Randomized Prospective Comparison of Everolimus-Eluting vs. Sirolimus-Eluting Stents in Patients Undergoing Percutaneous Coronary Intervention

— 3-Year Clinical Outcomes of the EXCELLENT Randomized Trial —

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Background: Everolimus-eluting stents (EES) have equivalent short-term angiographic and clinical outcomes to sirolimus-eluting stents (SES), but EES may be superior to SES with regard to long-term clinical safety. We report the 3-year clinical outcomes of EES and SES from the prospective EXCELLENT Randomized Trial (NCT00698607).

Methods and Results: We randomly assigned 1,443 patients undergoing percutaneous coronary intervention 3:1 to receive EES and SES, respectively. We investigated endpoints including target lesion failure (TLF) and individual clinical outcomes including stent thrombosis (ST) at 3 years. For EES and SES, the TLF rate was 4.82% and 4.12% (risk ratio [RR], 1.16, 95% CI: 0.65–2.06, $P=0.62$), respectively. Results were similar in other efficacy endpoints including target lesion revascularization. For safety endpoints, rate of all-cause death was significantly lower for EES (1.67%) than SES (3.57%; RR, 0.46; 95% CI: 0.23–0.94, $P=0.03$), while the incidence of cardiac death or myocardial infarction was numerically lower in EES. On 1-year landmark analysis, rates of all-cause death and major adverse cardiovascular events were significantly lower for EES than SES. Definite or probable ST was numerically 3-fold higher for SES (1.37%) compared with EES (0.46%).

Conclusions: EES and SES had similar efficacy with regard to 3-year outcomes in the EXCELLENT trial, while delayed safety events all trended to favor EES.

Key Words: Everolimus; Percutaneous coronary intervention; Sirolimus; Stent

Drug-eluting stents (DES) have revolutionized the field of percutaneous coronary intervention (PCI).^{1,2} First-generation DES, however, such as paclitaxel- or sirolimus-eluting stents (SES), have potential long-term problems such as delayed healing, leading to risk of very late stent thrombosis (ST).^{3–5} Second-generation DES with a thinner strut and biocompatible polymer coating, such as everolimus-eluting stents (EES), have possible long-term

Editorial p1497

advantages in safety compared with first-generation DES.^{6–8}

We previously reported the 1-year outcome of the Efficacy of Xience/promus vs. Cypher in rEDucing Late Loss after stenting (EXCELLENT) Trial, comparing SES with EES. We analyzed 9-month in-segment lumen loss as a

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primary endpoint and other clinical outcomes including target lesion failure (TLF), showing that EES was non-inferior compared with SES up to 1 year.⁹ In that report, although it did not reach statistical significance, safety endpoints such as cardiac death, myocardial infarction (MI) and ST had a tendency to favor EES.

We now report the long-term 3-year clinical outcomes of the EXCELLENT trial, focusing specifically on the delayed adverse events after 1 year.

Methods

Extended description of the study methods is presented in the **Supplementary File 1**.

Study Design, Subjects, and Procedures

The EXCELLENT trial was a prospective, randomized, multicenter trial that enrolled 1,443 patients between June 2008 and July 2009 in order to compare the efficacy of EES vs. SES in reducing late loss in patients undergoing PCI. The study design, eligibility or exclusion criteria, and the primary results including 1-year clinical outcomes have been reported previously.⁹ In brief, all patients were randomly assigned 3:1 to receive EES (Xience V; Abbott Vascular, Santa Clara, CA, USA; and Promus; Boston Scientific, Natick, MA, USA) or SES (Cypher Select; Cordis, Bridgewater, NJ, USA), respectively. 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. 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.

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 cross-over to another device at the discretion of the operator was permitted. Before the index procedure, all patients received ≥ 300 mg aspirin and a 300–600-mg loading dose of clopidogrel. After the procedure, all patients were maintained with aspirin (≥ 75 mg/day) indefinitely and clopidogrel (75 mg/day) for at least 6 months.

Follow-up and Data Collection

After the index PCI, clinical follow-up was performed at 1, 3, 9, 12, 24 and 36 months. For evaluation of the angiographic endpoints, all patients were recommended to undergo angiographic follow-up at 9 months. Patients were followed up by telephone contact or office visit. At follow-up, patients were specifically questioned regarding the occurrence of any adverse events or the presence of angina symptoms.

