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Everolimus-Eluting Versus Sirolimus-Eluting Stents in Patients Undergoing Percutaneous Coronary Intervention

The EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) Randomized Trial

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Objectives The goal of this study was to compare the angiographic outcomes of everolimus-eluting stents (EES) and sirolimus-eluting stents (SES) in a head-to-head manner.

Background EES have been shown to be superior to paclitaxel-eluting stents in inhibiting late loss (LL) and clinical outcome. Whether EES may provide similar angiographic and clinical outcomes compared with SES is undetermined.

Methods This was a prospective, randomized, open-label, multicenter trial to demonstrate the noninferiority of EES compared with SES in preventing LL at 9 months. A total of 1,443 patients undergoing percutaneous coronary intervention were randomized 3:1 to receive EES or SES. Routine follow-up angiography was recommended at 9 months. The primary endpoint was in-segment LL at 9 months, and major secondary endpoints included in-stent LL at 9 months, target lesion failure, cardiac death, nonfatal myocardial infarction, target lesion revascularization, and stent thrombosis at 12 months. Data were managed by an independent management center, and clinical events were adjudicated by an independent adjudication committee.

Results Clinical follow-up was available in 1,428 patients and angiographic follow-up in 924 patients (1,215 lesions). The primary endpoint of the study (in-segment LL at 9 months) was 0.11 ± 0.38 mm and 0.06 ± 0.36 mm for EES and SES, respectively (p for noninferiority = 0.0382). The in-stent LL was also noninferior (EES 0.19 ± 0.35 mm; SES 0.15 ± 0.34 mm; p for noninferiority = 0.0121). The incidence of clinical endpoints was not statistically different between the 2 groups, including target lesion failure (3.75% vs. 3.05%; p = 0.53) and stent thrombosis (0.37% vs. 0.83%; p = 0.38).

Conclusions EES were noninferior to SES in inhibition of LL after stenting, which was corroborated by similar rates of clinical outcomes. (Efficacy of Xience/Promus Versus Cypher in Reducing Late Loss After Stenting [EXCELLENT]; NCT00698607) (J Am Coll Cardiol 2011;58:1844–54) © 2011 by the American College of Cardiology Foundation

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Drug-eluting stents (DES) have revolutionized the field of interventional cardiology. Newer stents are developed with hopes of improving efficacy and/or safety. Everolimus-eluting stents (EES) are second-generation DES using the MULTI-LINK VISION stent platform (Abbott Vascular, Santa Clara, California) combined with everolimus contained in a polymer coating (1). In the SPIRIT II (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients With de novo Native Coronary Artery Lesions) and SPIRIT III randomized trials, EES were noninferior and subsequently superior to paclitaxel-eluting stents (PES) with regard to in-stent late loss (LL) at 180 days (2,3). Moreover, the clinical outcomes of EES were superior to PES in the recent SPIRIT IV and COMPARE (Comparison of the everolimus eluting Xience V stent with the paclitaxel eluting Taxus Liberte stent in all-comers: a randomized open label trial) trials, in which the primary clinical endpoints were reduced by 38% and 31%, respectively (4,5).

See page 1855

However, EES have not been compared with sirolimus-eluting stents (SES), which are the most efficacious of the first-generation DES with the least amount of LL reported (6–10). SES showed lower cardiovascular event rates compared with both PES and zotarolimus-eluting stents in the ZEST (Comparison of the Efficacy and Safety of Zotarolimus-Eluting Stent with Sirolimus-Eluting and PacliTaxel-Eluting Stent for Coronary Lesions) and SORT-OUT III (Danish Organisation for Randomised Trials with Clinical Outcome) randomized trials, respectively (11,12). However, the stent and polymer platform is different between EES and SES, and EES have the thinnest stent and polymer thickness (88.6 μm) of all the available DES in Korea. Therefore, the present trial was designed to compare the efficacy of EES versus SES in reducing LL in patients undergoing percutaneous coronary intervention (PCI).

Methods

Study design and population. The prospective, open-label, blinded endpoint adjudication, randomized, EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) trial enrolled patients from 19 cardiac centers in Korea between June 2008 and July 2009. The study design has been published previously (13). The study protocol was approved by the ethics committee at each participating center and was conducted according to the principles of the Declaration of Helsinki. All patients provided written informed consent for participation in the trial.

Patients were eligible if they had at least 1 lesion in the native coronary vessel with a reference diameter of 2.25 to 4.25 mm, stenosis of more than 50% by visual estimation, and evidence of myocardial ischemia (stable angina, unstable angina, recent myocardial infarction [MI], silent ischemia, positive functional study, or reversible changes on electrocardiogram consistent with ischemia). Documentation of ischemia was not mandatory for lesions with >75% stenosis. There were no limitations for inclusion in the number of lesions, or involved vessels, or on the length of the lesions in efforts to reflect real-life clinical practice. Exclusion criteria were ST-segment elevation MI within 72 h; severely compromised ventricular dysfunction (ejection fraction <25%) or cardiogenic shock; significant left main disease (defined as stenosis of more than 50%); in-stent or in-segment restenosis of a previously implanted stent; chronic total occlusion; true bifurcation lesions requiring a planned 2-stent strategy; allergy to antiplatelet drugs, heparin, stainless steel, contrast agents, everolimus, or sirolimus; serum creatinine ≥3.0 mg/dl or dependence on dialysis; life expectancy <1 year; or active participation in another clinical study.

Abbreviations and Acronyms

CI = confidence interval
DES = drug-eluting stent(s)
EES = everolimus-eluting stent(s)
LL = late loss
MI = myocardial infarction
MLD = minimal luminal diameter
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stent(s)
QCA = quantitative coronary angiography
RR = relative risk
SES = sirolimus-eluting stent(s)
TLF = target lesion failure
TLR = target lesion revascularization

Randomization and procedures. Patients were randomized 3:1 to either receive EES (Xience V [Abbott Vascular, Santa Clara, California] and Promus [Boston Scientific, Natick, Massachusetts]) or SES (Cypher Select [Cordis Corporation, Bridgewater, New Jersey]). Randomization was conducted using a Web-based online randomization system after diagnostic angiography and before PCI. Randomization was stratified according to enrolling sites, the presence of diabetes, and long lesions.

