

Two-Year Clinical, Angiographic, and Intravascular Ultrasound Follow-Up of the XIENCE V Everolimus-Eluting Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions: The SPIRIT II Trial

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Two-Year Clinical, Angiographic, and Intravascular Ultrasound Follow-Up of the XIENCE V Everolimus-Eluting Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions

The SPIRIT II Trial

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Background—This article reports the 2-year clinical, angiographic, and intravascular ultrasound outcomes of the everolimus-eluting stent (EES) compared with the paclitaxel-eluting stent (PES) in the randomized SPIRIT II trial.

Methods and Results—This was a prospective, single-blind clinical trial in which a total of 300 patients with de novo native coronary artery lesions were randomized to either EES or PES in a 3:1 fashion. Clinical follow-up was planned at 2 years in all patients. A subset of 152 patients underwent serial angiographic and intravascular ultrasound analyses at 6 months and 2 years. After 2 years, target lesion failure (cardiac death, myocardial infarction, and ischemia-driven target lesion revascularization) rates were 6.6% and 11% in EES and PES, respectively ($P=0.31$). At 6 months, a significant reduction in angiographic in-stent late loss and percentage volume obstruction measured by intravascular ultrasound was observed in the EES group. However, at 2-year follow-up, a late increased intimal hyperplasia growth after implantation of an EES was observed. There were no significant differences between EES and PES for in-stent late loss (EES, 0.33 ± 0.37 mm versus PES, 0.34 ± 0.34 mm; $P=0.84$) and percentage volume obstruction (EES, $5.18\pm 6.22\%$ versus PES, $5.80\pm 6.31\%$; $P=0.65$) at 2 years. The incidence of stent thrombosis was low and comparable in both groups (EES, 0.9%; PES, 1.4%).

Conclusions—Although the previously reported angiographic and clinical superiority of the EES has vanished over time, this report confirms and extends the previously demonstrated noninferiority in terms of in-stent late loss of the EES when compared with the PES up to 2-year follow-up. There were no significant differences between EES and PES in clinical, angiographic and intravascular ultrasound outcomes at 2 years. (*Circ Cardiovasc Intervent.* 2009;2:339-347.)

Key Words: stents ■ angioplasty ■ IVUS

Stenting of de novo lesions in native coronary arteries is an established and effective treatment of coronary narrowing due to atherosclerosis. However, long-term efficacy of bare metal stents (BMS) has been hampered by the development of restenosis, resulting in rehospitalization for percutaneous or surgical revascularization in 10% to 20% of patients.¹ Drug-eluting stents (DES) have been shown to be effective against restenosis by reducing neointimal hyperplasia after vascular injury, when compared with BMS.²

Clinical Perspective on p 347

The objective of the SPIRIT II trial was to evaluate the safety and performance of the everolimus-eluting coronary

stent (XIENCE V, Abbott Vascular, Santa Clara, Calif) compared with the paclitaxel-eluting coronary stent (TAXUS EXPRESS2 or Liberte, Boston Scientific, Natick, Mass) in the treatment of de novo native coronary artery lesions. The everolimus-eluting stent (EES) is comprised of the ACS MULTI-LINK VISION stent and delivery system and a drug-eluting coating. Everolimus, an analogue of rapamycin, is a powerful antiproliferative agent that blocks cell cycle progression between the G1 and S phases, inhibiting smooth muscle cell proliferation.³ The feasibility of the EES was first demonstrated in the FUTURE-I and FUTURE II studies and more recently in the SPIRIT FIRST study, which demonstrated both clinical safety and efficacy.⁴⁻⁷ In the SPIRIT

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FIRST study, the clinical outcome at 2-year follow-up was in favor of the EES group compared with the BMS group but did not reach statistical significance because of small patient numbers.

In this trial, the EES performed superior to the paclitaxel-eluting stent (PES) regarding angiographic late loss at 6 months (0.11 ± 0.27 versus 0.36 ± 0.39 mm). Furthermore, intravascular ultrasound (IVUS) results showed that the EES was more effective at reducing neointimal hyperplasia; both percentage volume obstruction and neointimal hyperplasia volume were significantly lower in patients treated with EES.⁸ The incidence of target lesion failure (TLF) was low and comparable between groups at 6 months (2.7% for EES versus 6.5% for PES). At 1 year, there was a significant benefit in TLF favoring the EES (2.7% versus 9.2%).⁹

This report focuses on the 2-year clinical outcomes of all patients enrolled in the SPIRIT II trial and the angiographic and IVUS follow-up in a subset of patients.

Methods

Study Population

The study design of the SPIRIT II trial has been previously described.^{8–10} In brief, this prospective, randomized (3:1) single-blind, parallel 2-arm trial was performed at 28 centers in Europe, India, and New Zealand and randomized 300 patients in a 3:1 ratio to either an EES (n=223) or a PES (n=77) between July 2005 and November 2005. The study protocol was approved by the ethics committee at each participating institution, and all patients gave written informed consent.

