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Randomized Comparison of Everolimus-Eluting Stent Versus Sirolimus-Eluting Stent Implantation for De Novo Coronary Artery Disease in Patients With Diabetes Mellitus (ESSENCE-DIABETES)

Results From the ESSENCE-DIABETES Trial

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Background—Drug-eluting stents significantly improved angiographic and clinical outcomes compared with bare metal stents in diabetic patients. However, a comparison of everolimus-eluting stents and sirolimus-eluting stents in diabetic patients has not been evaluated. Therefore we compared effectiveness of everolimus-eluting stents and sirolimus-eluting stents in patients with diabetes mellitus.

Methods and Results—This prospective, multicenter, randomized study compared everolimus-eluting stent (n=149) and sirolimus-eluting stent (n=151) implantation in diabetic patients. The primary end point was noninferiority of angiographic in-segment late loss at 8 months. Clinical events were also monitored for at least 12 months. Everolimus-eluting stents were noninferior to sirolimus-eluting stents for 8-month in-segment late loss (0.23±0.27 versus 0.37±0.52 mm; difference, −0.13 mm; 95% confidence interval, −0.25 to −0.02; upper 1-sided 95% confidence interval, −0.04; $P<0.001$ for noninferiority), with reductions in in-stent restenosis (0% versus 4.7%; $P=0.029$) and in-segment restenosis (0.9% versus 6.5%; $P=0.035$). However, in-stent late loss (0.11±0.26 versus 0.20±0.49 mm; $P=0.114$) was not statistically different between the 2 groups. At 12 months, ischemia-driven target lesion revascularization (0.7% versus 2.6%; $P=0.317$), death (1.3% versus 3.3%; $P=0.448$), and myocardial infarction (0% versus 1.3%; $P=0.498$) were not statistically different between the 2 groups. Major adverse cardiac events, including death, myocardial infarction, and ischemia-driven target lesion revascularization (2.0% versus 5.3%; $P=0.218$), were also not statistically different between the 2 groups.

Conclusions—Everolimus-eluting stents were noninferior to sirolimus-eluting stents in reducing in-segment late loss and reduced angiographic restenosis at 8 months in patients with diabetes mellitus and coronary artery disease.

Clinical Trial Registration—URL: http://www.ClinicalTrials.gov. Unique identifier: NCT00997763.

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Key Words: coronary artery disease ■ drug-eluting stent ■ diabetes mellitus

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Diabetic patients often present unfavorable coronary anatomy with small and/or diffusely diseased vessels[1] and exhibit exaggerated neointimal hyperplasia after bare metal stent implantation compared with nondiabetics.[2] Although drug-eluting stent (DES) implantation significantly reduced the neointimal hyperplasia and angiographic restenosis compared with bare metal stents in diabetic patients,[3] the presence of diabetes mellitus (DM) continues to be associated with an increased risk of restenosis and unfavorable clinical outcomes in the era of DES.[4,5] Recently, the relative efficacies of sirolimus-eluting stent (SES) and paclitaxel-eluting stent (PES) in patients with DM have been evaluated in randomized, registry, and meta-analysis studies,[6–10] which found SES to have promising efficacy compared with PES in diabetic patients. Recently, everolimus-eluting stents (EES) also showed superior efficacy over PES in large randomized trials.[11–14] In A Clinical Evaluation of the XIENCE V Everolimus-Eluting Coronary Stent System in the Treatment of Patients With De Novo Coronary Artery Lesions (SPIRIT) III and IV subgroup analysis, no significant differences were observed between EES and PES among diabetic patients, and a significant interaction was noted between stent type and event-free survival.[13–15] However, it is unclear whether there are differences in efficacy and safety between EES and SES in diabetic patients. This prospective randomized study compared angiographic and clinical outcomes of EES and SES in diabetic patients.

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Methods

Patient Selection

This prospective randomized study included 300 patients between 18 years and 75 years of age with coronary artery disease. The study involved 15 cardiac centers in Korea between June 2008 and August 2009. Patients were considered eligible if they had DM with either stable angina or an acute coronary syndrome and had at least 1 coronary lesion (defined as stenosis of >50% and visual reference diameter ≥2.5 mm) suitable for stent implantation. Patients were excluded if they had contraindication to aspirin or clopidogrel; unprotected left main disease (diameter stenosis ≥50% by visual estimate); graft vessel disease; left ventricular ejection fraction <30%; recent history of hematologic disease or leukocyte count <3000 per 1 mm^3 and/or platelet count <100 000 per 1 mm^3; hepatic dysfunction with aspartate aminotransferase or alanine aminotransferase ≥3 times the upper normal reference limit; history of renal dysfunction or serum creatinine level ≥2.0 mg/dL; serious noncardiac comorbid disease with a life expectancy <1 year; primary angioplasty for acute myocardial infarction (MI) within 24 hours; or inability to follow the protocol. In patients with multiple lesions who fulfilled the inclusion and exclusion criteria, the first stented lesion was considered the target lesion. The institutional review board at each participating center approved the protocol. All patients provided written informed consent.

