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Impact of Lesion Length and Vessel Size on Clinical Outcomes After Percutaneous Coronary Intervention With Everolimus- Versus Paclitaxel-Eluting Stents

Pooled Analysis From the SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) and COMPARE (Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice) Randomized Trials

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Objectives The aim of this study was to investigate the impact of reference vessel diameter (RVD) and lesion length (LL) on the relative safety and efficacy of everolimus-eluting stents (EES) and paclitaxel-eluting stents (PES).

Background Lesion length and RVD are well-known predictors of adverse events after percutaneous coronary intervention.

Methods Patient-level data were pooled from the randomized SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) II, III, IV and COMPARE (Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice) trials. Quantitative angiographic core laboratory data were available for 6,183 patients randomized to EES (n = 3,944) or PES (n = 2,239). Long lesions and small vessels were defined as LL >median (13.4 mm) and RVD ≤median (2.65 mm), respectively. Major adverse cardiac events (MACE) (consisting of cardiac death, myocardial infarction, or ischemia-driven target lesion revascularization) were assessed at 2 years, according to stent type in 3 groups: short lesions in large vessels (group A, n = 1,297); long lesions or small vessels but not both (group B, n = 2,981); and long lesions in small vessels (group C, n = 1,905).

Results The pooled 2-year MACE rates were 5.6%, 8.2%, and 10.4% in Groups A, B, and C, respectively ($p < 0.0001$). There was no significant interaction between lesion group and stent type ($p = 0.64$), indicating lower MACE with EES compared with PES regardless of LL and RVD. However, the absolute difference was largest in Groups B and C. In Group A, 2-year MACE rates were not significantly different between EES and PES (4.8% vs. 7.0%, respectively, $p = 0.11$). In contrast, EES was associated with lower 2-year rates of MACE in Group B (6.6% vs. 11.2%, $p < 0.01$) and in Group C (9.1% vs. 12.7%, $p = 0.008$) as well as lower rates of myocardial infarction, target lesion revascularization, and stent thrombosis. Multivariable analysis confirmed EES versus PES as an independent predictor of freedom from MACE in Groups B and C.

Conclusions Patients with short lesions in large vessels have low rates of MACE at 2 years after treatment with either EES or PES. In higher-risk patients with long lesions and/or small vessels, EES results in significant improvements in both clinical safety and efficacy outcomes. (A Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients With de Novo Native Coronary Artery Lesions; NCT00180310; SPIRIT III: A Clinical Evaluation of the Investigational Device XIENCE V Everolimus Eluting Coronary Stent System [EECSS] in the Treatment of Subjects With de Novo Native Coronary Artery Lesions; NCT00180479; SPIRIT IV Clinical Trial: Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Subjects With de Novo Native Coronary Artery Lesions; NCT00307047; A Randomized Controlled Trial of Everolimus-eluting Stents and Paclitaxel-eluting Stents for Coronary Revascularization in Daily Practice: The COMPARE Trial; NCT01016041) (J Am Coll Cardiol Intv 2011;4:1209–15) © 2011 by the American College of Cardiology Foundation

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First-generation drug-eluting stents (DES), introduced nearly 10 years ago, resulted in a substantial reduction in angiographic restenosis and the need for repeat revascularization procedures compared with bare-metal stents (BMS) (1,2). Nonetheless, restenosis still occurs after DES, and first-generation DES have been associated with increased rates of very late (>1 year) stent thrombosis compared with BMS (1,3). A new generation of DES has been designed with the aim to further enhance safety and efficacy in patients undergoing percutaneous coronary intervention (PCI). The XIENCE V everolimus-eluting stent (EES) (Abbott Vascular, Santa Clara, California; also distributed as PROMUS, Boston Scientific, Natick, Massachusetts) is a second-generation DES that has been compared with the TAXUS paclitaxel-eluting stent (PES) (Boston Scientific) in the randomized SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) II, SPIRIT III, SPIRIT IV, and COMPARE (Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice) trials. A recent meta-analysis of these 4 trials showed a significant reduction in target lesion revascularization (TLR), myocardial infarction (MI), and stent thrombosis at 1-year follow-up with EES compared with PES (4).