Patients enrolled in the study were older than 18 years with evidence of myocardial ischemia and had a maximum of 2 de novo native coronary artery lesions, located in different major epicardial vessels. Target lesions had to comply with the following inclusion criteria: a reference vessel diameter between 2.5 and 4.25 mm by visual estimation, a target lesion length ≤ 28 mm, a visually estimated stenosis between 50% and 99% of the luminal diameter, and a Thrombolysis In Myocardial Infarction flow grade of 1 or more. Patients were excluded from enrollment if they had documented acute myocardial infarction within 3 days prior to the baseline procedure, a left ventricular ejection fraction $< 30\%$, were awaiting a heart transplant or had a known hypersensitivity or contraindication to aspirin, heparin, bivalirudin, clopidogrel or ticlopidine, cobalt, chromium, nickel, tungsten, everolimus, paclitaxel, acrylic, and fluoropolymers. Angiographic exclusion criteria were target lesions within 2 mm of the origin of the left anterior descending or left circumflex coronary artery, heavy calcification, or a visible thrombus within the target vessel.

Study Procedure

Following the confirmation of angiographic in- and exclusion criteria before the procedure, patients were randomized through a telephone call to either an EES or a PES. Because of packaging differences, operators were not blinded to the device. Lesions were treated using standard interventional techniques with mandatory predilatation and stent implantation pressure not exceeding the burst pressure rate. Postdilatation was left to the discretion of the physician, and if performed was only to be done with balloons sized to fit within the boundaries of the stent. In the event of a bailout procedure and additional stent requirement, the stent had to be one from the same group as the first implanted stent. At baseline, IVUS was performed in a subset of 152 consecutive patients enrolled in preselected centers, after angiographically optimal stent placement had been obtained. IVUS was repeated if additional postdilatation was performed to optimize stent apposition and/or deployment. Patient preparation and pharmaceutical treatment during the hospital procedure

were to be in accordance with standard hospital practice. The use of GPIIb/IIIa inhibitors was left to the discretion of the physician. All patients were to receive 75 mg of clopidogrel for a minimum of 6 months and ≥ 75 mg of aspirin daily for a minimum of 1 year after the procedure.

Follow-Up

Clinical follow-up was scheduled at 30, 180, and 270 days and 1 and 2 years with further evaluations planned at 3, 4, and 5 years by protocol amendment. At outpatient visits, patients were asked specific questions about the interim development of angina or the occurrence of adverse events. Angiographic follow-up was planned at 180 days for all patients. In the subset of 152 consecutive patients (enrolled in selected centers), IVUS was planned at 180 days and both IVUS and angiographic follow-up were to be repeated at 2 years. There was a 28-day window for the visit at 2 years.

Clinical End Points

The clinical part of this 2-year follow-up study focuses on TLF (cardiac death, myocardial infarction [MI], and ischemia-driven target lesion revascularization [TLR], either by coronary artery bypass graft or percutaneous coronary intervention—defined as major adverse cardiac events in the study protocol). Secondary clinical end points included target vessel failure (cardiac death, MI, and ischemia-driven target vessel revascularization), TLR, target vessel revascularization, and stent thrombosis. All clinical end points were adjudicated by a blinded clinical events committee.

All deaths that could not be clearly attributed to a noncardiac cause were considered cardiac deaths. Q-Wave MI was defined as development of new pathological Q waves. Non-Q-wave MI was defined as a typical rise and fall of creatine kinase-MB with at least one of the following: ischemic symptoms, electrocardiographic changes indicative of ischemia, or associated with a coronary artery intervention. For nonprocedural/spontaneous MI, creatine kinase-MB had to be ≥ 2 times the upper limit of normal, for postpercutaneous coronary intervention ≥ 3 times upper limit of normal, and for postcoronary artery bypass grafting ≥ 5 times the upper limit of normal. For each MI, the relationship to the target vessel was adjudicated by the clinical events committee.

Ischemia-driven TLR was defined as a revascularization at the target lesion associated with any of the following: a positive functional ischemia study (exercise testing, fractional flow reserve, or coronary flow reserve), ischemic symptoms, and an angiographic diameter stenosis $\geq 50\%$ by core laboratory quantitative coronary angiography (QCA); or a diameter stenosis $\geq 70\%$ by core laboratory QCA without ischemic symptoms or a positive functional study.

Stent thrombosis was categorized according to the definitions proposed by the Academic Research Consortium for definite, probable, and possible stent thrombosis.¹¹

Angiographic End Points

The angiographic part of this article focuses on in-stent late loss at 2 years (in the subset of 152 patients). Secondary angiographic end points include in-segment late loss, proximal and distal late loss, in-stent and in-segment percentage diameter stenosis, and angiographic binary restenosis.

