

Outcomes After Unrestricted Use of Everolimus-Eluting and Sirolimus-Eluting Stents in Routine Clinical Practice

A Multicenter, Prospective Cohort Study

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Background—It remains unclear whether there are differences in the safety and efficacy outcomes between everolimus-eluting stents (EES) and sirolimus-eluting stents (SES) in contemporary practice.

Methods and Results—We prospectively enrolled 6166 consecutive patients who received EES (3081 patients) and SES (3085 patients) between April 2008 and June 2010, using data from the Interventional Cardiology Research In-Cooperation Society-Drug-Eluting Stents Registry. The primary end point was a composite of death, nonfatal myocardial infarction (MI), or target-vessel revascularization (TVR). At 2 years of follow-up, the 2 study groups did not differ significantly in crude risk of the primary end point (12.1% for EES versus 12.4% for SES; HR, 0.97; 95% CI, 0.84–1.12, $P=0.66$). After adjustment for differences in baseline risk factors, the adjusted risk for the primary end point remained similar for the 2 stent types (HR, 0.96; 95% CI, 0.82–1.12, $P=0.60$). There were also no differences between the stent groups in the adjusted risks of the individual component of death (HR, 0.93; 95% CI, 0.67–1.30, $P=0.68$), MI (HR, 0.97; 95% CI, 0.79–1.18, $P=0.74$), and TVR (HR, 1.10; 95% CI, 0.82–1.49, $P=0.51$). The adjusted risk of stent thrombosis also was similar (HR, 1.16; 95% CI, 0.47–2.84, $P=0.75$).

Conclusions—In contemporary practice of percutaneous coronary intervention procedures, the unrestricted use of EES and SES showed similar rates of safety and efficacy outcomes with regard to death, MI, stent thrombosis, and TVR. Future longer-term follow-up is needed to better define the relative benefits of these drug-eluting stents.

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First generation drug-eluting stents (DES) releasing sirolimus or paclitaxel have been shown to reduce the risk of restenosis and repeat revascularization after percutaneous coronary intervention (PCI), as compared with bare-metal stents.¹ However, these DES also have been associated with a risk of late stent thrombosis, likely due to chronic inflammation and delayed healing of the arterial wall, which in turn may be associated with cardiac death or myocardial infarction (MI).^{2,3}

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To improve the efficacy and safety profiles of early generation DES, a newer generation everolimus-eluting stent (EES) has been developed and widely used in clinical practice.⁴ In the large clinical trials comparing EES with paclitaxel-eluting stent (PES), EES demonstrated remarkable clinical benefit over PES.^{5,6} By contrast, given that sirolimus was more effective as a site specific agent than paclitaxel for reducing neointimal growth,^{7,8} differential treatment effect of EES versus sirolimus-eluting stent (SES) is expected. Recent randomized trials suggested similar 1 year clinical outcomes between EES and SES.⁹ However, neither study was adequately powered to evaluate the relative clinical safety and efficacy in all types of patients, including those with more complex clinical and anatomic subsets and in acute settings, in which adverse events would be more pronounced.¹⁰

The purpose of this study, therefore, compared the safety and efficacy of the second generation EES and the first generation SES in an unrestricted, multicenter, prospective cohort of patients undergoing PCI in everyday clinical practice, as recorded in the IRIS-DES (the Interventional Cardiology Research In-Cooperation Society-Drug-Eluting Stents) registry.

Methods

Study Design and Population

The IRIS-DES registry involves a prospective, multicenter recruitment of consecutive consenting patients undergoing PCI with DES from 46 academic and community hospitals in Korea between April 1, 2008, and June 30, 2010, and for whom complete follow-up data were available for at least 1 year and up to 3 years. During the enrollment period, DES has been used as the default device of PCI.¹¹

This registry consists of several different DES arms of first generation and newer generation devices recruited in contemporary PCI situations. The current analysis includes patients concurrently treated with EES (Xience V, Abbott Vascular) or SES (Cypher Select, Cordis, Johnson & Johnson). In our study, the major reason for the selection of EES or SES was the physician or patient choice and some variation in acceptance of the indications for the devices among the hospitals and geographic regions. Exclusion criteria are minimal: patients with cardiogenic shock, malignant disease, or other comorbid conditions with life expectancy less than 12 months, those treated with a mixture of different types of DES, and those with planned surgery necessitating interruption of antiplatelet drugs within 6 months after the procedure were excluded for the study. The study and the statistical analysis were designed and interpreted by the authors, all of whom contributed to the final report and participated in the decision to submit the findings for publication. No stent manufacturer had any role in the study.