Study Endpoints

The 3-year clinical endpoints analyzed in this study included TLF (a composite of cardiac death, target-vessel MI, and ischemia-driven target lesion revascularization [TLR]), individual components of TLF, all-cause death, any MI, any repeat revascularization, ischemia-driven target vessel revascularization (TVR), and ST defined as definite or

probable according to the Academic Research Consortium (ARC) definitions.¹⁰ Other composite endpoints that focused on the safety were also analyzed, including patient-oriented composite outcome (a composite of all-cause death, any MI, and any repeat revascularization), death or MI, cardiac death or target-vessel MI, and major adverse cardiovascular events (MACE; a composite of all-cause death, any MI, and definite or probable ST). Data were managed by an independent management center (Medical Research Collaborating Center, Seoul National University Hospital, Seoul, Korea), and all clinical events were adjudicated by an independent adjudication committee.

Statistical Analysis

Baseline data are presented as frequencies or mean $\pm$ SD. Categorical variables were compared using the chi-squared or Fischer's exact tests, while continuous variables were compared using Student's t-test. The event-free survival rates were analyzed using the Kaplan-Meier method, and the comparison of clinical outcomes between EES and SES was performed with the log-rank test. Analysis of independent predictors for TLF and death or MI was performed using a multivariable Cox proportional hazard regression model. The covariates were selected if they were significantly different between the 2 groups ($P < 0.1$), or if they had predictive value. Covariates included in the model predicting TLF were stent type (EES or SES), age increase per 10 years, hypertension, diabetes mellitus, previous history of stroke, current smoker, congestive heart failure, long lesion (≥ 28 mm), multivessel stenting, and bifurcation treated by 2 stents. Covariates included in the model predicting death or MI were stent type, age increase per 10 years, hypertension, diabetes mellitus, peripheral vascular disease, congestive heart failure, previous PCI, previous MI, chronic kidney disease, and multivessel disease. C-statistics with 95% CI were calculated to validate the discriminant function of the model. For subgroup analyses, comparisons for the efficacy endpoint (TLF) and safety endpoint (death or MI) between EES and SES according to the pre-specified subgroups

	Total (n=1,443)	EES (n=1,079)	SES (n=364)	P-value
Demographic features				
Age (years)	62.7±10.0	62.5±10.1	63.4±9.9	0.12
Men	931 (64.5)	703 (65.2)	228 (62.6)	0.39
BMI (kg/m ²)	25.0±3.1	25.0±3.1	25.0±2.9	0.89
Cardiovascular risk factors				
Hypertension	1,057 (73.3)	791 (73.3)	266 (73.1)	0.93
Diabetes mellitus	550 (38.1)	402 (37.3)	148 (40.7)	0.25
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
Previous MI	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 CABG	18 (1.2)	12 (1.1)	6 (1.6)	0.42
Previous CVA	95 (6.6)	58 (5.4)	37 (10.2)	<0.01
PAD	19 (1.3)	13 (1.2)	6 (1.6)	0.59
Multivessel disease	750 (52.0)	564 (52.3)	186 (51.1)	0.70
LVEF (%)	61.3±9.5	61.4±9.4	60.8±9.8	0.33
Clinical indication of PCI				0.12
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)	
Silent ischemia	55 (3.8)	39 (3.6)	16 (4.4)	
Medication 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
ACEI	467 (32.8)	352 (33)	115 (32.5)	0.87
ARB	475 (33.4)	355 (33.2)	120 (33.9)	0.82
β-blocker	872 (61.3)	660 (61.8)	212 (59.9)	0.52
CCB	487 (34.2)	360 (33.7)	127 (35.9)	0.46

Data given as mean±SD or n (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CCB, calcium channel blocker; CHF, congestive heart failure; CVA, cerebrovascular accident; EES, everolimus-eluting stent; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non ST-segment elevation myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SES, sirolimus-eluting stent; STEMI, ST-segment elevation myocardial infarction.

were followed, and interaction between the treatment and each subgroup was assessed with Cox proportional hazard models. All clinical outcomes were analyzed on an intention-to-treat basis. Patients treated with SES were defined as the reference group. All probability values were 2-sided, and $P<0.05$ was considered statistically significant. Analyses were performed using SPSS version 19.0 for Windows (SPSS, Chicago, IL, USA).