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Abbreviations and Acronyms

BMS = bare-metal stent(s)
CI = confidence interval
DES = drug-eluting stent(s)
HR = hazard ratio
ID-TLR = ischemia-driven target lesion revascularization
LL = lesion length
MACE = major adverse cardiac event(s)
PCI = percutaneous coronary intervention
RVD = reference vessel diameter
TLR = target lesion revascularization

Greater lesion length (LL) and smaller reference vessel diameter (RVD) are 2 of the 3 main risk factors for restenosis after PCI (5–11), the third being diabetes mellitus. However, the interaction between these parameters and the relative safety and efficacy of first- compared with second-generation DES has not been studied. Therefore, we evaluated the impact of LL and RVD on the 2-year clinical outcomes after PCI with EES compared with PES from a patient-level pooled analysis from the SPIRIT and COMPARE randomized trials.

Methods

Study description. For the present analysis, the databases from the 4 prospective, single-blind, randomized trials of EES versus PES were pooled for a patient level analysis. These trials included the SPIRIT II, SPIRIT III, and SPIRIT IV trials (12–14), in which patients with noncomplex de novo coronary artery lesions were randomized to treatment with the Xience V EES or the Taxus Express PES, and the COMPARE trial (15), in which an unselected cohort of consecutive patients with coronary artery disease were randomized to treatment with the Xience V EES or the Taxus Liberté PES. Details of study design, conduct of the trials, and primary study results have been published previously (12–16). A total of 6,789 patients with 8,823 treated lesions were included in the 4 trials. Baseline core laboratory-assessed quantitative coronary angiography data on LL and RVD were complete and available for 6,183 patients (91.1%) with 7,716 lesions (87.5%), who constitute the study cohort for the current analysis.

Definitions and clinical endpoints. Follow-up in all 4 included trials is presently complete to at least 2 years, with annual follow-up continuing to 5 years. Endpoints included major adverse cardiac events (MACE) (a composite of cardiac death, MI, or ischemia-driven target lesion revascularization [ID-TLR]), death (cardiac and noncardiac), MI, ID-TLR, and stent thrombosis according to the Academic Research Consortium definite or probable criteria (17). Data from the original databases, as defined and adjudicated by the clinical events committees for each study, were used in our analysis. Common definitions of endpoints were used in all 4 trials (12–16).

Statistical analysis. Categorical variables were compared with the chi-square test or Fisher exact test. Continuous variables are described as mean ± SD and were compared by means of Student *t* test. To eliminate bias, long lesions and small vessels were defined as LL greater than the median and RVD less than or equal to the median, respectively. Two-year outcomes according to stent type were examined after PCI in short lesions in large vessels (Group A), in either long lesions in large vessels or short lesions in small vessels (Group B), and in long lesions in small vessels (Group C). Longitudinal results are displayed as time-to-event curves, and Kaplan-Meier estimates of event rates were compared by the log-rank test. We included data from all patients analyzed in each of the original study reports in our analysis, with follow-up data censored at the time of first event or latest known follow-up. To investigate the impact of EES versus PES randomization on the occurrence of the 2-year rate of MACE according to LL and RVD, stepwise Cox proportional hazards regression analysis was performed in each group with stent randomization type forced into the

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model. Interaction tests were performed by including the cross product of 2 variables (an interaction term) in the Cox model. In order not to overfit the model, a limited number of covariates that by chance were imbalanced between the stent types and other variables known to affect MACE were introduced into the model, including: acute coronary syndrome, diabetes mellitus, hypertension, hypercholesterolemia, treatment of any lesion with thrombus, treatment of any lesion with moderate or severe calcification, treatment of any lesion with baseline Thrombolysis In Myocardial Infarction flow grade 0 or 1, LL (in case of multiple lesions, the longest lesion was selected), RVD (in case of multiple lesions, the smallest RVD was selected), and randomization to EES versus PES.