Balloon angioplasty and stent implantation were performed according to standard techniques. It was recommended that all significant lesions be fully covered by one or multiple stents using the same randomly assigned stent, except when the allocated stent could not be inserted or was not suitable for the lesion, in which case crossover to another device at the discretion of the operator was permitted. Staged PCI (defined as procedures planned at the time of the index procedure) was allowed at the operators' discretion as long as the second PCI would be performed within 4 weeks of the index procedure using the allocated stent.

Before the index procedure, all patients received at least 300 mg of aspirin and a 300- to 600-mg loading dose of clopidogrel. Unfractionated heparin was administered throughout the procedure to maintain an activated clotting time of 250 s or longer. Administration of glycoprotein IIb/IIIa inhibitors was at the discretion of the operator. At discharge, all patients were maintained with at least 75 mg/day of aspirin and 75 mg/day of clopidogrel for at least 6 months.

Follow-up. For evaluation of the primary endpoint, all patients were recommended to undergo angiographic follow-up at 9 months. Clinical follow-up was performed at 1, 3, 9, and 12 months after index PCI and will be continued annually for up to 5 years. Patients were followed up by telephone contacts or office visits. At follow-up, patients were specifically questioned regarding the occurrence of any adverse events or the presence of anginal symptoms.

Quantitative coronary angiography. Quantitative analysis of coronary angiographic images was performed at a central core laboratory (Seoul National University Hospital Cardiovascular Clinical Research Center Angiographic Core Laboratory) by specialized quantitative coronary angiography (QCA) technicians unaware of the purpose of this study. The Cardiovascular Angiography Analysis System 5.7 QCA system (Pie Medical Imaging, Maastricht, the Netherlands) was used for automated contour detection and quantification. All angiograms performed more than 30 days after index PCI showing restenosis or thrombosis (diameter stenosis more than 50%) qualified as an endpoint angiogram. If an angiogram was performed between 1 and 5 months and restenosis was not present in any study lesion, the requirement for the 9-month angiogram was not considered to be met, and thus the 9-month angiographic follow-up was again recommended. All scheduled and unscheduled angiograms from 6 to 12 months were considered as 9-month follow-up angiograms.

Projections in which foreshortening of the analysis segment could be minimized and where the severity of the stenosis could be maximized were used in analysis. Same views with identical projections for baseline and first and second angiographic follow-ups were used. Using the guiding catheter for calibration, the minimal luminal diameter (MLD) and reference vessel diameter were measured before and after the index procedure and at first and second angiographic follow-up. Diameter stenosis was defined as the ratio of MLD and diameter of reference segment, and angiographic binary restenosis was denoted as diameter stenosis more than 50% within the target lesion. LL was the difference in MLD between angiograms immediately after the index procedure and follow-up angiogram. Acute gain was defined as the increment of MLD immediately after the index procedure. All measurements were performed for both the stented segment (in-stent) and 5-mm proximal and distal margins of the stented segment (in-segment).

Study endpoints. The primary endpoint for this study was in-segment LL at 9 months. The major secondary angiographic endpoint was in-stent LL at 9 months. Secondary clinical endpoints included target lesion failure (TLF) (defined as the composite of cardiac death, target vessel–related MI, and clinically indicated target lesion revascularization [TLR] at 12 months), target vessel failure (defined as the composite of cardiac death, target vessel–related MI, and clinically indicated target vessel revascularization at 12 months), individual components of TLF and target vessel revascularization, all deaths, periprocedural and spontaneous MI, and stent thrombosis (defined according to the Academic Research Consortium criterion) (14). Other angiographic endpoints were angiographic pattern of restenosis and in-stent and in-segment percentage diameter stenosis at 9 months. Data were managed by an independent management center, and clinical events were adjudicated by an independent adjudication committee.

Statistical analysis. On the basis of QCA results from the SIRIUS (Sirolimus-Eluting Stent in De Novo Native Coronary Lesions), E-SIRIUS, C-SIRIUS, SIRTAX (Randomized Comparison of a Sirolimus- vs. a Paclitaxel-Eluting Stent for Coronary Revascularization), and the SPIRIT II and III trials (2,3,6,15-17), we assumed the LL of EES to be 0.2 ± 0.41 mm and SES to be 0.2 ± 0.48 mm. Enrollment of 1,233 patients (924 in the EES arm and 309 in the SES arm) would provide the study with a statistical power of 90% to confirm noninferiority within 0.1 mm at a 1-sided significance level of 0.05, allowing for 20% of patients not undergoing follow-up angiography. Angiographic analysis was performed on a per-patient (index lesion only, primary analysis) and a per-lesion (all lesions) basis. The index lesion to be included in the primary per-patient analysis was determined randomly by using a computer program before QCA analysis (Online Appendix). For the per-lesion analysis, a generalized estimating equations model using an exchangeable working correlation matrix was used to assess the treatment effect by taking the clustering effect within patient into account.

For baseline characteristics and clinical outcomes, categorical variables were analyzed by using the chi-square or Fisher exact tests, whereas continuous variables were assessed by using the Student *t* test. For subgroup analysis of TLF, the logistic regression model was used to assess the interaction between the treatment and each subgroup. The time to each clinical endpoint was assessed using the Kaplan-Meier method, and the log-rank test was used to compare the incidence of each endpoint between groups. All clinical outcomes were analyzed on an intention-to-treat basis whereas angiographic outcome was analyzed on a per-protocol basis (those that received allocated stents and received follow-up angiography).