The study protocol was approved by the ethics committee at each participating center and all patients provided written, informed consent for participation in this study.

WHAT IS KNOWN

- First generation drug-eluting stents (DES; ie, sirolimus-eluting [SES] and paclitaxel-eluting stents) have been associated with a risk of late stent thrombosis, likely due to chronic inflammation and delayed vascular healing.
- Newer generation DES, such as everolimus-eluting stent (EES), may not have these limitations.
- Clinical trials suggested similar 1 year clinical outcomes between EES and SES; however, limited data are available in unselected patients treated in clinical practice.

WHAT THE STUDY ADDS

- This prospective, large-scale, observational study showed that the unrestricted use of EES and SES showed similar rates of safety and efficacy outcomes with regard to death, myocardial infarction, stent thrombosis, and repeat revascularization in contemporary practice.
- Very long-term clinical follow-up is mandatory to provide a critical appraisal of relative safety and to confirm the long term durability of EES as compared with SES.

Procedures and Follow-Up

Both treatment groups were studied concurrently. All interventions were performed according to current practice guidelines for PCI. The operator was responsible for the decision to choose a specific treatment strategy. The registry did not specify PCI treatment protocols. Before or during the procedure, all patients received at least 200 mg of 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 or longer. Administration of glycoprotein IIb/IIIa inhibitors was at the discretion of the operator. After the intervention, all patients were prescribed 100 to 200 mg/d aspirin indefinitely and clopidogrel 75 mg/d for at least 12 months, irrespective of specific DES type. The protocols of the dual antiplatelet therapy were identical for patients treated with EES and SES. Treatment beyond this duration was at the discretion of the physician.

Baseline demographics, clinical and angiographic features, and procedural and outcome events were assessed. Clinical follow-up was conducted during hospitalization and at 30 days, 6 months, 12 months, and every 6 months thereafter. At these visits, data pertaining to patients' clinical status, all interventions, and outcome events were recorded. The follow-up period extended through July 31, 2011, to ensure that all patients had an opportunity for at least 12 months of follow-up information.

All of the baseline characteristics and outcome data were collected using a dedicated, electronic case report form by specialized personnel at each center who were unaware of treatment assignments. The Internet based system provides each center with immediate and continuous feedback on processes and quality of care measures. Monitoring and verification of registry data have been periodically performed in participating hospitals by members of the academic coordinating center (Clinical Research Center, Asan Medical Center, Seoul, Korea). All outcomes of interest were confirmed by source documentation collected at each hospital and were centrally adjudicated by an independent clinical events committee, whose members were blinded as to study devices.

Study End Points and Definitions

The primary end point of the study was the composite of death, nonfatal MI, or target-vessel revascularization (TVR). Secondary

clinical end points were individual component of the primary end point, a composite of death or MI, repeat revascularization, stent thrombosis, stroke, and bleeding (all-type and major).

Death was defined as death from any cause. The diagnosis of MI was based on the universal definition of MI.¹² Procedure related MI was defined as the presence of new Q waves or an elevation of creatine kinase-myocardial band isoenzyme or troponin I concentration >3 times the normal upper limit. Spontaneous MI was defined as any creatine kinase-myocardial band isoenzyme or troponin increase above the upper range limit with or without the development of Q waves on ECG. Stent thrombosis was defined according to the Academic Research Consortium definitions,¹³ and the definite and definite/probable occurrences of a thrombotic event were regarded as the secondary end point. Stroke, as detected by the occurrence of a new neurological deficit, was confirmed by a neurologist and on imaging. Repeat revascularization was defined as any percutaneous or surgical revascularization procedure, and categorized as revascularization of any lesion, target lesion, and target vessel. Bleeding events were defined according to the thrombolysis in myocardial infarction definition.¹⁴

Statistical Analysis

We anticipated an incidence of the primary end point of 12% in patients receiving EES and 15% in patients receiving SES in unrestricted clinical practice assumed on previous available data.^{5,6,15,16} A total sample of 6000 observations (3000 patients per group) was computed to achieve 90% power at a 2-sided 0.05 significance level to detect a significant difference of primary outcome, expecting that 5% of the patients would not return for clinical follow-up.