Results

Baseline Characteristics

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**). The median follow-up duration was 1,095 days, and 1,368 patients (94.8%) completed a 3-year follow-up; 1,021 of 1,079 (94.6%) in the EES group and 347 of 364 (95.3%) in the SES group. Baseline patient, lesion, and procedural characteristics are listed in **Tables 1,2**. Most baseline characteristics were similar between the EES and SES

groups except for the history of cerebrovascular accident, number of implanted stents per patient, and final balloon pressure.

Three-Year Clinical Outcomes

The cumulative 3-year clinical outcomes are listed in **Table 3**. The incidence of TLF was 4.82% for EES and 4.12% for SES, which was not significantly different (risk ratio [RR], 1.16; 95% CI: 0.65–2.06, $P=0.62$; **Figure 2**). Rates of ischemia-driven TVR (RR, 1.27; 95% CI: 0.66–2.47, $P=0.48$) and TLR (RR, 1.41; 95% CI: 0.65–3.05, $P=0.38$) also showed similar trends. In a landmark analysis from 1 year, the occurrence of TLF from 1 to 3 years was similar (RR, 1.01; 95% CI: 0.33–3.15, $P=0.98$), and the efficacy outcomes including TVR and TLR were similar (**Table S1**).

For safety endpoints, the differences between the 2 groups were more prominent. The rate of all-cause death was significantly lower in EES (1.67%) than in SES (3.57%; RR, 0.46; 95% CI: 0.23–0.94, $P=0.03$; **Figure 3**). The incidence of death or MI, MACE, cardiac death, and target-

Table 2. Baseline Lesion and Procedural Characteristics

	Total (n=1,927)	EES (n=1,459)	SES (n=468)	P-value†
Before index procedure				
Location of target lesion				0.79
LAD	956 (49.8)	721 (49.6)	235 (50.4)	
LCX	421 (21.9)	320 (22.0)	101 (21.7)	
RCA	542 (28.2)	412 (28.3)	130 (27.9)	
Coronary graft	1 (0.1)	1 (0.1)	0 (0.0)	
ACC/AHA B2 or C type	991 (53.3)	746 (53.0)	245 (54.2)	0.62
Total occlusion	66 (3.5)	48 (3.4)	18 (4.0)	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
MLD (mm)	0.87±0.48	0.87±0.48	0.88±0.50	0.68
RVD (mm)	2.88±0.50	2.87±0.49	2.88±0.52	0.65
Diameter stenosis (%)	69.7±15.3	69.7±15.3	69.6±15.4	0.94
Lesion length (mm)	20.4±11.9	20.3±12.1	20.5±11.5	0.80
After index procedure				
No. stents per lesion	1.21±0.46	1.21±0.47	1.19±0.42	0.26
No. stents per patient	1.61±0.95	1.64±0.97	1.53±0.86	0.04§
Total stent length/lesion (mm)	28.1±13.4	27.9±13.5	28.5±13.2	0.43
Total stent length/patient (mm)	37.5±25.0	37.8±25.1	36.8±24.7	0.50§
Glycoprotein IIb/IIIa inhibitors	24 (1.7)	19 (1.8)	5 (1.4)	0.62†
Final balloon pressure (atm)	14.3±3.63	14.1±3.57	15.0±3.72	<0.01
IVUS	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

Data given as mean±SD or n (%). †Calculated using generalized estimating equations except for per-patient comparisons, which were calculated using ‡chi-squared test or §Student t-test. ACC/AHA, American College of Cardiology/American Heart Association; IVUS, intravascular ultrasound; LAD, left anterior descending artery; LCX, left circumflex artery; MLD, minimum lumen diameter; RCA, right coronary artery; RVD, reference vessel diameter. Other abbreviations as in Table 1.