Analyses were performed using SPSS version 17.0 for Windows (SPSS Inc., Chicago, Illinois) and SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

Results

Baseline characteristics and procedural results. A total of 1,443 patients (1,927 lesions) were enrolled in the study and randomly assigned to receive EES (n = 1,079; 1,459 lesions) or SES (n = 364; 468 lesions). Figure 1 shows the trial profile and flow of the study patients. The baseline patient characteristics are shown in Table 1, and the baseline lesion and procedural characteristics are displayed in Table 2. The baseline patient, lesion, and procedural characteristics were mostly similar and comparable between

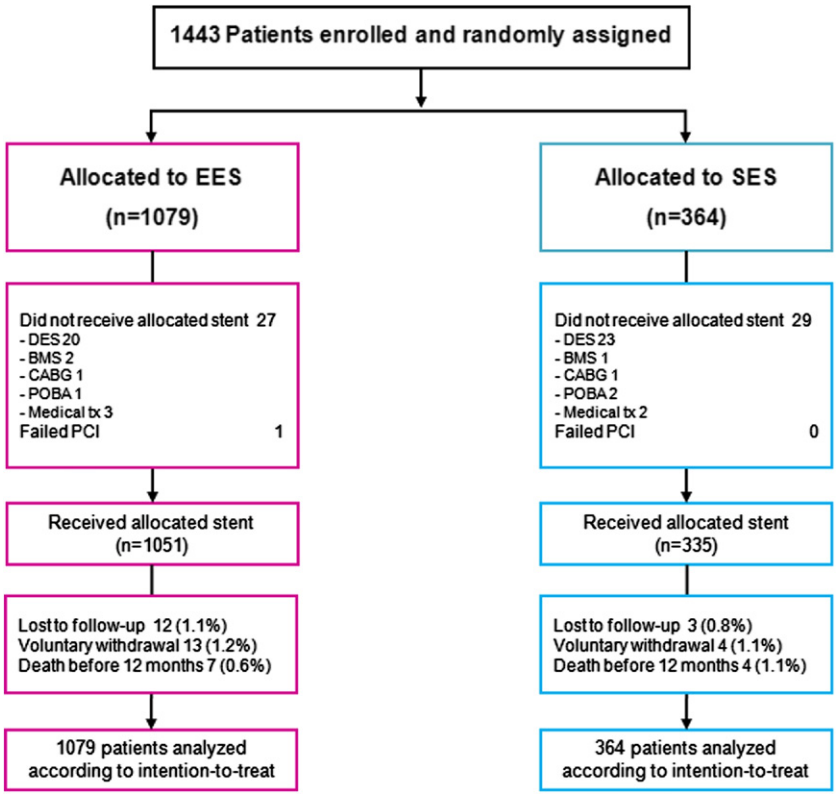

Figure 1 **Trial Profile**

A total of 1,443 patients were randomized 3:1 to receive everolimus-eluting stents (EES) or sirolimus-eluting stents (SES). Clinical outcomes of the patients were analyzed according to the intention-to-treat basis. BMS = bare-metal stents; CABG = coronary artery bypass graft; DES = drug-eluting stents; PCI = percutaneous coronary intervention; POBA = "plain old balloon angioplasty"; tx = treatment.

the 2 groups except the frequency of patients with a history of cerebrovascular accident, which was more common in the SES group; the number of implanted stents per patient, which was marginally higher in the EES group; and the final balloon pressure, which was significantly higher in the SES group ($p < 0.01$). The proportion of patients presenting with acute coronary syndrome was 52%, those with diabetes was 38.1%, and those with multivessel disease was 52.0%; the mean stented length was 28.05 mm/lesion and 37.54 mm/patient, reflecting the near real-world nature of the patients enrolled in the study. One notable characteristic of the present study was the high percentage of patients receiving intravascular ultrasound–guided stenting (43.5%). The device success rate was excellent (both more than 99%) and did not differ significantly between groups.

Angiographic results. Quantitative angiographic results at baseline, after the procedure, and at follow-up for the per-protocol patients are shown in Table 3 (index lesion) and Online Table 1 (all lesions). There were no significant differences in angiographic measurements of lesions before and after the procedure. Angiographic follow-up at 9 months was performed in 66.7% of the total patients (n = 924; 1,215 lesions), 67.4% (n = 708; 948 lesions) in the EES group, and 64.5% (n = 216; 267 lesions) in the SES group. The primary endpoint of the study, mean in-segment LL, was 0.11 ± 0.38 mm in the EES group and 0.06 ± 0.36 mm in the SES group (difference in LL: 0.05 mm [1-sided 95% upper confidence interval (CI): 0.096], p for noninferiority = 0.0382). The upper CI was within the pre-specified noninferiority margin, and thus the results of the in-segment LL met the criteria for noninferiority of EES versus SES (noninferiority margin = 0.1 mm). The in-stent LL showed similar findings; the mean in-stent LL was 0.19 ± 0.35 mm and 0.15 ± 0.34 mm for the EES and SES groups, respectively (difference in LL: 0.04 [1-sided 95% upper CI: 0.083], p for noninferiority = 0.0121). The cumulative in-stent and in-segment MLD curves of the 2 groups at 3 time points (before, immediately after, and 9 months after PCI) are shown in Online Figure 1. The angiographic results (noninferiority of EES) were similar in the intention-to-treat population, including those who did not receive the allocated stents (Online Table 2).

Clinical outcomes up to 1 year. The cumulative clinical outcomes at 1 month and up to 1 year after PCI are shown in Table 4. At 1 month, the incidence of clinical events was similar between the 2 groups. Clinical follow-up at 1 year