Differences between treatment groups were evaluated by Student *t* test for continuous variables and by the χ^2 or Fisher exact test for categorical variables. Cumulative event curves were constructed using Kaplan-Meier estimates and compared with the log-rank test. Unadjusted (observed) outcomes between the stent groups were compared with the use of the Cox proportional-hazards models. Then, to reduce the impact of treatment selection bias and potential confounding in an observational study, we performed rigorous adjustment for differences in baseline characteristics of patients by use of the weighted Cox proportional-hazards regression models with the inverse probability of treatment weighting (IPTW).¹⁷ With that technique, the weights for patients undergoing SES were the inverse of 1 propensity score, and weights for patients receiving EES were the inverse of the propensity score. The propensity scores were estimated without regard to outcomes, using multiple logistic-regression analysis. All the variables listed in Table 1 were included in this model, along with significant interactions. Model discrimination was assessed with *c*-statistics, and model calibration was assessed with Hosmer-Lemeshow statistics.

All reported probability values are 2-sided, and probability values of less than 0.05 were considered statistically significant. SAS software, version 9.1, and the R programming language were used for statistical analyses.

Results

Characteristics of the Study Patients

During 2008 and 2010, a total of 6166 patients were treated with EES (n=3081) or SES (n=3085) and were entered into the database. Table 1 shows the baseline clinical, lesion, and procedural characteristics of the study population. On average, as compared with patients who received SES, patients with EES had a lower prevalence of diabetes mellitus, hyperlipidemia, previous PCI, previous MI, and family history of coronary artery disease, and stable angina was less

Table 1. Baseline Characteristics of Patients

Characteristics	Everolimus-Eluting Stent (3081 Patients)	Sirolimus-Eluting Stent (3085 Patients)	P Value
Demographics			
Age, y	63.7±10.8	63.5±10.8	0.35
Male sex	2079 (67.5)	2052 (66.5)	0.42
Cardiac or coexisting condition, no. (%)			
Diabetes mellitus	1028 (33.4)	1121 (36.3)	0.01
Hypertension	1924 (62.4)	1923 (62.3)	0.93
Hyperlipidemia	1159 (37.6)	1238 (40.1)	0.04
Current smoker	888 (28.8)	841 (27.3)	0.17
Previous PCI	453 (14.7)	582 (18.9)	<0.001
Previous CABG	62 (2.0)	81 (2.6)	0.11
Previous myocardial infarction	158 (5.1)	226 (7.3)	<0.001
Previous congestive heart failure	66 (2.1)	75 (2.4)	0.45
Family history of CAD	112 (3.6)	158 (5.1)	0.004
Renal failure	105 (3.4)	118 (3.8)	0.38
Cerebrovascular disease	250 (8.1)	219 (7.1)	0.13
Peripheral vascular disease	35 (1.1)	32 (1.0)	0.71
Chronic lung disease	92 (3.0)	82 (2.7)	0.44
Left ventricular ejection fraction, %	59.4±10.1	59.1±9.9	0.28
Clinical indication			
Stable angina	1266 (41.1)	1363 (44.2)	
Unstable angina	1069 (34.7)	1040 (33.7)	
NSTEMI	337 (10.9)	359 (11.6)	
STEMI	409 (13.3)	323 (10.5)	
Lesion and procedural characteristics, no. (%)			
Multivessel disease	1634 (53.0)	1614 (52.3)	0.57
Left main disease	290 (9.4)	154 (5.0)	<0.001
LAD disease	1907 (61.9)	2053 (66.5)	<0.001
Bifurcation disease	970 (31.5)	919 (29.8)	0.15
Total obstruction	477 (15.5)	430 (13.9)	0.09
Restenotic lesions	186 (6.0)	217 (7.0)	0.11
No. of lesions treated	1.4±0.7	1.4±0.7	0.15
No. of stents per patient	1.8±1.1	1.8±1.0	0.04
Stent length (mm)	41.6±29.9	45.4±27.9	<0.001
Stent diameter (mm)	3.2±0.4	3.1±0.3	<0.001

Data are shown as mean (SD) for continuous variables and absolute numbers (percentage) for dichotomous variables.