Results

The median LL was 13.4 mm (interquartile range: 10.0 to 19.4 mm), and the median RVD was 2.65 mm (interquartile range: 2.31 to 3.01 mm). Thus, patients were divided into 3 increasingly complex groups: Group A, LL ≤13.4 mm and RVD >2.65 mm (n = 1,297, 21.0%); Group B, LL >13.4 mm or RVD ≤2.65 mm but not both (n = 2,981, 48.2%); and Group C, LL >13.4 mm and RVD ≤2.65 mm (n = 1,905, 30.8%). The proportion of patients randomized in the all-comers COMPARE trial increased with lesion complexity (Group A 13.0%, Group B 18.1%, Group C 27.4%, p for trend <0.01).

The baseline demographic and angiographic characteristics stratified according to the 3 groups appear in Table 1. Patients randomized to EES compared with PES in Groups A and B less often had acute coronary syndromes as the indication for their index procedure. Moreover, patients randomized to EES in group A more often had hypercholesterolemia; those in group B less often had intracoronary thrombus, moderate or severe calcifications, and a baseline Thrombolysis In Myocardial Infarction flow grade 0 or 1; and those in group C more often had hypertension, hypercholesterolemia, and moderate or severe calcifications compared with patients randomized to the PES. The LL was also somewhat shorter in group C in patients randomized to EES compared with PES. There were no significant differences in clopidogrel usage between patients randomized to ESS compared with PES at discharge (Group A 96.9% vs. 96.1%, p = 0.53, Group B 97.0% vs. 97.2%, p = 0.82, Group C 97.6% vs. 97.4%, p = 0.88) and at 1 year (Group A 76.2% vs. 77.1%, p = 0.74, Group B 79.5% vs. 78.1%, p = 0.37, Group C 79.9% vs. 80.2%, p = 0.91).

Table 2 shows procedural results and angiographic outcomes. In Group A, there were no significant differences in acute outcomes between patients randomized to EES versus PES. In Group B, the post-procedural in-segment diameter stenosis was slightly lower in the EES arm (14.8% vs. 15.6%, p = 0.01). In Group C, the total stent length (41.6 mm vs. 45.0 mm, p < 0.01) was less in the EES arm, concordant with the longer mean lesion length in the PES arm. Other slight post-procedural angiographic differences between EES and PES in Group C were present.

Clinical outcomes. The overall pooled 2-year MACE rates were lowest in Group A, intermediate in Group B, and highest in Group C (5.6% vs. 8.2% vs. 10.4%, p < 0.0001). Within Group B, 2-year clinical outcome was similar in patients with long lesions in large vessels and patients with short lesions in small vessels, with the exception of a higher ID-TLR rate in patients with short lesions in small vessels (4.0% vs. 6.1%, p = 0.01). Table 3 shows the components of MACE and stent thrombosis at 2-year follow-up in the 3 groups. Higher lesion complexity was also associated with higher rates of MI (3.3% vs. 3.0% vs. 4.5%, p = 0.02) and ID-TLR (2.9% vs. 5.0% vs. 6.3%, p = 0.0002).

Among patients treated with PES, as lesion complexity increased from Group A to B to C, the 2-year rate of MACE also increased (7.0% vs. 11.2% vs. 12.8%, respectively, p for trend = 0.007). The same relationship was noted among patients treated with EES (4.8% vs. 6.6% vs. 9.1%, respectively, p for trend = 0.001). In contrast, although the 2-year rate of definite or probable stent thrombosis also increased with greater lesion complexity after PES implantation (0.7% vs. 1.9% vs. 2.8%, p for trend = 0.03), a similar relationship for stent thrombosis was not present after EES implantation (0.9% vs. 0.6% vs. 0.6%, p for trend = 0.65).