QCA was performed using the CAAS II analysis system (Pie Medical BV, Maastricht, The Netherlands) by an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands) with observers blinded to treatment assignment. In each patient, the stented segment and the peri-stent segments (defined by a length of 5 mm proximal and distal to the stent edge) were analyzed. The following QCA parameters were computed: minimal luminal diameter, reference vessel diameter obtained by an interpolated method, and percentage diameter stenosis. Binary restenosis was defined in every segment as a diameter stenosis $\geq 50\%$ at follow-up. Late loss was defined as the difference between minimal luminal diameter post-procedure and minimal luminal diameter at follow-up. If a patient

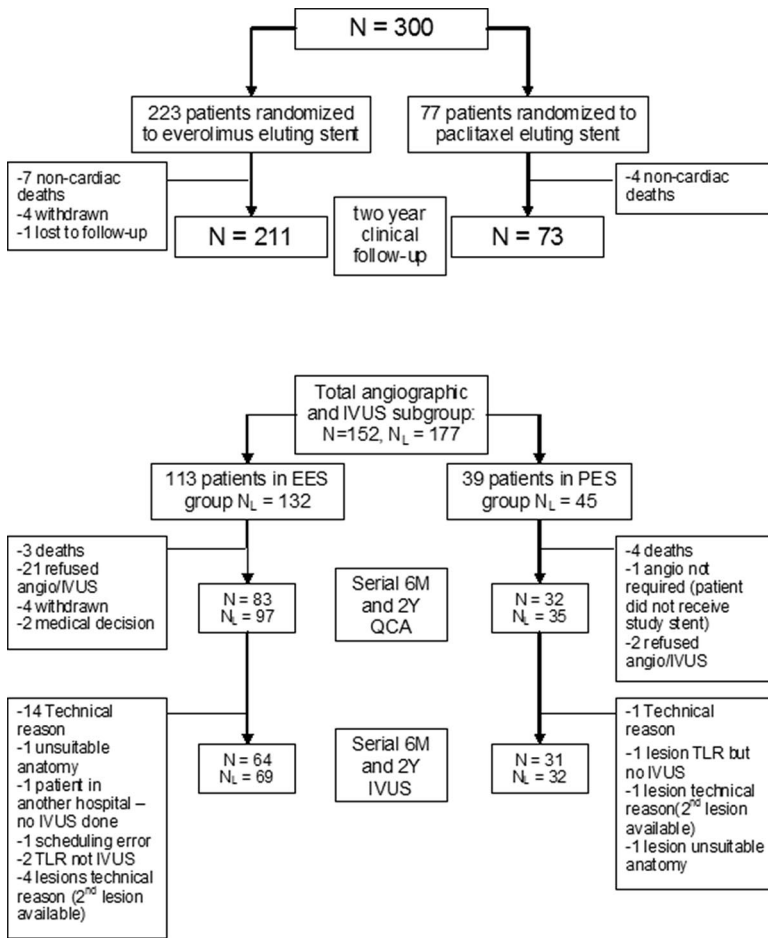


Figure 1. Patient flow chart and clinical, angiographic, and intravascular ultrasound follow-up in the SPIRIT II trial.

underwent TLR before the scheduled 2-year angiography, QCA was performed on the preinterventional angiography, and its results were imputed into 2-year follow-up angiography outcomes.

IVUS End Points

The IVUS part of this article focuses on percentage in-stent volume obstruction at 2 years (in the subset of 152 patients). Secondary IVUS end points include in-stent neointimal volume and vessel, stent, and lumen volumes.

Postprocedure and follow-up stented vessel segments were examined with mechanical or phased array IVUS (Eagle-eye Volcano, Rancho Cordova, Calif; Atlantis, Boston Scientific, Natick, Mass) using automated pull-back at 0.5 mm per second after administration of 0.2 mg intracoronary nitroglycerin. The coronary segment beginning 5-mm distal to and extending 5-mm proximal to the stented segment was examined. IVUS analyses were also performed by an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands) with observers blinded to treatment assignment. A computer-based contour detection program was used for automated 3D reconstruction of the stented and adjacent segments. The lumen, stent boundaries, and external elastic membrane (vessel boundaries) were detected using a minimum cost algorithm.¹² The stent volume and lumen volume were calculated according to Simpson’s rule.¹³ The in-stent neointimal volume was calculated as the difference between stent volume and lumen volume. The percentage obstruction of the stent volume was calculated as intrastent neointimal volume/stent volume × 100. Feasibility, reproducibility, and inter- and intra-observer variability of this system have been validated in vitro and in vivo.¹³ Incomplete apposition was defined as one or more stent struts separated from the vessel wall with evidence of blood speckles behind the strut on ultrasound, whereas late-acquired

incomplete apposition was defined as incomplete apposition of the stent at follow-up which was not present postprocedure.^{14–16}

Statistical Methods

Final 2-year results are presented in this article. Six-month results in patients whose 2-year results were available are presented for comparative purposes. (These results may differ from those in previous publications with more patients) Binary variables are presented as percentages and compared using the Fisher exact test. Continuous variables are presented as mean ± standard deviation and compared using the Student *t* test. Confidence intervals for the differences are based on normal assumption. Noninferiority probability values for in-stent late-loss in the subset of lesions with serial 6 months and 2 years measurements are calculated with a 1-sided asymptotic test and were not predefined in the protocol. The noninferiority margin used for those tests is 0.16 mm, corresponding to the prespecified margin for the primary end point analysis.⁸ 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. Data on patients who were lost to follow-up were censored at the time of the last contact. Data on patients who died of noncardiac causes were censored at the time of death. Statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc, Cary, NC).