PCI indicates percutaneous coronary intervention; CABG, coronary-artery bypass grafting; CAD, coronary artery disease; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; LAD, left anterior descending artery.

likely to be the indication for the procedure. In the group with SES, more patients had undergone PCI for left anterior descending artery disease, and had longer total stent length and smaller mean stent diameter.

Table 2. Hazard Ratios for Clinical Outcomes After Everolimus-Eluting Stents Compared With After Sirolimus-Eluting Stents

Outcome	Patients at Risk At 2 Years		Cumulative Event Rate At 2 y (%)*		Unadjusted		Adjusted by IPTW	
	Everolimus-Eluting Stent (N=3081)	Sirolimus-Eluting Stent (N=3085)	Everolimus-Eluting Stent (N=3081)	Sirolimus-Eluting Stent (N=3085)	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Primary end point								
Death, MI, or target-vessel revascularization	579	566	12.1	12.4	0.97 (0.84–1.12)	0.66	0.96 (0.82–1.12)	0.60
Secondary end points								
Death	633	601	2.9	2.7	0.95 (0.69–1.32)	0.78	0.93 (0.67–1.30)	0.68
MI	604	572	6.8	6.9	0.98 (0.81–1.19)	0.86	0.97 (0.79–1.18)	0.74
Death or MI	604	572	9.4	9.4	0.97 (0.82–1.14)	0.69	0.94 (0.79–1.12)	0.49
Repeat revascularization								
Target-lesion	611	592	3.2	3.3	1.05 (0.78–1.41)	0.76	1.10 (0.80–1.51)	0.55
Target-vessel	607	592	3.6	3.8	1.05 (0.79–1.39)	0.75	1.10 (0.82–1.49)	0.51
Any	595	589	5.3	5.4	1.01 (0.80–1.28)	0.91	1.09 (0.85–1.39)	0.51
Stent thrombosis								
Definite	631	600	0.3	0.2	1.43 (0.55–3.76)	0.47	1.70 (0.64–4.53)	0.29
Definite or probable	631	600	0.3	0.4	0.99 (0.41–2.38)	0.98	1.16 (0.47–2.84)	0.75
Stroke	625	598	0.9	1.1	0.85 (0.51–1.42)	0.54	0.87 (0.51–1.48)	0.61
Bleeding								
Major	629	600	0.8	0.6	1.31 (0.72–2.39)	0.37	1.36 (0.73–2.53)	0.33
All	596	586	5.2	5.2	1.13 (0.90–1.42)	0.30	1.08 (0.85–1.38)	0.52

*Cumulative rates of events are based on Kaplan-Meier estimates.

IPTW indicates inverse probability of treatment weighting; MI, myocardial infarction.

Clinical Outcomes

By July 31, 2011, complete follow-up data for major clinical events were obtained in 6067 patients (98.4%) of the overall population (EES=98.5%, SES=98.3%). During the 1 to 3 years of follow-up (median, 1.3 years; interquartile range, 1.1–1.9), 710 events (11.5%) of primary end point occurred, including 146 deaths (2.4%), 422 MI (6.8%), and 195 TVR (3.2%). Twenty patients (0.3%) had a definite or probable stent thrombosis, 60 (1.0%) had a stroke, and 44 (0.7%) had major bleeding. Any repeat revascularization was performed in 284 patients (4.6%).

The Kaplan-Meier estimate of the event rate for the primary end point (death, nonfatal MI, or TVR) at 2 years was 12.1% in the EES group, as compared with 12.4% in the SES group (HR, 0.97; 95% CI, 0.84–1.12; $P=0.66$; Table 2 and Figure 1A). There also was no significant difference between the 2 treatment groups in the unadjusted risk of individual and composite secondary end points (Table 2 and Figures 1B, C, and D). Overall incidence of definite or probable stent thrombosis at year 2 of follow-up was extremely low and similar between the 2 groups (0.3% in the EES group and 0.4% in the SES group).