The 2-year clinical outcomes according to stent type in each group appear in Figure 1 and Table 4. There was no significant interaction between lesion group and stent type (p = 0.64), indicating lower 2-year MACE with EES compared with PES, regardless of LL and RVD. However, the absolute difference was largest in Groups B and C. In Group A, although the MACE rates were numerically less with EES compared with PES, the difference did not reach statistical significance. In contrast, EES was associated with significantly lower rates of MACE, MI, ID-TLR, and stent thrombosis in Groups B and C. Cardiac mortality was also significantly lower in the EES arm in Group B (1.0% vs. 2.1%, p = 0.03).

Multivariable analysis. Table 5 shows the predictors of 2-year MACE in Groups A, B, and C. Use of EES rather than PES was an independent predictor of freedom from MACE in Group B (hazard ratio [HR]: 0.62, 95% confidence interval [CI]: 0.49 to 0.79, p < 0.0001) and Group C (HR: 0.67, 95% CI: 0.51 to 0.88, p = 0.004) but not in Group A (HR: 0.76, 95% CI: 0.50 to 1.15, p = 0.19).

Discussion

The principal findings from this large patient-level pooled analysis from 4 randomized trials in which EES and PES were compared for the treatment of coronary artery disease are: 1) 2-year MACE rates in these contemporary DES trials were highest in patients with long lesions in small vessels (10.4%), intermediate in patients with either long lesions or small vessels but not both (8.2%), and lowest in patients with short lesions in

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Table 1. Baseline Demographic and Angiographic Characteristics

	Group A LL ≤13.4 mm and RVD >2.65 mm (n = 1,297)			Group B RVD ≤2.65 mm and LL ≤13.4 mm or RVD >2.65 mm and LL >13.4 mm (n = 2,981)			Group C RVD ≤2.65 mm and LL >13.4 mm (n = 1,905)		
	EES (n = 807, N_L = 1,056)	PES (n = 490, N_L = 632)	p Value	EES (n = 1,934, N_L = 2,379)	PES (n = 1,047, N_L = 1,316)	p Value	EES (n = 1,203, N_L = 1,460)	PES (n = 702, N_L = 873)	p Value
Demographic data									
Age (yrs)	63.4 ± 10.8	63.2 ± 10.6	0.76	62.8 ± 10.5	63.0 ± 10.4	0.72	63.6 ± 10.5	64.3 ± 10.8	0.17
Male	69.4%	72.4%	0.26	68.2%	67.4%	0.68	67.8%	67.7%	0.96
Diabetes mellitus	27.4%	27.6%	1.0	28.3%	28.1%	0.93	30.7%	27.7%	0.18
Insulin-treated	7.3%	7.8%	0.83	6.9%	7.1%	0.88	9.0%	8.3%	0.67
Hypertension	73.4%	69.4%	0.13	72.3%	69.6%	0.13	71.5%	65.5%	<0.01
Hypercholesterolemia	73.6%	68.1%	0.04	71.4%	69.3%	0.23	72.3%	68.0%	0.047
Current smoker	21.7%	22.2%	0.89	24.3%	27.5%	0.06	25.4%	22.1%	0.12
Prior PCI	17.0%	13.1%	0.07	14.4%	14.6%	0.91	13.8%	12.9%	0.62
Prior CABG	7.7%	3.9%	<0.01	6.8%	6.5%	0.82	8.3%	6.1%	0.09
Prior MI	20.7%	18.1%	0.28	20.0%	18.7%	0.44	21.8%	20.5%	0.52
Acute coronary syndrome	25.5%	33.3%	<0.01	29.7%	37.1%	<0.01	34.4%	35.5%	0.65
Unstable angina	21.4%	26.5%	0.047	24.1%	24.2%	<0.01	25.5%	21.9%	0.08
NSTEMI	2.5%	3.7%	0.23	2.9%	7.5%	<0.01	4.2%	4.3%	1.0
STEMI	2.0%	3.7%	0.07	3.0%	5.7%	<0.01	5.0%	9.4%	<0.01
Lesion characteristics									
Coronary artery location									
Left main	0.2%	0.7%	0.21	0.1%	0.5%	0.08	0.6%	0.4%	0.78
Left anterior descending	38.4%	39.3%	0.74	41.7%	41.0%	0.68	39.9%	39.5%	0.85
Left circumflex	22.9%	22.8%	1.0	24.2%	24.9%	0.63	27.7%	29.2%	0.37
Right coronary artery	38.5%	37.1%	0.62	34.0%	33.7%	0.86	31.8%	30.8%	0.59
Saphenous vein graft	0.7%	0.7%	1.0	0.3%	0.6%	0.29	0.6%	0.3%	0.27
Presence of thrombus	4.4%	6.3%	0.13	5.0%	8.1%	<0.01	4.8%	5.9%	0.20
Moderate/severe calcification	12.1%	10.2%	0.30	12.1%	14.8%	0.02	15.1%	21.1%	<0.01
TIMI flow grade 1 or 0	2.8%	3.4%	0.45	3.3%	4.8%	0.03	5.5%	5.7%	0.76
ACC/AHA class B2/C lesions	43.3%	42.3%	0.76	53.9%	53.7%	0.92	64.8%	65.4%	0.98
Lesion length (mm)	10.06 ± 2.33	9.94 ± 2.27	0.30	15.79 ± 9.15	16.24 ± 11.31	0.22	22.91 ± 10.58	25.34 ± 13.05	<0.01
Reference vessel diameter (mm)	3.07 ± 0.34	3.09 ± 0.35	0.14	2.67 ± 0.50	2.765 ± 0.55	0.28	2.25 ± 0.28	2.25 ± 0.28	0.87
Minimal lumen diameter (mm)	0.96 ± 0.45	1.00 ± 0.46	0.06	0.83 ± 0.40	0.85 ± 0.40	0.13	0.71 ± 0.36	0.76 ± 0.39	<0.01
Diameter stenosis (%)	69.0 ± 13.5	67.9 ± 13.8	0.12	69.3 ± 13.7	68.6 ± 13.6	0.12	69.5 ± 14.2	67.6 ± 15.4	<0.01