Table 1 Baseline Patient Characteristics

Characteristic	Total (N = 1,443)	EES (n = 1,079)	SES (n = 364)	p Value
Age (yrs)	62.7 ± 10.0	62.5 ± 10.1	63.4 ± 9.9	0.12
Male	931 (64.5)	703 (65.2)	228 (62.6)	0.39
Body mass index	25.0 ± 3.1	25.0 ± 3.1	25.0 ± 2.9	0.89
Diabetes	550 (38.1)	402 (37.3)	148 (40.7)	0.25
Chronic renal failure	15 (1.0)	12 (1.1)	3 (0.8)	0.77
Hypertension	1,057 (73.3)	791 (73.3)	266 (73.1)	0.93
Dyslipidemia	1,093 (75.7)	823 (76.3)	270 (74.2)	0.42
Current smoker	384 (26.6)	278 (25.8)	106 (29.1)	0.21
Family history of CAD	127 (8.8)	99 (9.2)	28 (7.7)	0.39
Previous myocardial infarction	74 (5.1)	56 (5.2)	18 (4.9)	0.85
Previous PCI	129 (8.9)	99 (9.2)	30 (8.2)	0.59
Previous bypass surgery	18 (1.2)	12 (1.1)	6 (1.6)	0.42
Previous congestive heart failure	9 (0.6)	8 (0.7)	1 (0.3)	0.46
Cerebrovascular disease	95 (6.6)	58 (5.4)	37 (10.2)	<0.01
Peripheral arterial disease	19 (1.3)	13 (1.2)	6 (1.6)	0.59
Multivessel disease	750 (52.0)	564 (52.3)	186 (51.1)	0.70
Left ventricular ejection fraction	61.3 ± 9.5	61.4 ± 9.4	60.8 ± 9.8	0.33
Clinical indication				0.12
Silent ischemia	55 (3.8)	39 (3.6)	16 (4.4)	
Chronic stable angina	644 (44.6)	472 (43.7)	172 (47.3)	
Unstable angina	601 (41.6)	464 (43.0)	137 (37.6)	
NSTEMI	98 (6.8)	76 (7.0)	22 (6.0)	
STEMI	45 (3.1)	28 (2.6)	17 (4.7)	
Medications at discharge				
Aspirin	1,411 (99.2)	1,061 (99.3)	350 (98.9)	0.48
Clopidogrel	1,410 (99.2)	1,058 (99.1)	352 (99.4)	0.74
Statin	1,186 (83.4)	888 (83.1)	298 (84.2)	0.65
ACE inhibitor	467 (32.8)	352 (33)	115 (32.5)	0.87
Angiotensin-II receptor antagonist	475 (33.4)	355 (33.2)	120 (33.9)	0.82
Beta-blocker	872 (61.3)	660 (61.8)	212 (59.9)	0.52
Calcium-channel blocker	487 (34.2)	360 (33.7)	127 (35.9)	0.46

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; CAD = coronary artery disease; EES = everolimus-eluting stent(s); NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; SES = sirolimus-eluting stent(s); STEMI = ST-segment elevation myocardial infarction.

was completed for 1,428 patients (99.0%); 1,067 of 1,079 (98.9%) in the EES group and 361 of 364 (99.2%) in the SES group. At 1 year, the incidence of TLF was 3.75% for EES and 3.05% for SES, which was not significantly different (relative risk [RR]: 1.23 [95% CI: 0.64 to 2.37], p = 0.53). The rate of all death, cardiac death, and MI was not statistically different between the 2 groups. The rate of TLR was numerically lower in the SES group but was not statistically significant (RR: 1.47 [95% CI: 0.61 to 3.53], p = 0.39]. As for definite and definite/probable stent thrombosis, the rates numerically favored EES but also were not statistically significant (definite/probable stent thrombosis 0.37% vs. 0.83% for EES vs. SES; RR: 0.45 [95% CI: 0.1 to 2.01], p = 0.38). Most stent thrombosis events occurred within 30 days of the index procedure and only 2 cases occurred after 30 days, 1 case in EES (0.1%) at 173 days resulting in TLR, and 1 case in SES (0.3%) at 273 days resulting in MI (Fig. 2). When TLF rates were analyzed separately between those who received routine angiographic follow-up versus those who did not, there were no significant differences (Online Fig. 2).

Subgroup analysis. Subgroup analysis regarding in-segment and in-stent LL was performed according to the presence of diabetes, long lesion, and multiple stenting. The results in various subgroups were similar to those observed in the entire population (i.e., SES showed statistically insignificant but lower LL than EES) except in the diabetic and multivessel stenting subgroups (Online Table 3 for index lesions, Online Table 4 for all lesions, Online Table 5 for sensitivity analysis). In the diabetes subgroup, both the in-stent and in-segment LL were significantly higher in the EES group compared with the SES group (in-stent LL in diabetes subgroup 0.23 ± 0.36 mm vs. 0.10 ± 0.27 mm; p for superiority = 0.0034). In the multivessel stenting subgroup, the in-segment LL was significantly higher in the EES group, but the difference in in-stent LL was not statistically different (in-stent LL in the multivessel subgroup 0.21 ± 0.36 mm vs. 0.11 ± 0.28 mm; p for superiority = 0.11). As for the clinical endpoint of TLF, subgroup analysis was performed for diabetes, long lesion, multivessel stenting, sex, acute MI, reference vessel diameter 2.75 mm, and estimated creatinine clearance of 60