We performed adjustments of all covariates (listed in Table 1) using the weighted Cox proportional hazard regression model with IPTW. The area under the receiver-operating-characteristic curve for the propensity score model was 0.68, and the Hosmer-Lemeshow statistics ($P=0.57$) indicates good model fit. In this analysis, the adjusted HR for the primary end point in the EES group compared with the SES group was 0.96 (95% CI, 0.82–1.12; $P=0.60$; Table 2). The

adjusted risks for each secondary end point with regard to clinical safety and efficacy also did not differ significantly between the EES group and the SES group (Table 2).

Discussion

In this large scale, multicenter, prospective cohort of patients undergoing PCI with DES, we found no significant differences between EES and SES in terms of clinical efficacy and safety. Clinical outcomes after use of EES and SES were excellent, with low rate of repeat revascularization and very low incidence of stent thrombosis. However, longer term follow-up would be mandatory to address whether EES could positively affect the late occurring events beyond 1 to 2 years reported after SES implantation, such as late restenosis and very late stent thrombosis.

It has been announced that SES (Cypher stent) is removed from the market of DES devices. Therefore, the results of current study could not provide guidance for the optimal choice of coronary DES in the present clinical practice. However, because SES has been the most widely used and most extensively studied first generation DES, clinical outcomes after SES implantation could be regarded as the benchmark for the future generation DES platforms.

The second generation EES is currently one of the most commonly used DES in daily clinical practice, and there have been several randomized trials and registries comparing EES and the first generation DES. In long term follow-up of clinical trials comparing EES with early generation PES,^{18,19} all efficacy outcomes (ie, repeat revascularization) and critical safety issues (ie, stent thrombosis and MI) were better