Values are mean ± SD or %.

ACC = American College of Cardiology; AHA = American Heart Association; CABG = coronary artery bypass graft surgery; EES = everolimus-eluting stent(s); LL = lesion length; MI = myocardial infarction; N_L = number of lesions; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent(s); RVD = reference vessel disease; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

large vessels (5.6%); 2) MACE rates at 2 years were increased with lesion complexity after treatment with EES and PES; however, although the frequency of stent thrombosis increased steadily from Group A to Group C after PES implantation, stent thrombosis rates after EES were independent of lesion complexity; and 3) there was no significant interaction between lesion group and stent type on 2-year MACE, although absolute differences were greatest in Groups B and C, resulting in significantly lower MACE rates with EES in these patients with either long lesions and/or small vessels.

Lesion length and RVD are known to be associated with adverse events after PCI (6–10,18). The present analysis demonstrates that LL and RVD are still important correlates of clinical outcomes even in the era of next-generation DES. The relationship between RVD and restenosis has been particularly well-described (6–9,19). Studies from the BMS era demonstrated that the degree of late lumen loss was relatively independent of coronary arterial diameter, resulting in higher rates of binary angiographic restenosis (and subsequent TLR) in small vessels (6). The same relationship has been shown to hold true with first-generation DES (11). Greater LL and/or use of longer stents have also been associated with greater rates of restenosis with both BMS and DES (9,10,18). Longer