Table 2 Baseline Lesion and Procedural Characteristics

Parameter	Total (N = 1,927)	EES (n = 1,459)	SES (n = 468)	p Value*
Before index procedure				
Location				
Left anterior descending	956 (49.8)	721 (49.6)	235 (50.4)	0.79
Left circumflex	421 (21.9)	320 (22)	101 (21.7)	
Right coronary	542 (28.2)	412 (28.3)	130 (27.9)	
Coronary graft	1 (0.1)	1 (0.1)	0 (0)	
Multivessel disease	750 (52)	564 (52.3)	186 (51.1)	0.70†
ACC/AHA B2 or C type	991 (53.3)	746 (53)	245 (54.2)	0.62
Total occlusion	66 (3.5)	48 (3.4)	18 (4)	0.58
Thrombus-containing	147 (7.9)	114 (8.1)	33 (7.3)	0.57
Bifurcation lesions	209 (10.8)	155 (10.6)	54 (11.5)	0.54
Calcification	772 (41.4)	589 (41.7)	183 (40.4)	0.64
Minimal luminal diameter	0.87 ± 0.48	0.87 ± 0.48	0.88 ± 0.5	0.68
Reference vessel diameter	2.88 ± 0.5	2.87 ± 0.49	2.88 ± 0.52	0.65
Diameter stenosis	69.68 ± 15.31	69.69 ± 15.29	69.64 ± 15.39	0.94
Lesion length (mm)	20.35 ± 11.92	20.31 ± 12.05	20.48 ± 11.51	0.80
Lesion length ≥20 mm	729 (40.8)	546 (40.3)	183 (42.2)	0.53
After index procedure				
No. of stents per lesion	1.21 ± 0.46	1.21 ± 0.47	1.19 ± 0.42	0.26
No. of stents per patient	1.61 ± 0.95	1.64 ± 0.97	1.53 ± 0.86	0.04‡
Total stent length per lesion (mm)	28.05 ± 13.38	27.91 ± 13.46	28.51 ± 13.16	0.43
Total stent length per patient (mm)	37.54 ± 24.98	37.79 ± 25.09	36.77 ± 24.68	0.50‡
Use of glycoprotein IIb/IIIa inhibitors	24 (1.7)	19 (1.8)	5 (1.4)	0.62†
Final balloon pressure	14.32 ± 3.63	14.09 ± 3.57	15.03 ± 3.72	<0.01
Minimal luminal diameter (in-stent)	2.6 ± 0.46	2.6 ± 0.46	2.6 ± 0.49	0.84
Minimal luminal diameter (in-segment)	2.22 ± 0.51	2.22 ± 0.51	2.24 ± 0.53	0.55
Diameter stenosis (in-stent)	8.52 ± 8.79	8.59 ± 8.94	8.3 ± 8.3	0.46
Diameter stenosis (in-segment)	18.85 ± 11.1	19.01 ± 11.07	18.37 ± 11.19	0.24
Acute gain (in-stent)	1.73 ± 0.54	1.73 ± 0.54	1.72 ± 0.53	0.76
Acute gain (in-segment)	1.35 ± 0.58	1.35 ± 0.58	1.35 ± 0.57	0.87
Use of intravascular ultrasound	627 (43.5)	467 (43.3)	160 (44)	0.82†
Lesion success	1,905 (99.7)	1,445 (99.7)	460 (99.8)	0.82
Device success	1,904 (99.7)	1,447 (99.9)	457 (99.1)	0.10
Procedure success	1,891 (99.0)	1,434 (99.0)	457 (99.1)	0.93

Values are n (%) or mean ± SD. *All p values calculated using generalized estimating equations except for per-patient comparisons, which were calculated using †chi-square test or the ‡Student *t* test.

ACC/AHA = American College of Cardiology/American Heart Association; other abbreviations as in Table 1.

ml/min. There were no significant differences in clinical outcomes between EES and SES, and the results were consistent across all subgroups, with no significant interaction p values (Online Table 6, Fig. 3).

Discussion

In this randomized, prospective comparison of EES and SES, the efficacy of EES in inhibiting neointimal growth (expressed as LL) was noninferior to the SES. Both stents showed excellent LL profiles at 9-month angiographic follow-up. Clinical outcomes, including cardiac death, MI, TLR, and TLF, were mostly similar between the 2 stents, although this study was underpowered to show differences in clinical outcome between them. In addition, the definite and probable stent thrombosis rates were not statistically different between the 2 stents, although they were numerically lower in the EES.

There are some similarities and differences between the EES and SES. Both everolimus and sirolimus are inhibitors of the mammalian target of rapamycin, but everolimus is a derivative of sirolimus, and the drug load in the EES is smaller than in the SES (88 μg vs. 150 μg). In vitro experiments reported greater efficacy of sirolimus in inhibition of smooth muscle cell proliferation (18). Furthermore, the polymer technology and stent delivery systems differ, which could result in differences in efficacy and clinical outcomes between the 2 systems. Despite these differences, it was shown in a porcine coronary model that SES and EES are equally effective in the suppression of neointimal formation (19).

In previous clinical trials, EES were superior to PES in reduction of major clinical events after PCI. The relative reductions in the incidence of the primary endpoints (TLF in SPIRIT IV, major adverse cardiac events in the COMPARE

JACC Vol. 58, No. 18, 2011
October 25, 2011:1844–54

Table 3 Quantitative Coronary Angiography Analysis (Per-Patient Analysis, Index Lesion)

Parameter	Total (N = 924)	EES (n = 708)	SES (n = 216)	p Value
Before procedure				
Lesion length (mm)	21.27 ± 12.36	21.22 ± 12.54	21.41 ± 11.77	0.84
Reference vessel diameter (mm)	2.88 ± 0.49	2.88 ± 0.48	2.88 ± 0.51	0.95
Minimal luminal diameter (mm)	0.86 ± 0.47	0.87 ± 0.47	0.85 ± 0.47	0.62
Diameter stenosis (%)	69.97 ± 15.03	69.8 ± 15.1	70.55 ± 14.79	0.52
Immediately after procedure				
Minimal luminal diameter (mm)				
In-stent	2.62 ± 0.45	2.62 ± 0.44	2.63 ± 0.49	0.80
In-segment	2.23 ± 0.51	2.23 ± 0.5	2.24 ± 0.53	0.66
Diameter stenosis (%)				
In-stent	8.39 ± 8.77	8.58 ± 8.79	7.77 ± 8.68	0.23
In-segment	18.87 ± 11.24	19.15 ± 11.26	17.92 ± 11.14	0.16
Acute gain (mm)				
In-stent	1.76 ± 0.54	1.75 ± 0.54	1.78 ± 0.54	0.52
In-segment	1.37 ± 0.57	1.36 ± 0.58	1.39 ± 0.57	0.42
Follow-up at 9 months				
Minimal luminal diameter (mm)				
In-stent	2.44 ± 0.54	2.43 ± 0.53	2.48 ± 0.55	0.20
In-segment	2.14 ± 0.53	2.12 ± 0.52	2.19 ± 0.54	0.11
Diameter stenosis (%)				
In-stent	14.35 ± 13.18	14.6 ± 13.49	13.54 ± 12.1	0.30
In-segment	22.31 ± 13.82	22.75 ± 14.04	20.89 ± 12.98	0.08
Late luminal loss (mm)				
In-stent	0.18 ± 0.35	0.19 ± 0.35	0.15 ± 0.34	0.09
In-segment	0.1 ± 0.37	0.11 ± 0.38	0.06 ± 0.36	0.09
Binary restenosis (%)				
In-stent	17 (1.8)	14 (2.0)	3 (1.4)	0.77
In-segment	30 (3.2)	24 (3.4)	6 (2.8)	0.66
Restenosis pattern (%)				1.00
Focal	28 (93.3)	22 (91.7)	6 (100.0)	
Diffuse	1 (3.3)	1 (4.2)	0 (0.0)	
Proliferative	0 (0.0)	0 (0.0)	0 (0.0)	
Total occlusion	1 (3.3)	1 (4.2)	0 (0.0)	