Results

Patients and Enrollment

Two-year clinical follow-up was available for 211 of the 223 patients (94.6%) in the EES group and in 73 of the 77 patients

Table 1. Baseline Characteristics

	EES (n=223)	PES (n=77)
Patient characteristics, % (unless otherwise specified)		
Age (mean±SD), y	62±10	62±9
Men	71	79
Hypertension-requiring medication	67	65
Hypercholesterolemia-requiring medication	69	75
Diabetes mellitus	23	24
Current smoker	32	30
Prior myocardial infarction	35	25
Unstable angina	27	32
Target vessel, %	N _L =260	N _L =91
Left anterior descending	41	47
Left circumflex	29	19
Right coronary artery	30	34
Target lesion characteristics, mean±SD		
Reference vessel diameter, mm	2.70±0.52	2.82±0.58
Minimal lumen diameter, mm	1.06±0.42	1.14±0.36
Diameter stenosis, %	61±12	59±10
Lesion length, mm	13.0±5.7	13.2±6.4

There were no significant differences in baseline variables between the groups, with the exception of a smaller MLD in the EES group ($P=0.03$).

(94.8%) of the PES group (Figure 1). In the EES group, 4 patients withdrew, 1 patient was lost to follow-up, and 7 patients died from a noncardiac cause. In the PES group with no patients lost to follow-up, 4 patients died from a noncardiac cause. Baseline demographic, clinical, and angiographic characteristics of the treatment groups have previously been reported and are summarized in Table 1.⁸ There were no significant differences between treatment groups in any of the tabulated characteristics, with the exception of a smaller minimal lumen diameter (MLD) in the EES group ($P=0.03$). Of the subset of 152 patients in the angiography and IVUS subgroup, a further subset of 115 patients underwent serial and analyzable angiography (EES, 97 lesions, 83 patients, 73%; PES, 35 lesions, 32 patients, 82%) and 95 patients underwent serial and analyzable IVUS (EES, 69 lesions, 64 patients, 57%; PES, 32 lesions, 31 patients, 79%). The angiography and IVUS patient subgroup was comparable with the total cohort (data not shown). There were no differences in baseline characteristics between the EES and PES patient groups in the angiography and IVUS subset of patients with the exception of a higher prevalence of previous MI in the EES patient group (EES: 42%; PES: 18%, $P<0.01$) and a smaller MLD in the EES group ($P=0.01$).

Clinical Outcomes

Table 2 shows target vessel failure (TLF) at 2 years and each of its components. At 2 years, TLF occurred in 6.6% of the EES group compared with 11.0% in the PES group. In each treatment group, 1 patient died of a cardiac cause (0.5% versus 1.4%). The incidence of MI at 2 years was 2.8% (6

Table 2. Clinical Outcome at 2 Years

	EES (n=211), %	PES (n=73), %	<i>P</i>
Death	3.7	6.5	0.33
Cardiac death	0.5	1.4	0.45
MI related to target vessel	2.8	4.1	0.7
Q-wave	0	0	NA
Non-Q-wave	2.8	4.1	0.70
Any MI	2.8	5.5	0.29
Q-wave	0	0	NA
Non-Q-wave	2.8	5.5	0.29
Composite of cardiac death or MI*	3.3	5.5	0.48
ID TLR	3.8	6.8	0.33
Percutaneous	3.8	6.8	0.33
Surgical	0	0	NA
TLF*	6.6	11.0	0.31
Any TLR	4.6	9.1	0.16
Percutaneous	4.6	9.1	0.16
Surgical	0	0	NA
ID target vessel revascularization	7.1	9.6	0.46
Percutaneous	6.6	9.6	0.44
Surgical	0.5	0	1.00
TVF*	10.0	12.3	0.66
Any target vessel revascularization	8.7	11.7	0.50
Percutaneous	7.8	11.7	0.35
Surgical	0.9	0.0	1.00
Any repeat revascularization	15.6	15.1	1.00

P values were calculated using Fisher exact test. Denominators for TVF components and any repeat revascularization are 211 for EES and 73 for PES; denominators for other non-TVF components are 218 for EES and 77 for PES. ID indicates ischemia driven; TVF, target vessel failure.

*Hierarchical.

patients) and 5.5% (4 patients) in the EES and PES groups, respectively. Ischemia-driven TLR comprised the majority of TLF within both groups with 3.8% (8 patients) and 6.8% (5 patients) in the EES and PES groups, respectively. The temporal distribution of TLF and its component events is shown in Kaplan–Meier curves (Figure 2). Although TLF rates in the EES group are consistently lower, the significant separation in TLF rate observed at 1 year was not maintained at the 2-year follow-up ($P_{\text{logrank}}=0.223$).

Definite or probable stent thrombosis occurred once in 2 patients (0.9%) in the EES treatment group and twice in one patient (1.4%) in the PES treatment group. Both the stent thromboses in the everolimus group occurred after 1 year. Characteristics of the stent thrombosis episodes are shown in Table 3.