Randomization and Procedures

Once the guidewire had crossed the target lesion, patients were randomly assigned in a 1:1 ratio to EES (Xience V, Abbott Vascular) or SES (Cypher Select and Cypher Select Plus, Cordis, Johnson & Johnson) implantation through the use of an interactive Web response system. The allocation sequence was computer generated, stratified according to participating center, and blocked with block sizes of 4 and 6 that varied randomly. Random assignments were stratified according to participation sites. Before or during the procedure, all patients received at least 100 mg aspirin and a 300- to 600-mg loading dose of clopidogrel. Heparin was administered throughout the procedure to maintain an activated clotting time of ≥250 seconds. Administration of glycoprotein IIb/IIIa inhibitors was at the discretion of the operator. After the procedure, all patients received 100 mg/d aspirin indefinitely and 75 mg/d clopidogrel for at least 12 months. A 12-lead ECG was obtained after the procedure and before discharge. Serum levels of creatine kinase and its MB isoenzyme were assessed 8, 12, and 24 hours after the procedure and thereafter if considered necessary.

Study End Point and Definitions

The primary end point of this trial was in-segment late loss at the 8-month angiographic follow-up. The secondary end points included 8-month angiographic outcomes of in-stent late loss and in-stent and in-segment restenosis at 8 months (defined as in-stent or in-segment stenosis of at least 50%). At 12 months, stent thrombosis, ischemia-driven target lesion revascularization, ischemia-driven target vessel revascularization, and major adverse cardiac events, including death resulting from any cause, MI, or ischemia-driven target lesion revascularization, were also assessed.

The diagnosis of DM was considered confirmed in all patients receiving active treatment with an oral hypoglycemic agent or insulin. For patients with a diagnosis of DM who were on a dietary therapy alone, enrollment in the trial required documentation of an abnormal blood glucose level after an overnight fast.

Angiographic success was defined as in-segment diameter stenosis <30% by quantitative coronary angiographic analysis. We defined MI as creatine kinase-MB elevation >3 times or creatine kinase elevation >2 times the upper normal limit with at least one of the following: ischemic symptoms, development of pathological Q waves, and ischemic ECG changes. Revascularization was defined as ischemia driven if there was stenosis of at least 50% of the diameter, as documented by a positive functional study, ischemic changes on an ECG, or ischemic symptoms, or, in the absence of documented ischemia, if there was stenosis of at least 70% as assessed by quantitative coronary analysis. Stent thrombosis was assessed according to the Academic Research Consortium definitions[16] and was classified by the timing of the event (acute, 0 to 24 hours; subacute, 0 to 30 days; late, >31 days).

Follow-Up

Repeat coronary angiography was mandatory at 8 months after stenting or earlier if indicated by clinical symptoms or evidence of myocardial ischemia. Clinical follow-up visits were scheduled at 30, 120, and 240 days and 1 year. At every visit, physical examination, ECG, cardiac events, and angina recurrence were monitored. At each participating center, patient data were recorded prospectively on standard case report forms and gathered in the central data management center (Asan Medical Center, Seoul, Korea). All adverse clinical events were adjudicated by an independent events committee blinded to the treatment groups.

Quantitative Coronary Angiographic Analysis

Coronary angiograms were obtained after intracoronary nitroglycerin administration. Procedure (baseline), postprocedure, and follow-up angiograms were submitted to the angiographic core analysis center (Asan Medical Center, Seoul, Korea). Digital angiograms were analyzed with an automated edge detection system (CASS II; Pie Medical, Maastricht, the Netherlands). Angiographic variables included absolute lesion length, stent length, reference vessel diameter, minimum lumen diameter, percent diameter stenosis, binary restenosis rate, acute gain, late loss, and the patterns of recurrent restenosis. Quantitative coronary angiographic measurements of target lesions were obtained for both the stented segment only (in stent) and the region including the stented segment and the margins 5 mm proximal and distal

Table 1. Baseline Clinical Characteristics

Variable	EES (n=149)	SES (n=151)	P
Age, y	63.2±8.3	63.5±8.1	0.831
Men, n (%)	78 (52.3)	99 (65.6)	0.020
Hypertension, n (%)	102 (68.5)	110 (72.8)	0.404
Treatment of diabetes mellitus, n (%)			
Oral hypoglycemic agent	105 (70.5)	115 (76.2)	0.265
Insulin	27 (18.1)	19 (12.6)	0.183
Dietary therapy alone	17 (11.4)	17 (11.3)	0.967
Glycosylated hemoglobin, %	7.9±1.6	7.7±1.4	0.274
Total cholesterol ≥200 mg/dL, n (%)	62 (41.6)	53 (35.1)	0.246
Current smoker, n (%)	31 (20.8)	41 (27.2)	0.199
Previous PCI, n (%)	11 (7.4)	6 (4.0)	0.222
Previous CABG, n (%)	1 (0.7)	1 (0.7)	0.999
Previous MI, n (%)	2 (1.3)	3 (2.0)	0.999
Clinical diagnosis, n (%)			
Stable angina	85 (57.0)	90 (59.6)	0.653
Unstable angina	60 (40.3)	49 (32.5)	0.159
Acute MI	4 (2.7)	12 (7.9)	0.043
Left ventricular ejection fraction, %	59.9±7.6	61.4±5.9	0.084
Multivessel disease, n (%)	84 (56.4)	81 (53.6)	0.634

EES indicates everolimus-eluting stent; SES, sirolimus-eluting stent; PCI, percutaneous coronary intervention; CABG, coronary artery bypass surgery; and MI, myocardial infarction.

to the stent (in segment). In-segment late loss was calculated within the analysis segment itself but separately considering stented segment and the proximal and distal edges, taking the maximum change in minimum lumen diameter within those 3 segments, and applying it to this segment as a whole (maximal regional late loss method).[17] Patterns of angiographic restenosis were quantitatively assessed with the Mehran et al[18] classification.