Values are expressed as mean ± SD or n (%).
Abbreviations as in Table 1.

trial) were reportedly 38% and 31%, respectively (4,5). However, EES have not been previously compared with SES, which have been shown to have the lowest event rates. Of all the commercially available DES, SES have been shown to accumulate the least amount of LL and are the most efficacious with regard to repeat revascularization (6–10,20,21). Furthermore, SES outperformed PES in the ZEST trial and zotarolimus-eluting stents in the SORT-OUT III trial (11,12). Therefore, a head-to-head comparison of EES and SES regarding efficacy and safety was needed. In the present trial, the efficacy of EES was noninferior to SES. The difference in mean LL was 0.04 ± 0.02 mm and 0.05 ± 0.02 mm for in-stent and in-segment analyses, respectively, which were well within the noninferiority margin of 0.10 mm. The in-stent LL (0.19 ± 0.35 mm) in the present study was in accord with previous trials of EES, which showed LL of 0.11 ± 0.27 mm in the SPIRIT II trial at 6 months and 0.14 ± 0.39 mm in the SPIRIT III trial at 8 months after PCI (2,3). It should be noted that in the present study, the LL observed was less than what was expected at the onset of the trial, and although the noninferiority was met, there was a consistent trend in the superiority analysis toward lower LL (in-stent and in-segment, all-lesion and index lesion) in the SES group over the EES group. However, there were no differences in the rate of clinical events. The TLR rate, which is the best clinical correlate of efficacy and LL, was 2.5% and 1.7% for EES and SES, respectively. These data are in line with the recently presented but to-date-unpublished clinical trials comparing EES versus SES, such as SORT-OUT IV and ISAR-TEST-4 (Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents Trial), in which EES showed similar clinical efficacy compared with SES up to 1 year (5,22,23). Event rates in this study were extremely low for patients with such complexity in both stents. In Asian subjects, the TLR rate for SES was reported to be 5.7% at 1 year in an unrestricted population of Japanese patients (24) and 1.4% in a selected group of patients in a randomized Korean trial (11). Previous reports regarding the repeat revascularization rates of EES were

Table 4 Cumulative Incidence of Clinical Events Up to 1 Year (Intention-to-Treat Per Patient)

30-Day Clinical Outcome	Total (N = 1,442)	EES (n = 1,079)	SES (n = 363)	RR (95% CI)	p Value
Death					
All	5 (0.35)	3 (0.28)	2 (0.55)	0.50 (0.08–3.01)	0.60
Cardiac	2 (0.14)	1 (0.09)	1 (0.28)	0.34 (0.02–5.36)	0.44
Noncardiac	3 (0.21)	2 (0.19)	1 (0.28)	0.67 (0.06–7.40)	1.00
Myocardial infarction					
All	15 (1.04)	11 (1.02)	4 (1.1)	0.93 (0.3–2.89)	1.00
Periprocedural	11 (0.76)	9 (0.83)	2 (0.55)	1.51 (0.33–6.97)	0.74
Spontaneous	4 (0.28)	2 (0.19)	2 (0.55)	0.34 (0.05–2.38)	0.26
Target vessel	15 (1.04)	11 (1.02)	4 (1.1)	0.93 (0.30–2.89)	1.00
Nontarget vessel	0 (0)	0 (0)	0 (0)	—	—
Death or myocardial infarction	20 (1.39)	14 (1.3)	6 (1.65)	0.78 (0.30–2.03)	0.62
Ischemia-driven TLR	2 (0.14)	1 (0.09)	1 (0.28)	0.34 (0.02–5.36)	0.44
Ischemia-driven TVR	4 (0.28)	3 (0.28)	1 (0.28)	1.01 (0.11–9.67)	1.00
Stent thrombosis (ARC)					
Definite	4 (0.28)	2 (0.19)	2 (0.55)	0.34 (0.05–2.38)	0.26
Probable	1 (0.07)	1 (0.09)	0 (0)	—	1.00
Definite or probable	5 (0.35)	3 (0.28)	2 (0.55)	0.50 (0.08–3.01)	0.60
Target lesion failure	17 (1.18)	12 (1.11)	5 (1.38)	0.81 (0.29–2.28)	0.78
Target vessel failure	19 (1.32)	14 (1.3)	5 (1.38)	0.94 (0.34–2.60)	1.00
1-Year Clinical Outcome	**Total (N = 1,428)**	**EES (n = 1,067)**	**SES (n = 361)**		
Death					
All	11 (0.77)	7 (0.66)	4 (1.11)	0.59 (0.17–2.01)	0.48
Cardiac	5 (0.35)	3 (0.28)	2 (0.55)	0.51 (0.09–3.03)	0.61
Noncardiac	6 (0.42)	4 (0.37)	2 (0.55)	0.68 (0.12–3.68)	0.65
Myocardial infarction					
All	20 (1.4)	15 (1.41)	5 (1.39)	1.01 (0.37–2.77)	0.98
Periprocedural	13 (0.91)	11 (1.03)	2 (0.55)	1.86 (0.41–8.36)	0.54
Spontaneous	7 (0.49)	4 (0.37)	3 (0.83)	0.45 (0.1–2.01)	0.38
Target vessel	18 (1.26)	13 (1.22)	5 (1.39)	0.88 (0.32–2.45)	0.79
Nontarget vessel	2 (0.14)	2 (0.19)	0 (0)	—	1.00
Death or myocardial infarction	31 (2.17)	22 (2.06)	9 (2.49)	0.83 (0.38–1.78)	0.63
Ischemia-driven TLR	32 (2.24)	26 (2.44)	6 (1.66)	1.47 (0.61–3.53)	0.39
Ischemia-driven TVR	41 (2.87)	33 (3.09)	8 (2.22)	1.40 (0.65–2.99)	0.39
Stent thrombosis (ARC)					
Definite	6 (0.42)	3 (0.28)	3 (0.83)	0.34 (0.07–1.67)	0.17
Probable	1 (0.07)	1 (0.09)	0 (0)	—	1.00
Definite or probable	7 (0.49)	4 (0.37)	3 (0.83)	0.45 (0.10–2.01)	0.38
Target lesion failure*	51 (3.57)	40 (3.75)	11 (3.05)	1.23 (0.64–2.37)	0.53
Target vessel failure	60 (4.2)	47 (4.4)	13 (3.6)	1.22 (0.67–2.23)	0.51