Angiographic Outcomes

Angiographic results from 132 lesions in the subset of 115 patients who underwent serial angiography at 6 months and 2 years are shown in Table 4. Two-year mean in-stent late loss was 0.33 ± 0.37 mm for the EES group and 0.34 ± 0.34 mm for the PES group ($P=0.84$) against 0.17 ± 0.32 and

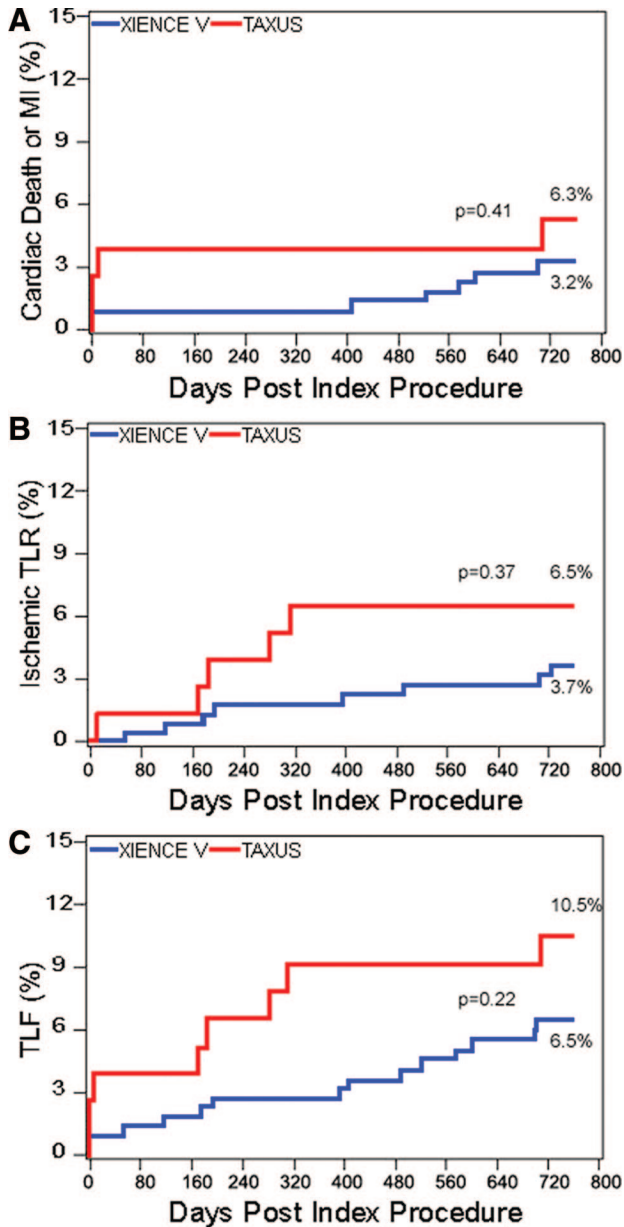


Figure 2. Cumulative distribution curves for 2-year and 180-day in-stent late loss. The probability value for noninferiority of the EES at 2 years was 0.005 (non prespecified analysis in this subgroup).

0.33±0.32 ($P=0.01$) at 6 months. If we would apply the noninferiority margin prespecified for the analysis of the primary end point at 6 months of 0.16 mm, the results at 2 years would still show noninferiority (post hoc analysis).⁸ Figure 3 shows the cumulative distribution frequency curve

of in-stent late loss at 6-month and 2-year follow-up. Proximal and distal mean late loss were 0.24 ± 0.49 and 0.08 ± 0.38 , respectively, for EES and 0.33 ± 0.45 and 0.11 ± 0.40 for PES. Mean in-stent percent diameter stenosis was 19.21 ± 14 in the everolimus group compared with 18.76 ± 11 in the paclitaxel group ($P=0.85$). Two-year in-stent angiographic binary restenosis rate was 2.1% for EES and 2.9% for PES ($P=1.000$).

IVUS Outcomes

IVUS results from 101 lesions in 95 patients who underwent IVUS at 6 months and 2 years are shown in Table 5. IVUS evaluation at 2-year follow-up showed no significant differences in percentage volume obstruction between EES and PES treatment groups. Mean percentage volume obstruction was 5.18 ± 6.22 versus 5.80 ± 6.31 ($P=0.65$) for EES and PES, respectively. Similarly, the neointimal hyperplasia volume at 2 years did not differ between both groups. Mean neointimal hyperplasia volume was 8.42 ± 10.25 mm³ in the everolimus group and 11.56 ± 16.12 mm³ in the paclitaxel group. IVUS evaluation showed no significant differences between EES and PES with respect to vessel, stent, and lumen volumes at 2 years.

Discussion

This article reports the 2-year clinical, angiographic, and IVUS follow-up of the EES compared with the PES in patients with a maximum of 2 de novo coronary artery lesions. The results of this trial confirm the efficacy of the EES from earlier results reported in the FUTURE I and II and SPIRIT FIRST, II, and III studies.^{4,6-10,17} In addition, this is the first study that provides 2-year angiographic and IVUS data for the EES. Two-year TLF rates in the current trial were 6.6% for the EES and 11.0% for the PES ($P=0.31$).