Table 3. Clinical Outcomes at 3 Years in the Intention-to-Treat Population

	Total (n=1,443)	EES (n=1,079)	SES (n=364)	RR (95% CI)†	P-value
All-cause death	2.15 (31)	1.67 (18)	3.57 (13)	0.46 (0.23–0.94)	0.03
Cardiac death	0.76 (11)	0.56 (6)	1.37 (5)	0.40 (0.12–1.31)	0.13
Non-cardiac death	1.39 (20)	1.11 (12)	2.20 (8)	0.50 (0.20–1.22)	0.13
Any MI	1.80 (26)	1.67 (18)	2.20 (8)	0.75 (0.33–1.73)	0.50
Target-vessel MI	1.59 (23)	1.39 (15)	2.20 (8)	0.63 (0.27–1.48)	0.29
MI due to ST	0.49 (7)	0.28 (3)	1.10 (4)	0.25 (0.06–1.11)	0.07
Any repeat revascularization	7.69 (111)	7.88 (85)	7.14 (26)	1.09 (0.70–1.68)	0.72
Ischemia-driven TVR	3.67 (53)	3.89 (42)	3.02 (11)	1.27 (0.66–2.47)	0.48
Ischemia-driven TLR	2.91 (42)	3.15 (34)	2.20 (8)	1.41 (0.65–3.05)	0.38
Definite ST	0.55 (8)	0.37 (4)	1.10 (4)	0.33 (0.08–1.33)	0.12
Definite or probable ST	0.69 (10)	0.46 (5)	1.37 (5)	0.33 (0.10–1.15)	0.08
Cerebrovascular accident	0.97 (14)	0.83 (9)	1.37 (5)	0.60 (0.20–1.78)	0.35
TIMI major bleeding	0.83 (12)	0.83 (9)	0.82 (3)	1.02 (0.28–3.77)	0.98
Target lesion failure‡	4.64 (67)	4.82 (52)	4.12 (15)	1.16 (0.65–2.06)	0.62
Patient-oriented composite outcome§	10.67 (154)	10.47 (113)	11.26 (41)	0.92 (0.64–1.31)	0.64
Death or MI	3.74 (54)	3.24 (35)	5.22 (19)	0.62 (0.35–1.07)	0.09
Cardiac death or target-vessel MI	2.22 (32)	1.95 (21)	3.02 (11)	0.64 (0.31–1.32)	0.23
MACE¶	3.95 (57)	3.43 (37)	5.49 (20)	0.62 (0.36–1.06)	0.08

Data given as % (n). †Risk ratios were calculated using Cox regression modeling with the SES group as a reference. Median follow-up duration was 1,095 days. ‡Composite of cardiac death, target-vessel MI, and ischemia-driven TLR. §Composite of all-cause death, any MI, and any repeat revascularization. ¶Composite of all-cause death, any MI, and definite or probable ST. MACE, major adverse cardiovascular event; RR, risk ratio; ST, stent thrombosis; TIMI, Thrombolysis in Myocardial Infarction; TLR, target lesion revascularization; TVR, target vessel revascularization. Other abbreviations as in Table 1.

Figure 2. Kaplan-Meier (A,C) cumulative event curves up to 3 years and (B,D) 1-year landmark analysis of (A,B) target lesion failure (TLF) and (C,D) death or myocardial infarction (MI) for everolimus-eluting stent (EES) vs. sirolimus-eluting stent (SES).

vessel MI were numerically lower in the EES group than in the SES group, although this did not reach statistical significance. From 1 to 3 years, however, rates of death or MI, MACE, and all-cause death were significantly lower in the EES group. Although non-significant, the rates of cardiac death or target-vessel MI were also lower in EES, with 3–4-fold numerical difference.

Rates of definite or probable ST at 3 years was 0.46% vs. 1.37% for EES vs. SES (RR, 0.33; 95% CI: 0.10–1.15, $P=0.08$). Very late ST was rare but its rate was numerically higher in the SES group (0.09% vs. 0.55% for EES vs. SES, $P=0.14$). MI due to ST also showed a trend favoring EES over SES (RR, 0.25; 95% CI: 0.06–1.11, $P=0.07$). One case of very late ST from EES presented as MI but the patient completely recovered. Both patients with very late ST in SES, however, died due to cardiac cause (Figure 4).