Values are n (%). *The main secondary clinical endpoint was target lesion failure, the composite of cardiac death, target lesion-related myocardial infarction, and target lesion revascularization. ARC = Academic Research Consortium; CI = confidence interval; RR = relative risk; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table 1.

2.4% and 2.3% in the SPIRIT IV and COMPARE trials, respectively (4,5), which were very similar to our results.

In subgroup analysis, several subgroups showed significant differences in in-stent LL; namely, the diabetic subgroup and multivessel stenting subgroup. In these 2 subgroups, the difference in LL between EES and SES was 0.12 and 0.09 mm, respectively. The 1-sided upper 95% CI was well above the noninferiority margin of 0.10 mm. This could be due to a basic difference in the antiproliferative efficacy of the 2 drugs. Although both stents showed equivalent efficacy that probably will not significantly affect efficacy outcome clinically, SES may be stronger in inhibiting neointimal formation after PCI due to the higher drug load and greater smooth muscle cell–inhibiting efficacy. This could have resulted in the significant difference in LL in subgroups that are prone to greater accumulation of neointima. Second, there is intense controversy regarding whether EES may be less efficacious in diabetic patients compared with other DES. In both the SPIRIT IV and COMPARE trials, in which EES were superior to the PES in the entire population, the only subgroup in which this was not seen was patients with diabetes (4,5). Third, there is a possibility that our findings are the result of a play of chance because the LL observed in patients with diabetes receiving SES was extraordinarily low (lower than nondiabetic subjects receiving SES). The LL did not differ significantly between diabetic (0.23 ± 0.36 mm) and nondiabetic (0.17 ± 0.34 mm) subjects in those receiving

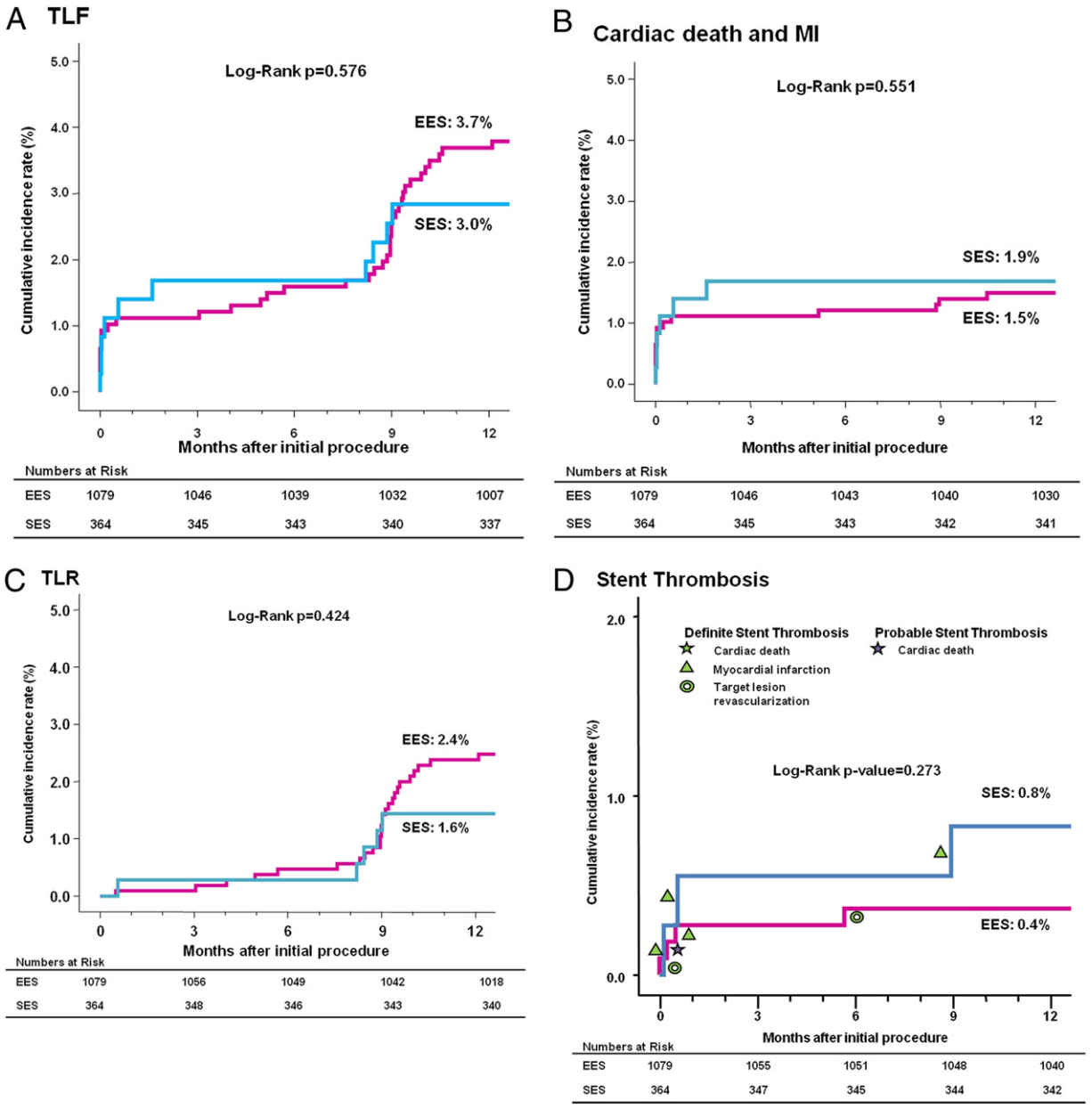

Figure 2 **Clinical Outcomes**

Kaplan-Meier cumulative event curves up to 12 months are shown for **(A)** target lesion failure (TLF), **(B)** cardiac death and myocardial infarction (MI), **(C)** ischemia-driven target lesion revascularization (TLR), and **(D)** stent thrombosis.