To date, results from one other randomized clinical trial comparing EES and PES are available. The large-scale SPIRIT III trial enrolled 1002 patients in the North America with a maximum of 2 de novo coronary artery lesions who were randomized 2:1 to EES or PES. Inclusion and exclusion criteria were similar to the SPIRIT II trial. As a result, baseline variables were comparable between both trials; mean lesion length was 13.0 and 14.7 mm, mean reference vessel diameter was 2.7 and 2.8 mm for SPIRIT II and SPIRIT III, respectively.^{9,17} In the SPIRIT III trial, at 2 years, TLF rates remained significantly lower for the EES; 7.7% for EES and 13.8% for PES ($P=0.005$),¹⁸ with continued divergence of the event rates between 1 and 2 years. The reduced TLF rate in the EES group was attributable to fewer non-Q-wave MIs and TLRs. Although the difference in 2-year TLF rate did not reach statistical significance in the current SPIRIT II trial, a

Table 3. Listing of Definite/Probable Stent Thrombosis During 2-Year Follow-Up

Patient Characteristics	PES/EES	Day	Location	Type	Angiographic Confirmation	MI	Fatal	Repeat Revascularization
55-y-old man	PES	9	Mid LAD	Definite	Yes	Non-Q-wave	No	Yes
55-y-old man	PES	56	Mid LAD	Probable	No	Non-Q-wave	Yes	No
54-y-old man	EES	538	Mid RCA	Definite	Yes	Non-Q-wave	No	No
61-y-old man	EES	721	Distal RCA	Probable	Yes	Non-Q-wave	No	Yes

LAD indicates left anterior descending; RCA, right coronary artery.

Table 4. Comparison of Angiographic Outcomes Between EES and PES at 6-Month and 2-Year Follow-Up

	EES (83,* 97†)	PES (32,* 35†)	Difference [95% CI]	P
6-mo angiographic outcomes				
Late loss (mean±SD), mm				
In-stent late loss	0.17±0.32	0.33±0.32	-0.16 [-0.29, -0.03]	<0.01
In-segment late loss	0.12±0.33	0.14±0.32	-0.02 [-0.14, 0.11]	0.79
Proximal late loss	0.20±0.41	0.28±0.43	-0.08 [-0.25, 0.09]	0.35
Distal late loss	0.08±0.35	0.06±0.35	0.01 [-0.12, 0.15]	0.86
Diameter stenosis (mean±SD), %				
In-stent percent diameter stenosis	16±11	18±11	-2 [-7, 2]	0.28
In-segment percent diameter stenosis	24±13	26±13	-2 [-7, 3]	0.42
Binary angiographic restenosis, %				
In-stent BAR	1.0	2.9	-1.8%	0.46
In-segment BAR	3.1	5.7	-2.6%	0.61
2-y angiographic outcomes				
Late loss (mean±SD), mm				
In-stent late loss	0.33±0.37	0.34±0.34	-0.01 [-0.15, 0.12]	0.84
In-segment late loss	0.21±0.37	0.17±0.38	0.04 [-0.11, 0.19]	0.63
Proximal late loss	0.24±0.49	0.33±0.45	-0.09 [-0.27, 0.09]	0.34
Distal late loss	0.08±0.38	0.11±0.40	-0.03 [-0.19, 0.13]	0.70
Diameter stenosis (mean±SD), %				
In-stent percent diameter stenosis	19±14	19±11	0 [-4, 5]	0.85
In-segment percent diameter stenosis	26±14	27±14	-1 [-6, 5]	0.86
Binary angiographic restenosis, %				
In-stent BAR	2.1	2.9	-0.8	1.00
In-segment BAR	5.2	8.6	-3.4	0.44

P values for continuous variables were calculated using Student *t* test, and P values for dichotomous variables were calculated using Fisher exact test. BAR indicates binary angiographic restenosis.

*No. of patients.

†No. of lesions.

trend in favor of the EES was observed. The results of the SPIRIT III trial indicate that this nonsignificance is most likely due to the lower number of patients enrolled in SPIRIT II.

The incidence of definite or probable stent thrombosis as defined by the Academic Research Consortium¹¹ was 0.9% for EES and 1.4% for PES after 2 years in the current study.

Two-year stent thrombosis rates have been reported for 3 randomized trials evaluating the EES, SPIRIT FIRST, II, and III.^{4,18} In these 3 trials combined, 2-year follow-up data were available for 866 patients treated with an EES. The occurrence of stent thrombosis was low; in total, 10 patients (1.2%) had suffered a definite or probable stent thrombosis within