Statistical Analysis

On the basis of results from previous trial,[10] we assumed an in-segment angiographic late loss of 0.43±0.45 mm in both arms. Calculation of the sample size was based on a margin of noninferiority for in-segment late loss of 0.15 mm, which is equal to 35% of an assumed mean late loss after the implantation of SES. Using a 1-sided 5% significance level, we estimated that 112 patients per group were needed to demonstrate noninferiority of EES with a statistical power of 80%. Expecting that ≈20% of the patients would not return for follow-up angiography, the total sample size was estimated to be 280 patients (140 patients per group). Analyses of the 2 groups were performed according to the intention-to-treat principle. Continuous variables are presented as mean±SD or median (interquartile range) and compared by use of the Student unpaired *t* or Mann–Whitney *U* test. Categorical variables are presented as numbers or percentages and were compared by use of the χ^2 or Fisher exact test. The noninferiority hypothesis was assessed statistically with the use of a *z* test, by which 1-sided *P* values for noninferiority were calculated to compare differences between groups with margins of noninferiority, according the method of Chow and Liu.[19] All *P* values are 2 sided except those from noninferiority testing of the primary end point. A value of $P<0.05$ was considered to indicate a significant difference. All statistical analyses were performed with SAS version 9.1 (SAS Institute, Cary, NC).

Results

Baseline Characteristics of the Patients

Table 1 shows the baseline clinical characteristics of study groups. Most of the clinical characteristics were similar between the 2 groups, although the SES group included significantly more men and acute MI.

Table 2. Angiographic Characteristics and Procedural Results

Variable	EES (n=149)	SES (n=151)	P
Target vessel, n (%)			
Left anterior descending artery	91 (61.1)	89 (58.9)	0.706
Left circumflex artery	21 (14.1)	25 (16.6)	0.554
Right coronary artery	37 (24.8)	37 (24.5)	0.947
Procedure-related non–Q-wave MI, n (%)	11 (7.4)	10 (6.6)	0.825
Maximal inflation pressure, atm	12.9±3.8	13.6±3.8	0.077
Use of intravascular ultrasound, n (%)	117 (78.5)	119 (78.8)	0.952
Use of glycoprotein IIb/IIIa inhibitor, n (%)	2 (1.3)	7 (4.6)	0.173
Predilation before stenting, n (%)	134 (89.9)	135 (89.4)	0.880
Poststenting adjunctive balloon dilatation, n (%)	102 (68.5)	113 (75.3)	0.186
Largest balloon size for adjunctive dilatation, mm	3.52±0.48	3.54±0.45	0.744
Multivessel stenting, n (%)	41 (27.5)	46 (30.5%)	0.574
Used stents at the target lesion, n	1.3±0.6	1.3±0.5	0.865
Patients with angiographic follow-up, n (%)	108 (72.5)	107 (70.9)	0.755

EES indicates everolimus-eluting stent; SES, sirolimus-eluting stent; and MI, myocardial infarction.

Procedural Results and In-Hospital Outcomes

Table 2 shows the angiographic characteristics and procedural results. The 2 groups have similar anatomic and procedural characteristics. All stents were successfully implanted, and the angiographic success rate was 100% in all groups. The 2 groups were treated with similar stented lengths and the number of implanted stents per target lesion. Procedure-related non–Q-wave MI occurred similarly in both arms. In-hospital events, including Q-wave MI, emergency bypass surgery, or death, did not occur in either group.

Angiographic Outcomes

Baseline and postprocedural quantitative coronary angiographic outcomes for the study groups are shown in Table 3. The 2 groups had similar baseline and postprocedural quantitative coronary angiographic characteristics.

Follow-up angiography was performed in 215 patients (71.7%): 108 EES patients (72.5%) and 107 SES patients (70.9%). The median duration of angiographic follow-up was similar in the 2 groups (247 days [interquartile range, 228 to 261 days] and 249 days [interquartile range, 238 to 264 days] for the EES and SES groups; $P=0.725$). Patients undergoing angiographic follow-up were more likely to have stable angina ($P=0.026$) than those who did not return for angiographic follow-up (Tables I and II in the online-only Data Supplement). The results of quantitative coronary angiographic measurements at follow-up are shown in Table 3. In-segment late loss of EES with maximal regional late loss method, the prespecified primary end point, was noninferior