Dual antiplatelet therapy was maintained in 55.0%, 17.3%, and 12.1% at 1, 2, and 3 years, respectively. The mean duration of dual antiplatelet therapy was not different between the 2 groups (Table S2).

Independent Predictors of Efficacy and Safety Endpoints

A multivariable Cox regression model was used to identify independent predictors of TLF and death or MI (Table 4). For both the efficacy and safety endpoints, congestive heart

failure (TLF: adjusted RR, 10.29; 95% CI: 3.212–32.97, $P<0.001$; death or MI: adjusted RR, 7.459; 95% CI: 2.246–24.77, $P=0.001$) was the strongest predictor outcome. Use of SES (EES as a reference group) had no effect on the occurrence of TLF, but marginally increased the risk of death or MI (adjusted RR, 1.601; 95% CI: 0.900–2.847, $P=0.109$) without statistical significance.

Subgroup Analysis

For the efficacy endpoint of TLF and safety endpoint of death or MI, subgroup analyses were performed for diabetes, renal dysfunction with estimated creatinine clearance <60 mL/min, acute MI, multivessel stenting, long lesion, and reference vessel diameter <2.75 mm. The results of efficacy and safety outcomes between EES and SES were consistent across all subgroups, with no significant interaction P -values (Figure S1).

Discussion

Three-year outcomes from the randomized, prospective EXCELLENT trial showed that the cumulative rates of TLF was low in both the EES and SES groups, and the clinical efficacy of both stents represented by ischemia-driven TLR or TVR was similar. As for safety outcomes,

Figure 3. Kaplan-Meier cumulative event curves up to 3 years for (A) all-cause death, (B) cardiac death, (C) target-vessel myocardial infarction (MI), and (D) ischemia-driven target lesion revascularization (TLR) for everolimus-eluting stent (EES) vs. sirolimus-eluting stent (SES).

cardiac death and target-vessel MI were numerically lower in EES than in SES, although not statistically significant. Despite the lack of sufficient power to validate differences in clinical outcomes, rates of all-cause death at 3 years and death or MI and MACE at 1–3 years were significantly lower in the EES group. Definite or probable ST and very late ST also favored the EES group, and had a 2–3-fold numerical difference without statistical significance, suggesting that although efficacy outcomes are similar between EES and SES, EES may have superior long-term safety outcomes.

Among the first-generation DES, SES was the most widely used stent and had the best outcomes.^{11,12} Therefore, although SES is no longer used in routine clinical practice, it is still the standard against which second-generation DES should be judged. In comparing the performance of SES and EES, the head-to-head randomized trials in all-comer populations reported to date have shown similar efficacy and safety. The possibility of delayed adverse events particularly in SES has been raised, but the results are controversial.

In this study, the efficacy outcomes including TLF were equivalent in the EES and SES groups, and similar results were obtained in the 5-year results of the ISAR-TEST 4

Figure 4. Kaplan-Meier cumulative event curves up to 3 years for definite or probable stent thrombosis (ST): everolimus-eluting stent (EES) vs. sirolimus-eluting stent (SES).

Table 4. Independent Predictors of Efficacy and Safety Composite Endpoints at 3 Years†

	Adjusted risk ratio	95% CI	P-value
Predictors of TLF‡			
Congestive heart failure	10.29	3.212–32.97	<0.001
Multivessel stenting	1.960	1.171–3.281	0.010
Bifurcation treated by 2 stents	1.776	1.135–2.778	0.012
SES use (EES as a reference)	0.950	0.528–1.711	0.865
Predictors of death or MI			
Congestive heart failure	7.459	2.246–24.77	0.001
Diabetes mellitus	2.582	1.490–4.475	0.001
Age increase per 10 years	1.777	1.341–2.355	<0.001
SES use (EES as a reference)	1.601	0.900–2.847	0.109

†Multivariable Cox proportional hazard regression modeling. Harrel's c-index was 0.675 (95% CI: 0.612–0.739) for TLF, and 0.628 (95% CI: 0.566–0.690) for death or MI. ‡Composite of cardiac death, target-vessel MI, and ischemia-driven TLR. TLF, target lesion failure. Other abbreviations as in Tables 1,3.