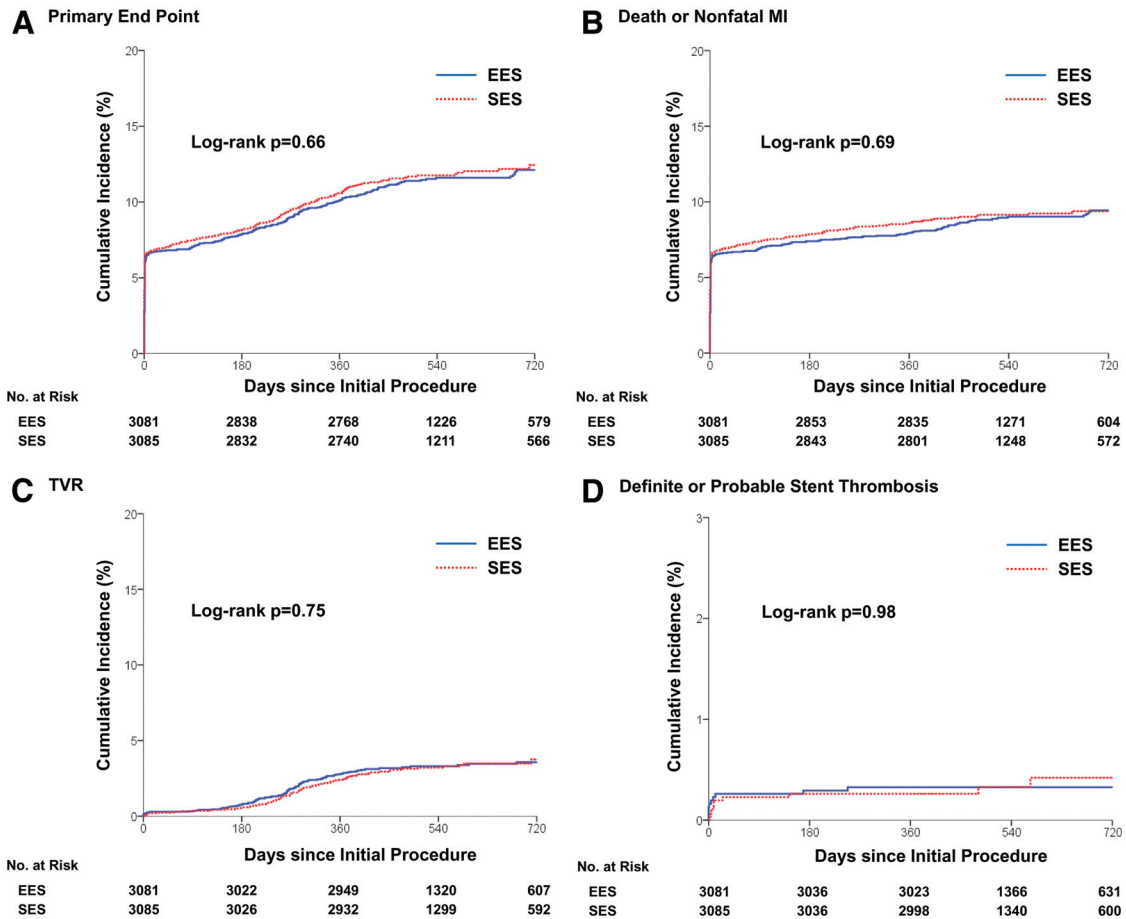


Figure. Cumulative incidence of the primary end point and selected secondary end points, according to stent group. Cumulative-incidence curves are shown for the primary end point of death, nonfatal myocardial infarction (MI), or TVR (A), death or nonfatal MI(B), TVR (C), and definite or probable stent thrombosis (D). Probability values were calculated with the use of the log-rank test. EES indicates everolimus-eluting stent; SES, sirolimus-eluting stent; TVR, target-vessel revascularization.

with EES than with PES. On the basis of these results, unrestricted use of PES is suggested to be no longer used in everyday clinical practice. However, because SES has been shown to be superior to PES, it is clinically relevant to determine whether EES provides therapeutic benefit over SES in routine practice. Consistent with our findings, a meta-analysis of randomized trials comparing EES with SES in 7370 patients demonstrated that there were no significant differences of clinical outcomes between the 2 stent groups.⁹ In addition, a recent large, all-comer design, RESET (Randomized Evaluation of Sirolimus-eluting versus Everolimus-eluting stent Trial) study, which is conducted in a similar ethnic group, showed consistent clinical findings.²⁰ By contrast, 1 real-practice registry suggested that EES appears to be associated with a lower risk of MI, stent thrombosis, and TVR compared with SES.²¹ However, this study was hampered by retrospective design and use of historical control, by which there might be a risk of bias due to systematic differences between the groups resulting from the rapid paradigm shift of PCI practice.

Our study has several strengths. These include the large sample size of more than 6000 patients, more rigorous approaches to adjustment for several potential confounding factors using the IPTW methods, and the generalizability of

our findings to daily clinical practice of the PCI procedures. From an analytic standpoint, the IPTW methods require fewer distributional assumptions about the underlying data, and so it would make more parsimonious use of observational data, by which the analyses can be applied more practically.²² From a clinical viewpoint, when the results of observational studies and randomized trials are congruent in both direction and magnitude, as is true for our findings, the case for broader therapeutic effectiveness is strengthened.

In our study, the incidence of stent thrombosis was extremely low. As compared with the Western population, a relatively low rate of stent thrombosis might be explained in part by differences in clinical or lesion characteristics, interventional practice, or race or ethnic groups, as previously noted.^{11,16,23}

Study Limitations

Despite the strengths of our study, there are several limitations that deserve consideration. First, this was not a randomized, observational cohort study. Although the nonrandomized comparison between the study groups was adjusted for all available confounders, there is always a possibility of selection bias because of unknown confounders. Second, our

study was underpowered to detect significant differences in serious safety outcomes such as mortality, stent thrombosis, and the component of major adverse cardiac events due to the limited number of events. Third, dual antiplatelet therapy was required for at least 12 months, according to the standard PCI guidelines, but no information on actual use by individual patients, even by those who had adverse events, was available. Thus, we cannot provide any specific insight into the question of whether dual antiplatelet therapy would differentially influence the risk of such events in each stent type. Finally, clinical follow-up duration of our study is currently limited and would limit the validity of the reported results due to potential differential in late occurrence of stent thrombosis and revascularization. Therefore, very long term observation is mandatory to provide a critical appraisal of relative safety and to confirm the long term durability of these devices.

Conclusions

This prospective, large-scale, observational study demonstrated that, during the median 1.3 year of follow-up, there were no significant differences between EES and SES in terms of clinical efficacy and safety, such as death, MI, stent thrombosis, and repeat revascularization. Longer term follow-up would be mandatory to better define the relative merits of 1 of the current standard devices (EES) as compared with the previous standard device (SES).

Disclosures

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