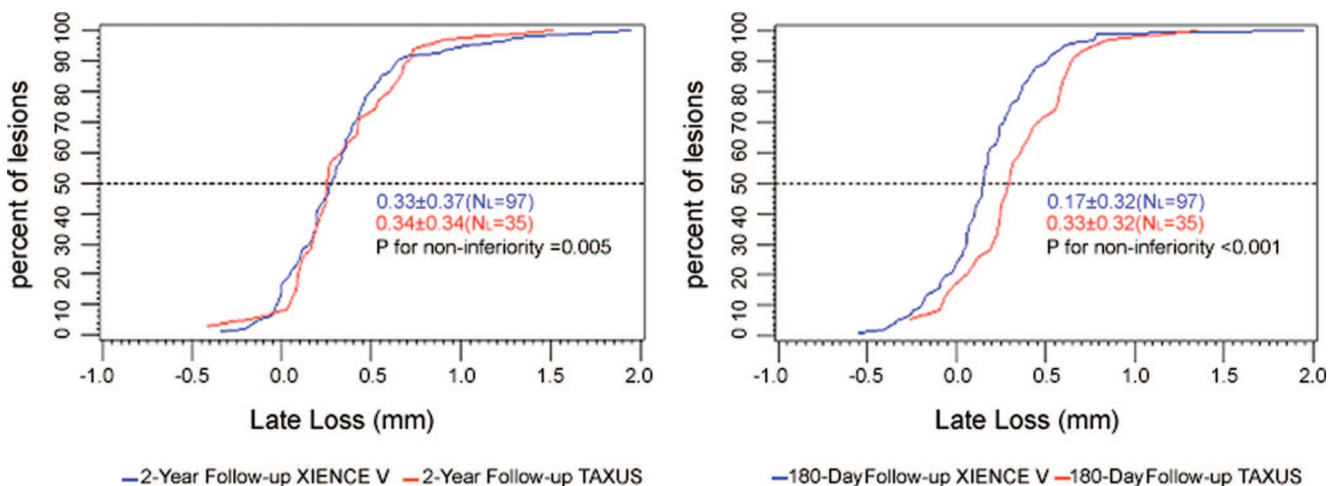


Figure 3. Kaplan-Meier curves of TLF and its components.

Table 5. Comparison of IVUS Outcomes Between EES and PES at 6-Month and 2-Year Follow-Up

	EES (64,* 69†)	PES (31,* 32†)	Difference [95% CI]	P
6-mo IVUS outcomes, mean±SD				
In-stent neointimal volume, mm ³	4.13±6.77	12.62±16.77	-8.49 [-14.72, -2.25]	<0.01
In-stent volume obstruction, %	2.77±5.02	6.48±6.69	-3.71 [-6.38, -1.04]	<0.01
Vessel volume, mm ³	330±135	393±154	-63 [-128, 1]	0.05
Stent volume, mm ³	163±71	182±74	-19 [-51, 12]	0.22
Lumen volume, mm ³	159±71	170±70	-11 [-41, 19]	0.47
2-y IVUS outcomes, mean±SD				
In-stent neointimal volume, mm ³	8.42±10.25	11.56±16.12	-3.14 [-9.40, 3.12]	0.32
In-stent volume obstruction, %	5.18±6.22	5.80±6.31	-0.62 [-3.31, 2.07]	0.65
Vessel volume, mm ³	332±150	384±158	-51 [-119, 16]	0.13
Stent volume, mm ³	162±68	182±77	-21 [-52, 11]	0.20
Lumen volume, mm ³	153±65	171±72	-17 [-48, 13]	0.25

P values for continuous variables were calculated using Student *t* test, and P values for dichotomous variables were calculated using Fisher exact test.

*No. of patients.

†No. of lesions.

2-year follow-up, indicating the safety of the EES up to 2-year follow-up. It must be born in mind that definitive statements about long-term safety of the EES can only be made after the results of larger registries have become available.

Angiographic and IVUS data of DES are limited beyond 6- to 9-month follow-up. At 6 months follow-up, in the subgroup with 6-month and 2-year angiography from the SPIRIT II trial the in stent late loss was 0.17±0.32 mm in the EES group and 0.33±0.32 mm in the PES group (*P*=0.01). Furthermore, significant differences in neointimal hyperplasia volume (4.13±6.77 versus 12.62±16.77 mm³, *P*<0.01) and percentage volume obstruction (2.77±5.02% versus 6.48±6.69%, *P*<0.01) in favor of the EES were observed. At 2 years, delayed neointimal hyperplasia was observed in the EES group with an in-stent late loss measured by QCA of 0.33±0.37 mm, whereas the late loss measured in the PES group was maintained (0.34±0.34 mm, *P*=0.6). IVUS measurements were in accordance with this as we no longer observed significant differences in neointimal hyperplasia volume (EES, 8.42±10.25 mm³; PES, 11.56±16.12 mm³) and percentage volume obstruction (EES, 5.18±6.22%; PES, 5.80±6.31%) at 2 years. Given the small number of late TLRs in this study one can only speculate whether the delayed neointimal hyperplasia in the EES group did lead to an increase in TLR.