Table 3. Quantitative Angiographic Measurements

Variable	EES (n=149)	SES (n=151)	*P*
Reference diameter, mm	2.77±0.53	2.77±0.45	0.965
Lesion length, mm	22.4±12.90	23.9±14.0	0.337
Stented length, mm	27.7±12.7	29.7±14.8	0.217
Minimum lumen diameter, mm			
In-segment			
Before procedure	0.90±0.41	0.87±0.46	0.497
After procedure	2.36±0.51	2.38±0.44	0.606
At follow-up	2.34±0.44	2.20±0.56	0.056
In-stent			
After procedure	2.65±0.46	2.64±0.41	0.819
At follow-up	2.57±0.45	2.48±0.56	0.203
Diameter stenosis, %			
In-segment			
Before procedure	69.1±13.6	70.7±14.4	0.318
After procedure	14.8±8.9	13.8±10.3	0.405
At follow-up	17.2±10.5	21.4±17.3	0.032
In-stent			
After procedure	6.8±5.1	7.4±5.2	0.255
At follow-up	12.0±10.4	14.4±15.5	0.190
Acute gain, mm			
In-segment	1.45±0.58	1.51±0.55	0.339
In-stent	1.75±0.53	1.77±0.55	0.717
Late loss, mm			
In-segment	0.23±0.27	0.37±0.52	0.020
In-stent	0.11±0.26	0.20±0.49	0.114
Binary angiographic restenosis, n/N (%)			
In-segment	1/108 (0.9)	7/107 (6.5)	0.035
In-stent	0/108 (0)	5/107 (4.7)	0.029

EES indicates everolimus-eluting stent; SES, sirolimus-eluting stent.

to that of the SES group (0.23±0.27 versus 0.37±0.52 mm; difference, −0.13 mm; 95% confidence interval, −0.25 to −0.02; upper 1-sided 95% confidence interval, −0.04; $P<0.001$ for noninferiority). In-segment late loss using the analysis segment late loss method was lower in EES versus SES patients (0.04±0.29 versus 0.18±0.51 mm; difference, −0.14 mm; 95% confidence interval, −0.25 to −0.03; $P=0.015$). However, in-stent late loss (0.11±0.26 versus 0.19±0.49 mm; difference, −0.09 mm; 95% confidence interval, −0.19 to −0.02; $P=0.11$) was not statistically different between the 2 groups. The rate of in-segment restenosis was 0.9% in the EES group and 6.5% in the SES group ($P=0.035$). The in-stent restenosis rate was also lower in the EES than the SES group (0% versus 4.7%; $P=0.029$). In patients with restenosis, the pattern of restenosis was not different between the 2 groups (Table 4).

Clinical Outcomes

Major adverse cardiac events during follow-up are shown in Table 5. A minimum 12-month clinical follow-up was performed in all patients. At 12 months, the incidence of individual and composite clinical outcomes did not differ significantly between the 2 groups. During 12 months, 1 stent thrombosis occurred in each group, which was subacute and probable stent thrombosis.

Table 4. Angiographic Patterns of Restenosis*

Variable	EES (n=1), n (%)	SES (n=7), n (%)	*P*
Focal	1 (100)	5 (71.4)	0.092
IA (articulation or gap)	0	0	
IB (margin)	1	2	
IC (focal body)	0	3	
ID (multifocal)	0	0	
Diffuse	0	2 (28.6)	0.092
II (intrastent)	0	2	
III (proliferative)	0	0	
IV (total occlusion)	0	0	

EES indicates everolimus-eluting stent; SES, sirolimus-eluting stent.
*Classified with the Mehran et al[18] criteria.

Discussion

The major finding of this study is that both EES and SES implantation showed favorable performance in diabetic patients. At 8 months, EES was noninferior to SES in reducing in-segment late loss and reduced angiographic restenosis in patients with DM and coronary artery disease.

Drug-eluting stents significantly reduced angiographic restenosis and cardiac events compared with bare metal stent in patients with DM. Compared with PES, SES showed promising efficacy in DM patients.[6–10] Recently, newer DES has

Table 5. Clinical Outcomes at 12 Months

Variable	EES (n=149), n (%)	SES (n=151), n (%)	*P*
Death	2 (1.3)	5 (3.3)	0.448
Cardiac	1 (0.7)	2 (1.3)	
Noncardiac	1 (0.7)	3 (2.0)	
MI	0	2 (1.3)	0.498
Q-wave	0	0	
Non–Q-wave	0	2 (1.3)	
Ischemia-driven TLR	1 (0.7)	4 (2.6)	0.371
Drug-eluting stent	1 (0.7)	1 (0.7)	
Cutting balloon	0	4 (2.6)	
Stent thrombosis	1 (0.7)	1 (0.7)	0.999
Acute	0	0	
Subacute	1 (0.7)	1 (0.7)	
Late	0	0	
Ischemia-driven TVR	1 (0.7)	6 (4.0)	0.121
Death/MI/ischemia-driven TVR	3 (2.0)	10 (6.6)	0.085
MACEs (death/MI/ischemia-driven TLR)	3 (2.0)	8 (5.3)	0.218

EES indicates everolimus-eluting stent; SES, sirolimus-eluting stent; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization; and MACE, major adverse cardiac events.

been a default strategy in routine practice in the treatment of coronary artery disease. In several randomized trials, EES showed superior efficacy over PES.[11–14] Furthermore, intravascular analysis study showed that EES showed greater neointimal suppression without significant vessel expansion than PES in diabetic patients.[20] However, the relative efficacy of EES versus SES in diabetic patients has not been tested in a randomized study.