trial.¹³ In RESET and SORT OUT IV trials, long-term efficacy has been shown to slightly favor EES.^{14,15} Although the present results support the excellent long-term efficacy of SES and its similarity to that of EES, it should be noted that the 3:1 randomization protocol may have led to underestimation of event rate in the SES group because the number of patients in the SES group was low. Furthermore, the patients were in general at lower risk compared with other trials, and therefore, the proportion of complex lesions was also low. The well-known advantages of EES and its superior efficacy in high-risk patients and complex lesions may not have been evident in the present study. Finally, we cannot completely rule out the possibility of undetected repeat revascularization events in those lost to follow-up.

For safety endpoints such as cardiac death, target-vessel MI and ST, the results were numerically favorable for EES rather than SES, although not statistically significant. In most of the previous trials, the long-term safety outcomes were consistent with the present study. In ISAR-TEST 4 the rates of cardiac death, target-vessel MI, and ST were numerically lower in the EES group.¹³ In SORT OUT IV, marginally lower target-vessel MI and significantly lower definite or probable ST, very late ST, and MACE rates were observed in the EES group.¹⁵ In contrast, in the RESET trial all safety outcomes including even ST were equivalent in EES and SES. More than two-thirds of patients, however, had maintained dual antiplatelet therapy up to 3 years, and the rate of intravascular ultrasound (IVUS)-guided PCI was high in the RESET trial.¹⁴ Notably, in the present study, incidence of all-cause death was significantly lower in EES at both 3-year and 1-year landmark analysis. In addition to cardiac death, EES has shown favorable results in non-cardiac deaths as well, resulting in the significant difference in all-cause death. Considering, however, the relatively small number of patients in the SES group due to 3:1 randomization, this difference may have occurred by chance and should be interpreted with caution.

In the present study, major clinical outcomes including efficacy and safety endpoints were overall lower than in other randomized trials, but there may be several reasons for these differences. First, clinical event rates in interventional clinical trials are in general lower in trials performed in East Asian patients. Furthermore, in this trial, the proportion of high-risk patients was significantly lower compared with other randomized trials. In particular, the

proportion of patients with a history of previous MI, previous PCI or bypass surgery, or those presenting with ST-elevation MI was significantly lower. This may have had a great impact on the lower rates of mortality, MI, or repeat revascularization in this study. Second, the present 3-year follow-up rate was 94.6%, which was slightly lower than in other trials. This can raise the possibility of under-reporting. The present adverse event data, however, were systematically collected and managed by an independent institution (Medical Research Collaborating Center, Seoul National University Hospital, Seoul, Korea), and follow-up of the patients who did not visit the hospital was rigorously done at each center via direct telephone contact. In addition, using the unique personal identification numbers of the Korean nationwide health-care system, the vital status of 100% of patients was cross-checked and fully confirmed even in patients who were lost to follow-up. In this way, the possibility of under-reporting of bias was minimized.

The 3-year rate of definite or probable ST in EES was 0.5% in this study, and 0.7%, 0.7%, and 1.4% in RESET,¹⁴ SORT OUT IV,¹⁵ and ISAR-TEST 4,¹³ respectively. In addition to the extremely low incidence of ST, most ST events occurred within 1 year in all trials. This suggests excellent long-term safety even after 1 year in EES, and is consistent with the 5-year outcome noted in the SPIRIT III trial.¹⁶ In contrast, the incidence of ST in SES was numerically 3–4-fold higher than that in EES, and the rate of very late ST was also high. These results were also confirmed in the long-term LEADERS and PROTECT studies comparing SES with biolimus-eluting or zotarolimus-eluting stents.^{17–19}

Although this study was not powered to show differences in clinical outcome, these consistent trends across many safety outcome measures, along with the data from numerous randomized trials, suggest that EES may have safety benefit over SES in the long term, and that the safety concern of SES is mostly driven by late thrombotic events. Similar results have been suggested in a large prospective cohort study.²⁰ It is also consistent with a recent network meta-analysis indicating that EES has lower long-term mortality, MI, and ST rate than first-generation DES or even bare metal stents.⁸