Table 2. Procedural Characteristics and Post-Procedural Angiographic Results

	Group A LL ≤13.4 mm and RVD >2.65 mm (n = 1,297)			Group B RVD ≤2.65 mm and LL ≤13.4 mm or RVD >2.65 mm and LL >13.4 mm (n = 2,981)			Group C RVD ≤2.65 mm and LL >13.4 mm (n = 1,905)		
	EES (n = 807, N_L = 1,056)	PES (n = 490, N_L = 632)	p Value	EES (n = 1,934, N_L = 2,379)	PES (n = 1,047, N_L = 1,316)	p Value	EES (n = 1,203, N_L = 1,460)	PES (n = 702, N_L = 873)	p Value
Procedural characteristics									
Stents/patient	1.2 ± 0.5	1.2 ± 0.6	0.19	1.5 ± 0.9	1.5 ± 0.9	0.89	2.1 ± 1.2	2.2 ± 1.3	0.07
Stents/lesion	1.1 ± 0.3	1.1 ± 0.3	0.36	1.2 ± 0.5	1.2 ± 0.5	0.14	1.4 ± 0.5	1.4 ± 0.6	0.02
Stent length/patient (mm)	20.2 ± 9.5	20.4 ± 12.2	0.79	29.0 ± 17.3	28.8 ± 19.1	0.83	41.6 ± 23.1	45.0 ± 29.4	<0.01
Stent length/lesion (mm)	18.6 ± 6.0	18.4 ± 8.9	0.36	23.6 ± 10.7	23.0 ± 11.9	0.12	28.5 ± 13.1	28.9 ± 18.8	0.53
Post-procedural angiographic results									
Minimal luminal diameter (mm)									
In-stent	2.98 ± 0.37	3.01 ± 0.34	0.11	2.76 ± 0.48	2.75 ± 0.48	0.85	2.44 ± 0.35	2.49 ± 0.34	0.01
In-segment	2.62 ± 0.39	2.61 ± 0.41	0.77	2.32 ± 0.47	2.31 ± 0.50	0.38	2.10 ± 0.38	2.09 ± 0.40	0.82
Diameter stenosis (%)									
In-stent	1.9 ± 8.0	1.3 ± 8.9	0.21	1.5 ± 8.9	1.3 ± 8.4	0.51	2.3 ± 8.4	1.3 ± 9.4	0.03
In-segment	13.9 ± 7.0	14.5 ± 7.8	0.16	14.8 ± 8.0	15.6 ± 9.0	0.01	15.9 ± 8.3	15.9 ± 8.8	0.88
Acute gain (mm)									
In-stent	2.05 ± 0.53	2.06 ± 0.49	0.62	1.90 ± 0.50	1.90 ± 0.48	0.93	1.79 ± 0.43	1.85 ± 0.44	0.01
In-segment	1.67 ± 0.54	1.62 ± 0.55	0.07	1.50 ± 0.54	1.46 ± 0.56	0.06	1.38 ± 0.49	1.33 ± 0.55	0.02

Values are mean ± SD.
Abbreviations as in Table 1.

lesions require treatment with longer balloons and stents, leading to greater arterial injury, which might result in exaggerated neointimal hyperplasia.

Although prior studies have shown greater freedom from MACE with the second-generation EES compared with the first-generation PES, clinical and angiographic restenosis rates are still increased after EES in small vessels and long lesions (11,12). In the present study, the 2-year rates of MACE with both EES and PES were greatest in long lesions in small vessels, intermediate in long lesions or in small vessels, and lowest when implanted in short lesions in large vessels. Of interest, however, is that although the 2-year rate of both definite and definite or probable stent thrombosis increased in smaller vessels and/or longer lesions with PES, a similar relationship was not seen with EES. This relative freedom from stent thrombosis with EES in complex lesions might underlie much of the benefit of EES in reducing thrombotic events compared with PES, as found in the randomized trials (11–14). The low stent thrombosis rate with EES in complex lesions in the present study might in part be attributable to the relatively thin (8 μm) nonthrombogenic fluoropolymer on the surface of the EES (20). In contrast, PES is coated with a thicker (17.8 μm) 3-layer styrene-isobutylene-styrene polymer. In vitro studies have also demonstrated pro-thrombotic effects associated with PES, including up-regulation of tissue factor and plasminogen activator inhibitor-1 (21,22). Moreover, EES has shown significantly faster re-endothelialization at 14 days after stent implantation in a rabbit iliac artery model compared with PES (23).