The present study shows that EES was noninferior to SES in reducing in-segment late loss and reduced angiographic restenosis. Although in-stent late loss may be served as a useful measure of the pure biological potency of DES and a more reliable predictor of restenosis,[21] we chose in-segment late loss as the primary end point because it is the most sensitive measure of the antiproliferative effectiveness of DES and accounts for the magnitude of lumen renarrowing that occurs at the margins of the stent. Because isolated stenoses at stent edges represent an increasingly greater proportion of target lesion revascularization events with a DES than a bare metal stent, in-segment measures might be a wise choice as a clinical event surrogate.[22]

In this trial, EES was noninferior to SES for in-segment late loss with the maximal regional late loss method, the prespecified primary end point, and reduced in-segment late loss with the analysis segment late loss method. However, in-stent late loss was not statistically different between the 2 groups. In the previous studies, the late loss of the SES group in diabetic patients (in-stent late loss, 0.09 to 0.26 mm; in-segment late loss, 0.31 to 0.43 mm) was comparable to that observed in our study.[3,9,10,23,24] Late loss of the EES group of a nonselective population study using the analysis segment late loss method (in-stent late loss, 0.11 to 0.19 mm; in-segment late loss, 0.06 to 0.10) was also comparable to that observed in our study.[12,13,25–27] Furthermore, a previous randomized trial comparing EES and SES also showed that in-stent late loss is lower in EES compared with SES (0.23 ± 0.52 versus 0.28 ± 0.57 mm; $P=0.08$).[28] In addition, a randomized trial comparing EES and SES showed that the relative efficacy of EES was noninferior to SES in inhibiting in-segment late loss as a primary end point (0.10 ± 0.36 versus 0.05 ± 0.34 mm; upper 1-sided 95% confidence interval, 0.09; $P=0.023$ for noninferiority).[29] Therefore, our findings demonstrated that the effectiveness of EES for neointimal suppression is extrapolated to the diabetic population.

We also observed that EES reduced in-stent and in-segment restenosis compared with SES. In a previous study, restenosis rates of the SES group in a diabetic population (in-stent restenosis, 3.4% to 4.9%; in-segment restenosis, 4.0% to 8.8%) were comparable to those observed in our study.[3,9,10,23,24] However, in our EES group, the restenosis rates were numerically lower than those of the previous nonselective population study (in-stent restenosis rate, 2.3% to 3.8%; in-segment restenosis rate, 4.7% to 6.5%).[12,13,25–27] A recently published EES study comparing Japanese and American populations showed that intravascular ultrasound–guided aggressive post–balloon dilation and stent optimization reduced percent neointimal obstruction.[30] Although the exact mechanism underlying our findings remains unclear, 79% patients of the EES group were treated by intravascular ultrasound guidance, which partially explained the low restenosis rate in the EES group in our diabetic population. The reduced strut thickness (81 versus 140 μm) and thinner polymer coating (7.6 versus 12.6 μm), in conjunction with improved biocompatibility of the EES polymer, may favorably affect neointimal hyperplasia.

Although a noninferior rate of late loss and reduction in angiographic restenosis was shown in the EES versus the SES group, all clinical end points, including stent thrombosis, death, MI, ischemia-driven target lesion revascularization, ischemia-driven target vessel revascularization, and major adverse cardiac events, ie, composite outcomes of death, MI, or ischemia-driven target vessel revascularization, were not statistically different, which is supported by previous studies showing similar efficacy and safety for EES and SES.[31–33] Recently, a large-scale randomized clinical study (A Prospective, Randomized Trial of Everolimus-Eluting and Sirolimus-Eluting Stents in Patients with Coronary Artery Disease [SORT-OUT IV]) which included >2600 patients across a wide range of lesion and patient complexity, also demonstrated a similar rate of the composite end point of major adverse cardiac events between the EES and SES groups (4.9% versus 5.2%).[33]

Study Limitations

The present study has limitations that should be addressed. First, in our study, in-segment late loss was calculated with the maximal regional late loss method.[17] However, a previous study showed that the clinical relevance of the maximal regional late loss was similar to that of the analysis segment late loss.[17] Second, the angiographic follow-up rate was lower than the protocol-based estimated rate. However, the number of patients undergoing angiographic follow-up provided a statistical power of 78% to demonstrate noninferiority of EES, which almost reached our protocol-based statistical power of 80%. Third, the SES group included significantly more men, a higher prevalence of acute MI, and marginally higher values of left ventricular ejection fraction. Therefore, we investigated whether these variables were effect modifiers and/or confounding effectors for in-segment and in-stent late loss. On linear regression adjusting for these variables, there were no significant interaction effects between groups and variables on both outcomes ($P>0.10$ for both). However, because of the low event number, we could not analyze the binary restenosis and clinical outcomes with adjustment of these variables. Finally, our study is a small angiographic outcomes study that was not powered for clinical outcomes. Therefore, our findings should be confirmed or rebutted by larger, longer-term follow-up study in diabetic patients.

Conclusion

The present study showed that EES implantation resulted in noninferior 8-month angiographic in-segment late loss and reduced 8-month angiographic restenosis rate without significant differences in MI, death, or stent thrombosis compared with SES implantation in patients with DM and coronary artery disease.

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Disclosures

None.