There may be several factors that may explain the differences between the 2 stent platforms. First, the nature of the polymer is different. EES (Xience/Promus) is a fluorinated

co-polymer-based stent composed of vinylidene fluoride and hexafluoropropylene, which has biocompatible and thromboresistant properties.^{21,22} Reduced inflammation and absence of hypersensitivity vasculitis was also observed in this biocompatible polymer-based stent.²³ In contrast, SES has a polymer composed of poly n-butyl methacrylate and polyethylene vinyl acetate, which had a stronger inflammatory response up to 1 year in preclinical studies, compared with EES.²⁴ Second, the stent design is different. Several preclinical studies have shown that thinner stent struts have less flow disturbance, greater endothelial cell coverage, and less thrombogenicity.^{22,23} The thicker strut thickness in SES (SES, 140 μm ; EES, 81 μm) could also result in delayed endothelialization, inflammation, and late adverse events. Moreover, in the rheologic study, the higher number of link connectors in SES (SES, 6 links; EES, 3 links) increased areas of low wall shear stress in the stent, which could further accelerate thrombus formation and neointimal proliferation.²⁵ Third, the anti-proliferative drug is different. Sirolimus has been known to inhibit smooth muscle cell proliferation more strongly than everolimus,²⁶ which explains the excellent efficacy of SES seen in this study. The drug load in EES, however, is more optimal than SES (EES, 88 μg ; SES, 150 μg), and has better release kinetics. Considering that the effect of cytotoxic drugs on fibrin deposition was dose dependent in in vivo studies,²⁷ the more frequent thrombotic events in SES may also be influenced by the amount and pharmacokinetics of coated drugs. This may be the reason why in the RESET optical coherence tomography substudy, stent struts not covered by neointima, malapposed struts, and intra-stent thrombi were more frequently observed in SES than in EES.²⁸ Further, on pathology analysis after implantation of EES and first-generation DES, inflammation, fibrin deposition, and late thrombosis were also more frequent in the SES than in the EES group.²³

Delayed arterial healing in SES seems to be associated with the development of late thrombotic events, increasing the rates of MI and even mortality. EES, in contrast, had favorable long-term efficacy and safety, and has shown the best performance among the stents used in current practice. Thus, EES should be the most important comparator in the development process after the second-generation DES era. In addition, efforts to improve late safety concerns (e.g., thinner struts, a more biocompatible polymer system, and more stabilized anti-proliferative drug control) while maintaining current efficacy would be important. Considering the RESET trial results, further studies are also warranted to determine the effect of procedural optimization, such as prolonged dual antiplatelet therapy and IVUS-guided PCI in selected patients, on long-term safety outcomes.

Study Limitations

This study was not powered to show differences in clinical outcomes. Thus, any positive findings or numerical differences observed in this study are hypothesis generating at best, and should be interpreted in the context of other trials of second-generation DES. In particular, because of the 3:1 randomization design, we need to be especially careful in interpretation of the SES group data. At the time of the study design, we wanted to obtain more data from the newly released EES. This led to the excessive dependence of the cumulative rate on the number of each events, especially for the SES group, making it difficult to interpret the comparative results. The possibility of underreporting

cannot be completely ruled out, but as mentioned previously, rigorous efforts were undertaken to minimize possible biases. Given, however, that this is one of the major head-to-head randomized trials in all-comers, the present 3-year outcomes could add important evidence, especially for the safety issue beyond 1 year after stent implantation.

Conclusions

At 3-year follow-up, efficacy endpoints including TLF were similar between EES and SES. EES showed a trend toward better safety profile, with the rate of cardiac death, target-vessel MI, and ST numerically lower than for SES. This effect was mainly driven by the lower risk of late thrombotic events beyond 1 year in EES. Due to the 3:1 randomization protocol, however, the difference in hard outcomes including all-cause death was possibly a chance finding, and should be interpreted with caution.

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Disclosures

The authors declare no conflicts of interest.

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Supplementary Files

Supplementary File 1

Supplementary Methods

Figure S1. Subgroup analysis of efficacy and safety outcomes.

Table S1. One-year landmark analyses of clinical outcomes in the intention-to-treat population

Table S2. DAPT status at 3 years

Please find supplementary file(s);
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