Table 3. 2-Year Outcomes According to Vessel Diameter and Lesion Length

	Group A LL ≤13.4 mm and RVD >2.65 mm (n = 1,297)	Group B RVD ≤2.65 mm and LL ≤13.4 mm or RVD >2.65 mm and LL >13.4 mm (n = 2,981)	Group C RVD ≤2.65 mm and LL >13.4 mm (n = 1,905)	p Value
Major adverse cardiac events	5.6%	8.2%	10.4%	<0.0001
Death	2.7%	2.6%	2.1%	0.50
Cardiac death	0.6%	1.4%	1.1%	0.13
Myocardial infarction	3.3%	3.0%	4.5%	0.02
ID target lesion revascularization	2.9%	5.0%	6.3%	0.0002
Definite or probable stent thrombosis	0.8%	1.1%	1.4%	0.25
Definite stent thrombosis	0.5%	0.8%	0.9%	0.37

ID = ischemia-driven; other abbreviations as in Table 1.

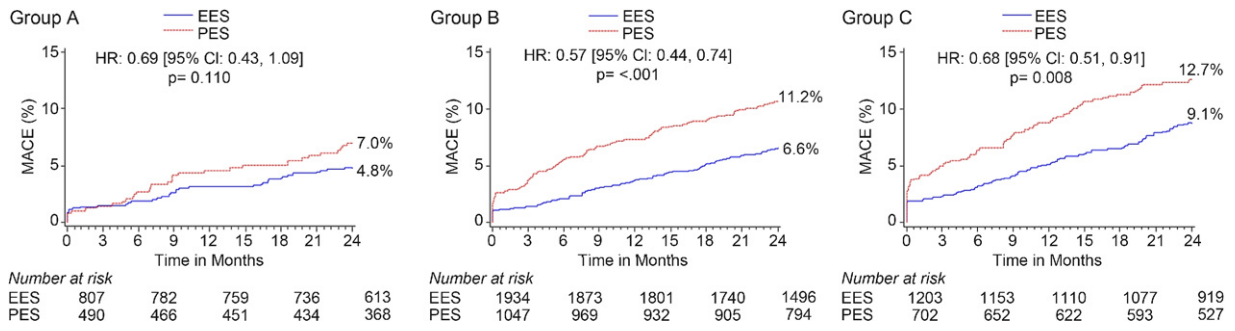

Figure 1. Time-to-Event Curves of MACE

Time-to-event curves of major adverse cardiac events (MACE) in patients randomized to everolimus-eluting stents (EES) versus paclitaxel-eluting stents (PES) according to lesion length and reference vessel diameter. See text for details. CI = confidence interval; HR = hazard ratio.

The present analysis confirms and extends previous observations regarding the relative safety and efficacy of EES compared with PES (4,12–15,24). We observed a significant reduction in 2-year MACE with EES in patients with either long lesions, small vessels, or both, indicating that the benefits of the EES relative to the PES are more pronounced in these more complex lesions. These results were confirmed by multivariable Cox regression analysis. The differences in 2-year MACE were mainly driven by lower MI and ID-TLR rates in the EES arms, although cardiac mortality was also significantly reduced in Group B with EES (1.0% vs. 2.1%, p = 0.03). In contrast, the 2-year rates of MACE were not significantly reduced with EES compared with PES in the low-risk Group A (short lesions in large vessels), although a numerical trend was present favoring EES (4.8% vs. 7.0%, p = 0.11). A larger study than even the current pooled analysis of these 4 trials is required to determine whether EES offers an advantage compared with PES in such lesions.

Study limitations. Several limitations of our analysis deserve comment. This study is a patient-level pooled analysis of 4 randomized clinical trials using different inclusion and exclusion criteria, clinical sites, core laboratories, and endpoint adjudication committees. Although the SPIRIT trials randomized noncomplex patients and lesions, COMPARE was a real world "all-comers" trial. Notwithstanding these differences in trial design, the results from these 4 individual trials were consistent. The PES tested was the TAXUS Liberté in the COMPARE trial and the TAXUS Express (Boston Scientific) in the SPIRIT trials. However, no major differences have been reported between the 2 versions of the stent (25), although it has been suggested that the Liberté platform might be superior in small vessels and long lesions (26). Randomization was not stratified according to LL or RVD, and small baseline clinical and angiographic differences between patients treated with EES and PES were present in the 3 groups. However, EES remained superior to PES in terms of 2-year MACE in Groups B and C after multivariable analysis after adjusting for these differences. Quantitative coronary angiography was performed by 2 different core laboratories (SPIRIT II, COMPARE: Cardialysis, Rotterdam, the Netherlands; SPIRIT III, SPIRIT IV, Cardiovascular Research Foundation, New York, New