References

1. Kip KE, Faxon DP, Detre KM, Yeh W, Kelsey SF, Currier JW. Coronary angioplasty in diabetic patients: the National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. *Circulation*. 1996;94:1818–1825.
2. Kornowski R, Mintz GS, Kent KM, Pichard AD, Satler LF, Bucher TA, Hong MK, Popma JJ, Leon MB. Increased restenosis in diabetes mellitus after coronary interventions is due to exaggerated intimal hyperplasia: a serial intravascular ultrasound study. *Circulation*. 1997;95:1366–1369.
3. Sabate M, Jimenez-Quevedo P, Angiolillo DJ, Gomez-Hospital JA, Alfonso F, Hernandez-Antolin R, Goicolea J, Banuelos C, Escaned J, Moreno R, Fernandez C, Fernandez-Aviles F, Macaya C; for the DIABETES Investigators. Randomized comparison of sirolimus-eluting stent versus standard stent for percutaneous coronary revascularization in diabetic patients: the Diabetes and Sirolimus-Eluting Stent (DIABETES) trial. *Circulation.* 2005;112:2175–2183.
4. Kumar R, Lee TT, Jeremias A, Ruisi CP, Sylvia B, Magallon J, Kirtane AJ, Bigelow B, Abrahamson M, Pinto DS, Ho KKL, Cohen DJ, Carrozza JP Jr, Cutlip DE. Comparison of outcomes using sirolimus-eluting stenting in diabetic versus nondiabetic patients with comparison of insulin versus non-insulin therapy in the diabetic patients. *Am J Cardiol*. 2007; 100:1187–1191.
5. Hong SJ, Kim MH, Ahn TH, Ahn YK, Bae JH, Shim WJ, Ro YM, Lim DS. Multiple predictors of coronary restenosis after drug-eluting stent implantation in patients with diabetes. *Heart*. 2006;92:1119–1124.
6. Zhang F, Dong L, Ge J. Meta-analysis of five randomized clinical trials comparing sirolimus- versus paclitaxel-eluting stents in patients with diabetes mellitus. *Am J Cardiol*. 2010;105:64–68.
7. Yang TH, Park SW, Hong MK, Park DW, Park KM, Kim YH, Han KH, Lee CW, Cheong SS, Kim JJ, Park SJ. Impact of diabetes mellitus on angiographic and clinical outcomes in the drug-eluting stents era. *Am J Cardiol*. 2005;96:1389–1392.
8. Lee SW, Park SW, Kim YH, Yun SC, Park DW, Lee CW, Hong MK, Rhee KS, Chae JK, Ko JK, Park JH, Lee JH, Choi SW, Jeong JO, Seong IW, Cho YH, Lee NH, Kim JH, Chun KJ, Kim HS, Park SJ. A randomized comparison of sirolimus- versus paclitaxel-eluting stent implantation in patients with diabetes mellitus: 2-year clinical outcomes of the DES-DIABETES trial. *J Am Coll Cardiol*. 2009;53:812–813.
9. Lee SW, Park SW, Kim YH, Yun SC, Park DW, Lee CW, Hong MK, Rhee KS, Chae JK, Ko JK, Park JH, Lee JH, Choi SW, Jeong JO, Seong IW, Cho YH, Lee NH, Kim JH, Chun KJ, Kim HS, Park SJ. A randomized comparison of sirolimus- versus paclitaxel-eluting stent implantation in patients with diabetes mellitus. *J Am Coll Cardiol.* 2008;52:727–733.
10. Dibra A, Kastrati A, Mehilli J, Pache J, Schühlen H, von Beckerath N, Ulm K, Wessely R, Dirschinger J, Schömig A. Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. *N Engl J Med*. 2005;353:663–670.
11. Kedhi E, Joesoef KS, McFadden E, Wassing J, van Mieghem C, Goedhart D, Smits PC. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. *Lancet*. 2010;375:201–209.
12. Serruys PW, Ruygrok P, Neuzner J, Piek JJ, Seth A, Schofer JJ, Richardt G, Wiemer M, Carrié D, Thuesen L, Boone E, Miquel-Herbert K, Daemen J. A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent: the SPIRIT II trial. *EuroIntervention*. 2006;2:286–294.
13. Stone GW, Midei M, Newman W, Sanz M, Hermiller JB, Williams J, Farhat N, Mahaffey KW, Cutlip DE, Fitzgerald PJ, Sood P, Su X, Lansky AJ. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease. *JAMA*. 2008;299: 1903–1913.
14. Stone GW, Rizvi A, Newman W, Mastali K, Wang JC, Caputo R, Doostzadeh J, Cao S, Simonton CA, Sudhir K, Lansky AJ, Cutlip DE, Kereiakes DJ. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. *N Engl J Med*. 2010;362:1663–1674.
15. Kereiakes DJ, Cutlip DE, Applegate RJ, Wang J, Yaqub M, Sood P, Su X, Su G, Farhat N, Rizvi A, Simonton CA, Sudhir K, Stone GW. Outcomes in diabetic and nondiabetic patients treated with everolimus- or paclitaxel-eluting stents: results from the SPIRIT IV clinical trial (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System). *J Am Coll Cardiol*. 2010;56:2084–2089.
16. Laskey WK, Yancy CW, Maisel WH. Thrombosis in coronary drug-eluting stents: report from the meeting of the Circulatory System Medical Devices Advisory Panel of the Food and Drug Administration Center for Devices and Radiologic Health, December 7–8, 2006. *Circulation*. 2007; 115:2352–2357.
17. Ellis SG, Popma JJ, Lasala JM, Koglin JJ, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Stone GW. Relationship between angiographic late loss and target lesion revascularization after coronary stent implantation: analysis from the TAXUS-IV trial. *J Am Coll Cardiol*. 2005;45:1193–1200.
18. Mehran R, Dangas G, Abizaid AS, Mintz GS, Lansky AJ, Satler LF, Pichard AD, Kent KM, Stone GW, Leon MB. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. *Circulation*. 1999;100:1872–1878.
19. Chow S-C, Liu J-P. *Design and Analysis of Clinical Trials*. 2nd ed. New York, NY: John Wiley and Sons; 2004.
20. Otake H, Ako J, Yamasaki M, Tsujino I, Shimohama T, Hasegawa T, Sakurai R, Waseda K, Honda Y, Sood P, Sudhir K, Stone GW, Fitzgerald PJ. Comparison of everolimus- versus paclitaxel-eluting stents implanted in patients with diabetes mellitus as evaluated by three-dimensional intravascular ultrasound analysis. *Am J Cardiol*. 2010;106:492–497.
21. Mauri L, Orav EJ, O'Malley AJ, Moses JW, Leon MB, Holmes DR Jr, Teirstein PS, Schofer J, Breithardt G, Cutlip DE, Kereiakes DJ, Shi C, Firth BG, Donohoe DJ, Kuntz RE. Relationship of late loss in lumen diameter to coronary restenosis in sirolimus-eluting stents. *Circulation*. 2005;111:321–327.
22. Pocock SJ, Lansky AJ, Mehran R, Popma JJ, Fahy MP, Na Y, Dangas G, Moses JW, Pucelikova T, Kandzari DE, Ellis SG, Leon MB, Stone GW. Angiographic surrogate end points in drug-eluting stent trials: a systematic evaluation based on individual patient data from 11 randomized, controlled trials. *J Am Coll Cardiol*. 2008;51:23–32.
23. Baumgart D, Klauss V, Baer F, Hartmann F, Drexler H, Motz W, Klues H, Hofmann S, Völker W, Pfannebecker T, Stoll H-P, Nickenig G. One-year results of the SCORPIUS study: a German multicenter investigation on the effectiveness of sirolimus-eluting stents in diabetic patients. *J Am Coll Cardiol*. 2007;50:1627–1634.
24. Tomai F, Reimers B, De Luca L, Galassi AR, Gaspardone A, Ghini AS, Ferrero V, Favero L, Gioffrè G, Prati F, Tamburino C, Ribichini F. Head-to-head comparison of sirolimus- and paclitaxel-eluting stent in the same diabetic patient with multiple coronary artery lesions. *Diabetes Care*. 2008;31:15–19.
25. Bartorelli AL, Serruys PW, Miquel-Hébert K, Yu S, Pierson W, Stone GW. An everolimus-eluting stent versus a paclitaxel-eluting stent in small vessel coronary artery disease: a pooled analysis from the SPIRIT II and SPIRIT III trials. *Catheter Cardiovasc Interv*. 2010;76:60–66.
26. Khattab AA, Richardt G, Verin V, Kelbaek H, Macaya C, Berland J, Miquel-Hebert K, Dorange C, Serruys PW. Differentiated analysis of an everolimus-eluting stent and a paclitaxel-eluting stent among higher risk subgroups for restenosis: results from the SPIRIT II trial. *EuroIntervention*. 2008;3: 566–573.
27. Serruys PW, Silber S, Garg S, van Geuns RJ, Richardt G, Buszman PE, Kelbæk H, van Boven AJ, Hofma SH, Linke A, Klauss V, Wijns W, Macaya C, Garot P, DiMario C, Manoharan G, Kornowski R, Ischinger T, Bartorelli A, Ronden J, Bressers M, Gobbens P, Negoita M, van Leeuwen F, Windecker S. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *N Engl J Med*. 2010;363:136–146.
28. Kastrati A. Clinical and angiographic results from a randomized trial sirolimus-eluting and everolimus-eluting stent: ISAR-TEST 4. Paper presented at: Transcatheter Cardiovascular Therapeutics 2009-Session V. Current generation DES; September 24, 2009; San Francisco, CA.
29. Kim HS. Efficacy of XIENCE/PROMUS versus Cypher to reduce late loss in stent: the EXCELLENT trial. Paper presented at: Transcatheter Cardiovascular Therapeutics 2010-First Report Investigations Sessions; September 25, 2010; Washington, DC.
30. Shimohama T, Ako J, Yamasaki M, Otake H, Tsujino I, Hasegawa T, Nakatani D, Sakurai R, Chang H, Kusano H, Waseda K, Honda Y, Stone