EES. But in those receiving SES, the in-stent LL was considerably and paradoxically lower in patients with diabetes (0.10 ± 0.27 mm) than in the nondiabetic subjects (0.18 ± 0.38 mm).

The safety clinical endpoints in the trial were all similar between EES and SES. However, there were similar trends in the same direction for differences in components of safety, including cardiac death, spontaneous MI, and stent thrombosis, all of which numerically favored EES over SES. Although this result in itself cannot be given any significant clinical relevance (because the study was underpowered to show differences in safety), it needs to be interpreted in context with the body of evidence that has been gathered for EES. In 4 other relatively large-scale randomized, controlled trials enrolling at least 1,000 patients (SPIRIT IV, COMPARE, SORT-OUT IV, and ISAR-TEST), the Academic Research Consortium definite and probable stent thrombosis rates were 0.3%, 0.2%, 0.9%, and 1.4%, respectively (4,5,22,23). Our results add to the existing evidence that EES have a very low rate of stent thrombosis at least up to 1

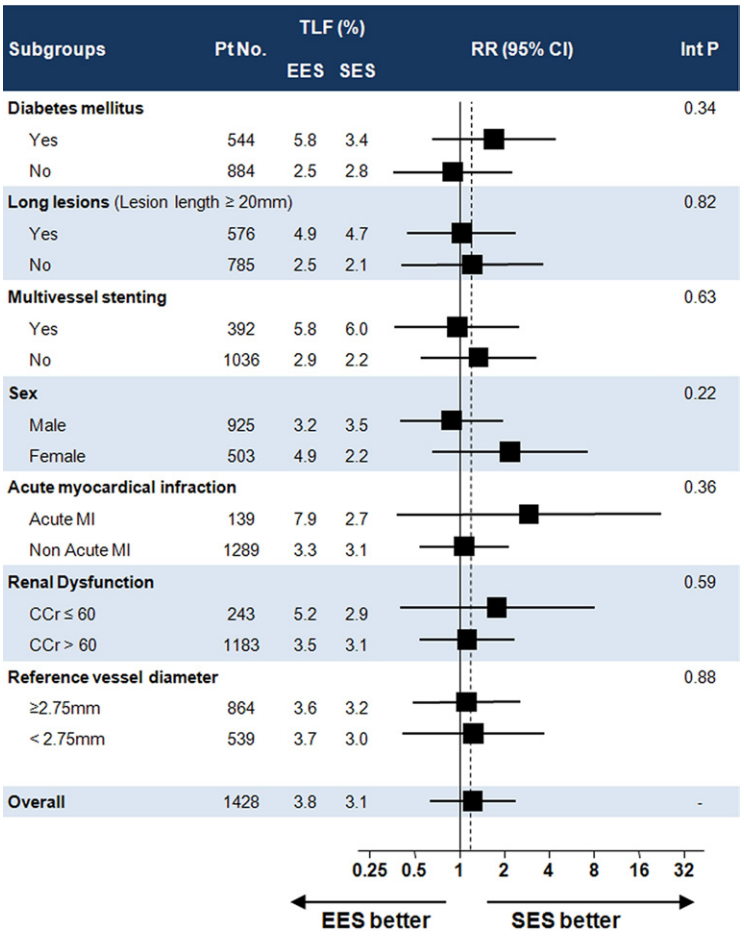

Figure 3 **Subgroup Analysis**

The rate of target lesion failure (TLF) was similar between everolimus-eluting stents (EES) and sirolimus-eluting stents (SES) across all subgroups.
CCr = creatinine clearance; CI = confidence interval; MI = myocardial infarction; RR = relative risk.

year. Whether the rates of stent thrombosis will continue to be this low at longer term follow-up will need to be carefully monitored because safety is an important issue.

Study limitations. First, although sufficiently powered to show noninferiority of EES compared with SES in LL using a very strict noninferiority margin, this study was underpowered to detect any possible difference in clinical endpoints because the primary endpoint was an angiographic outcome. Therefore, any trend or numerical difference in clinical outcome needs to be taken as hypothesis generating at best, and must be confirmed in larger randomized trials or a careful meta-analysis of trials with similar design. Second, the randomization of the stents was 3:1 rather than 1:1. This design was adapted to acquire as much data as possible regarding the newly released EES. The unbalanced randomization leads to sufficient number of patients undergoing implantation with EES but a limited number of patients receiving SES. This widens the possibility that SES could unexpectedly perform better or worse than its usual performance by chance, which could make any interpretation of the results very confusing. However, the low rate of clinical events in the SES group is comparable to another study enrolling similar complex, near real-world type of patients (11). SES performed similar if not better than any previous large-scale DES trial, and therefore, it is highly unlikely that EES were noninferior to SES due to unexpectedly poor outcomes in the SES group. Third, the rate of angiographic follow-up was lower than expected. However, because this study had another randomization scheme (duration of dual antiplatelet therapy), we finally enrolled 1,443 patients, which was much higher than the 1,223 patients necessary in the stent randomization scheme.

Conclusions

The EXCELLENT randomized prospective trial demonstrated that EES were noninferior to SES in inhibition of LL after stenting, which was corroborated by the similar rate of clinical outcomes.

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Key Words: everolimus ■ percutaneous coronary intervention ■ sirolimus ■ stents.

APPENDIX

For an expanded Methods section, Results data, and supplemental figures and tables, please see the online version of this article.