Table 4. 2-Year Outcomes With EES Versus PES According to Vessel Diameter and LL

	Group A LL ≤13.4 mm and RVD >2.65 mm (n = 1,297)			Group B RVD ≤2.65 mm and LL ≤13.4 mm or RVD >2.65 mm and LL >13.4 mm (n = 2,981)			Group C RVD ≤2.65 mm and LL >13.4 mm (n = 1,905)		
	EES (n = 807)	PES (n = 490)	p Value	EES (n = 1,934)	PES (n = 1,047)	p Value	EES (n = 1,203)	PES (n = 702)	p Value
Major adverse cardiac events	4.8%	7.0%	0.11	6.6%	11.2%	<0.0001	9.1%	12.7%	0.008
Death	2.7%	2.8%	0.93	2.2%	3.3%	0.13	2.1%	2.0%	0.90
Cardiac death	0.8%	0.4%	0.47	1.0%	2.1%	0.03	1.3%	0.7%	0.27
Myocardial infarction	2.7%	4.3%	0.14	2.3%	4.3%	0.003	3.3%	6.7%	0.0008
ID target lesion revascularization	4.3%	5.5%	0.37	3.9%	7.2%	<0.0001	5.5%	7.6%	0.04
Definite or probable stent thrombosis	0.9%	0.7%	0.62	0.6%	1.9%	0.001	0.6%	2.8%	0.0001
Definite stent thrombosis	0.6%	0.2%	0.29	0.5%	1.4%	0.005	0.3%	1.9%	0.0007

Abbreviations as in Tables 1 and 3.

Table 5. Independent Predictors of 2-Year Major Adverse Cardiovascular Events

Variable	Hazard Ratio (95% CI)	p Value
Group A (LL ≤13.4 mm and RVD >2.65 mm)		
EES (vs. PES)	0.76 (0.50–1.15)	0.19
Acute coronary syndrome	1.56 (1.02–2.39)	0.04
Diabetes mellitus	1.62 (1.05–2.49)	0.03
Hypercholesterolemia	0.64 (0.41–0.98)	0.04
Group B (RVD ≤2.65 mm and LL ≤13.4 mm or RVD >2.65 mm and LL >13.4 mm)		
EES (vs. PES)	0.62 (0.49–0.79)	0.0001
RVD (per 1-mm increase)	0.66 (0.51–0.87)	0.003
Hypertension	1.50 (1.12–2.02)	0.007
Lesion length (per 10-mm increase)	1.12 (0.99–1.26)	0.07
Hypercholesterolemia	0.79 (0.61–1.03)	0.09
Group C (LL ≤13.4 mm and RVD >2.65 mm)		
EES (vs. PES)	0.67 (0.51–0.88)	0.004
Diabetes mellitus	1.42 (1.07–1.88)	0.01

CI = confidence interval; other abbreviations as in Table 1.

York), and there are no data available with regard to intra- and interobserver variability.

Conclusions

Our study examined the impact of LL and RVD on 2-year clinical outcomes after PCI with EES compared with PES in a pooled, patient-level analysis from 4 randomized controlled trials. Two-year MACE rates increased with both stents with greater LL and smaller RVD, although stent thrombosis rates after EES were independent of lesion complexity. Use of EES was associated with reduced 2-year rates of MACE, MI, ID-TLR, and stent thrombosis in patients with long lesions and/or small vessels.

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Key Words: everolimus-eluting stent(s) ■ lesion length ■ paclitaxel-eluting stent(s) ■ reference vessel diameter.