GW, Saito S, Fitzgerald PJ, Sudhir K. SPIRIT III JAPAN versus SPIRIT III USA: a comparative intravascular ultrasound analysis of the everolimus-eluting stent. *Am J Cardiol*. 2010;106:13–17.
31. Byrne RA, Kastrati A, Kufner S, Massberg S, Birkmeier KA, Laugwitz K-L, Schulz S, Pache J, Fusaro M, Seyfarth M, Schömig A, Mehilli J. Randomized, non-inferiority trial of three limus agent-eluting stents with different polymer coatings: the Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST-4) trial. *Eur Heart J*. 2009;30:2441–2449.
32. Onuma Y, Kukreja N, Piazza N, Eindhoven J, Girasis C, Schenkeveld L, van Domburg R, Serruys PW. The everolimus-eluting stent in real-world patients: 6-month follow-up of the X-SEARCH (Xience V Stent Evaluated at Rotterdam Cardiac Hospital) registry. *J Am Coll Cardiol*. 2009;54:269–276.
33. Jensen LO. A prospective randomized trial of everolimus-eluting stents and sirolimus-eluting stents in patients with coronary artery disease: the SORT-OUT IV trial. Paper presented at: Transcatheter Cardiovascular Therapeutics 2010-Late Breaking Trial Sessions; September 24, 2010; Washington, DC.