Our results are in line with the results from the TAXUS II trial, comparing slow- and moderate-release PES to a BMS in patients with a single de novo coronary artery lesion, in which 6-month and 2-year angiographic and IVUS follow-up was obtained in a subset of 155 event-free patients.^{14,19} Angiographic late loss in the PES group was 0.25±0.30 mm at 2 years which was not different compared with 6-month late loss (0.29±0.32 mm) and is consistent with the findings reported in this article. Neointimal volume measured by IVUS increased significantly from 6 months to 2 years for the PES treatment group, whereas a trend toward a decrease was observed in the BMS group. This is inconsistent with IVUS

observations in this trial, where neointimal volume remained unchanged in the PES group between 6 months and 2 years. Patients in the PES treatment group in the TAXUS II trial were treated with a less advanced stent platform (NIR stent platform) with 2 different drug release kinetics (slow and moderate release), which could explain this discrepancy.

Previous animal studies already showed that despite marked early suppression of neointimal formation, late neointimal growth occurs within DES. In a porcine coronary artery model, long-term inhibition of neointimal formation after sirolimus-eluting stent placement was not maintained partly due to inflammation and delayed cellular proliferation. In addition, after PES placement similar findings were found with delayed healing and local toxicity after high-dose paclitaxel, which was associated with delayed intimal formation.^{20,21}

In vivo, the explanation for the delayed neointimal growth is multifactorial. In addition to an inflammatory response, shear stress-mediated remodeling could also attribute to the late “catch-up” phenomenon observed in the EES group.²² Shear stress is a primary signal for neointimal growth and is defined as the frictional force at the endothelial surface produced by flowing blood. Regions with low shear stress in the treated coronary segment have been found to be predisposed for neointimal growth.²² Differences in stent design could have led to different distributions of shear stress after stent placement. Finally, the differences in polymer and pharmacological release kinetics between both stent types could be another explanation. Everolimus is blended into an 8-μm-thick durable fluoropolymer layer, ≈75% of the drug on the EES is released within 30 days after implantation. Paclitaxel is blended into an 18-μm-thick polymer layer, during the first 48 hours after PES implantation there is an initial burst release followed by 10 days of continuous drug release.

The longest available angiographic and IVUS follow-up after DES is 4 years. From 2 to 4 years, neointimal growth was still observed. However, delayed restenosis after DES

implantation does not seem to have clinical significance as both PES and sirolimus-eluting stent markedly reduce TLR and target vessel revascularization after 4 years.² We will have to await the 3, 4, and 5 years clinical follow-up for the SPIRIT II and III studies to evaluate the long-term clinical implications for the EES. A preliminary analysis of the 3-year data from SPIRIT II has in fact shown significantly lower cardiac death and TLF event rates, and lower observed MI and ischemia-driven TLR rates for EES compared with PES (ACC 2009 abstract).²³ Furthermore, the performance of the EES will be evaluated in more complex patients in the SPIRIT IV, V, XIENCE V SPIRIT Women, and XIENCE V USA studies.

Study Limitations

This trial was not powered to detect significant differences in the safety profiles of PES and EES. Given the low frequency of the stent thromboses (3 patients total in this trial), no conclusions can be made about the relative safety profile of these stents. Furthermore, this was a single-blind trial. The operator was aware of the type of stent being implanted. However, it is unlikely that knowledge of the stent type would have influenced the operators' decisions to reintervene. Angiographic data were obtained on roughly half the cohort; serial analyses were performed on a further subset. Finally, we need more prolonged clinical follow-up to establish whether the late neointimal catch-up observed in the EES treatment group translates into an increased revascularization rate.

Conclusion

Although the previously reported angiographic and clinical superiority of the EES has vanished over time, this report confirms and extends the previously demonstrated noninferiority in terms of in-stent late loss of the EES when compared with the PES up to 2-year follow-up. There were no significant differences between EES and PES in clinical, angiographic, and IVUS outcomes at 2 years.

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Disclosures

Dr Miquel-Hebert and S. Veldhof are employees of Abbott Vascular. Dr Varenne served on the speaker's bureaus for Abbott Vascular and Boston Scientific.

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CLINICAL PERSPECTIVE

Drug-eluting stents have been shown to significantly reduce the need for repeat percutaneous coronary intervention compared with bare metal stents in percutaneous treatment of coronary artery disease. In the Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions, Spirit II trial, a next-generation everolimus-eluting stent (EES) was compared with the paclitaxel-eluting stent in 300 patients. Angiographic and intravascular follow-up was available at 2 years in a subset of 115 patients. At 2-year follow-up, a delayed neointimal hyperplasia was observed in the EES group. Two-year mean in-stent late loss was 0.33 ± 0.37 mm for the EES group and 0.34 ± 0.34 mm for the paclitaxel-eluting stent group ($P=0.84$) versus 0.17 ± 0.32 and 0.33 ± 0.32 ($P=0.01$) at 6 months. Despite this late catch-up in neointimal hyperplasia, no such trend in the composite clinical end point of target lesion failure (consisting of cardiac death, myocardial infarction, and ischemia-driven target lesion revascularization) was observed. At 2 years, target lesion failure rates were 6.6% for the EES group compared with 11.0% for the paclitaxel-eluting stent group ($P=0.31$). We will have to await more prolonged clinical follow-up from this study, and larger studies that are currently being performed to evaluate the long-term clinical implications of the observed late neointimal hyperplasia catch-up in the EES.