may be amplified as compared to larger vessels. Finally, the fact that there were no differences between SES and PES patients in the rate of glycoprotein IIb/IIIa inhibitor administration (18.4% vs. 17.0%) and in the size of the arterial introducer used suggests that the higher rates of bleeding and vascular complications observed in the PES group may have occurred by chance alone.

LIMITATIONS OF THE STUDY

First, this study suffers from the limitations of any pooled and post hoc analysis of data. Second, the inability to control the confounding factor of different stents, in terms of differences between the two stents in design, drug mechanism of action, drug-release kinetic, polymer composition and thickness, and pattern of drug distribution, is another limitation. Third, a higher rate of angiographic follow-up would have been desirable to fully evaluate the angiographic outcome after implantation of these two different DES in small coronary arteries. Fourth, our sample size is relatively limited to detect small differences in binary event rates. However, the late loss end point has been demonstrated to positively correlate with angiographic and clinical restenosis and, thus, to be particularly useful in studies in which the sample size is limited [24]. Finally, the SPIRIT II and SPIRIT III were open-label trials due to the impossibility of blinding the two stents provided by different manufacturers. Nevertheless, we believe that with the careful analysis of prospectively collected individual patient data up to 1-year follow-up from 2 randomized controlled trials, our study provides meaningful information regarding the comparative results of EES and PES use in patients with small coronary artery disease. Moreover, the accuracy of this analysis is increased by the completeness of patient-level data.

CONCLUSIONS

In patients with small vessel coronary artery disease, the EES was superior to PES in terms of a significant reduction of in-stent and in-segment late loss. The incidence of death and stent thrombosis was not significantly different between the 2 DES, but there was a significantly higher risk of 1-year MACE with PES, driven by a higher rate of non-Q-wave myocardial infarction and TLR.

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