CLINICAL PERSPECTIVE

Diabetic patients have worse clinical outcomes after coronary intervention compared with nondiabetics. With the introduction of drug-eluting stents, the rate of restenosis was reduced compared with bare metal stents in diabetic patients, although the presence of diabetes mellitus remains a significant predictor of adverse outcomes in the drug-eluting stent era. The Randomized Comparison of Everolimus-Eluting Stent Versus Sirolimus-Eluting Stent Implantation for De Novo Coronary Artery Disease in Patients with Diabetes Mellitus (ESSENCE-DIABETES) trial was a prospective randomized trial that compared everolimus-eluting stents (n=149) and sirolimus-eluting stents (n=151) in diabetic patients. Everolimus-eluting stents were noninferior to sirolimus-eluting stents for 8-month in-segment late loss (0.23±0.27 versus 0.37±0.52 mm; difference, −0.13 mm; 95% confidence interval, −0.25 to −0.02; upper 1-sided 95% confidence interval, −0.04; $P<0.001$ for noninferiority), with reductions in in-stent restenosis (0% versus 4.7%; $P=0.029$) and in-segment restenosis (0.9% versus 6.5%; $P=0.035$). However, in-stent late loss (0.11±0.26 versus 0.19±0.49 mm; difference, −0.09 mm; 95% confidence interval, −0.19 to −0.02; $P=0.11$) was not statistically different between the 2 groups. At 12 months, ischemia-driven target lesion revascularization (0.7% versus 2.6%; $P=0.317$), death (1.3% versus 3.3%; $P=0.448$), and myocardial infarction (0% versus 1.3%; $P=0.498$) were not statistically different between the 2 groups. In conclusion, everolimus-eluting stents were noninferior to sirolimus-eluting stents in reducing in-segment late loss and reduced angiographic restenosis at 8 months in patients with diabetes mellitus and coronary artery disease. Therefore, our findings suggested that everolimus-eluting stent implantation is a good option for the diabetic population.

SUPPLEMENTAL MATERIAL

Table 1. Baseline Clinical Characteristics

Variable	Follow-Up Angiography (+) (N=215)	Follow-Up Angiography (-) (N=85)	*P*
Age, years	62.9±8.3	64.6±7.9	0.113
Men	129 (60.0%)	48 (56.5%)	0.575
Hypertension	66 (30.7%)	22 (25.9%)	0.409
Treatment of diabetes mellitus			0.490
Oral hypoglycemic agent	157 (73.0%)	63 (74.1%)	
Insulin	31 (14.4%)	15 (17.6%)	
Dietary therapy alone	27 (12.6%)	7 (8.2%)	
Glycosylated hemoglobin	7.7±1.4%	7.8±1.8%	0.627
Total cholesterol ≥200 mg/dL	85 (39.5%)	30 (35.3%)	0.496
Current smoker	47 (21.9%)	25 (29.4%)	0.168
Previous PCI	13 (6.0%)	4 (4.7%)	0.786
Previous CABG	1 (0.5%)	1 (1.2%)	0.487
Previous MI	4 (1.9%)	1 (1.2%)	1.000
Clinical diagnosis			0.031
Stable angina	134 (62.3%)	41 (48.2%)	0.026
Unstable angina	73 (34.0%)	36 (42.4%)	0.173
Acute MI	8 (3.7%)	8 (9.4%)	0.082
Left ventricular ejection fraction, %	61.1±6.6	59.5±7.4	0.089

Multivessel disease	111 (51.6%)	54 (55.0%)	0.062

Abbreviations: PCI, percutaneous coronary intervention; CABG, coronary artery bypass surgery; MI, myocardial infarction.

Table 2. Angiographic Characteristics and Procedural Results

Variable	Follow-Up Angiography (+) (N=215)	Follow-Up Angiography (-) (N=85)	*P*
Target vessel			0.582
Left anterior descending artery	130 (60.5%)	50 (58.8)	
Left circumflex artery	35 (16.3%)	11 (12.9%)	
Right coronary artery	50 (23.3%)	24 (28.2%)	
Procedure-related non-Q MI	14 (6.5%)	7 (8.2%)	0.598
Maximal inflation pressure, atm	13.3±3.8	13.3±4.0	0.940
Use of intravascular ultrasound	173 (80.5%)	63 (74.1%)	0.277
Use of glycoprotein IIb/IIIa inhibitor	6 (2.8%)	3 (3.5%)	0.735
Predilation before stenting	193 (89.8%)	76 (89.4%)	0.927
Post-stenting adjunctive balloon dilatation	148 (69.2%)	67 (78.8%)	0.094
Largest balloon size for adjunctive dilatation, mm	3.53±0.44	3.53±0.50	0.930
Multivessel stenting	68 (31.6%)	19 (22.4%)	0.111
Number of used stents at the target lesion	1.3±0.5	1.3±0.6	0.584

Abbreviations: MI, myocardial infarction.