Randomized Comparison of Sirolimus-Eluting and Everolimus-Eluting Coronary Stents in the Treatment of Total Coronary Occlusions

Results From the Chronic Coronary Occlusion Treated by Everolimus-Eluting Stent Randomized Trial

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***Background*—**Patients with coronary total occlusions are at especially high risk for restenosis and new revascularizations. Sirolimus-eluting stents dramatically improved the clinical outcome of this subset of patients in randomized trials, but other drug-eluting stents, mainly the everolimus-eluting stent (currently the most frequently used stent), have not yet been evaluated in patients with coronary total occlusions. The objective was to compare the second-generation everolimus-eluting stent with the first-generation sirolimus-eluting stent in patients with coronary total occlusions.

***Methods and Results*—**A total of 207 patients with coronary total occlusions and estimated time since occlusion >2 weeks were randomized to everolimus- or sirolimus-eluting stent. The primary end point was in-stent late loss at 9-month angiographic follow-up (noninferiority trial). Clinical follow-up was performed at 1 and 12 months. In-stent late loss at 9 months was 0.29±0.60 versus 0.13±0.69 mm in patients allocated to sirolimus- and everolimus-eluting stent, respectively. The observed difference in in-stent late loss between both groups was –0.16 mm (95% confidence interval, 0.04 to –0.36 mm; *P* for noninferiority <0.01). The rate of binary angiographic restenosis was 10.8% and 9.1% in patients allocated to sirolimus- and everolimus-eluting stent, respectively (*P*=0.709), whereas the rate of vessel reocclusion was 3.2% and 1.1%, respectively (*P*=0.339). At 12 months, the rate of major adverse events was 15.9% versus 11.1% with sirolimus- and everolimus-eluting stent, respectively (*P*=0.335), and probable or definitive stent thrombosis occurred in 3.0% and 0.0% of patients, respectively (*P*=0.075).

***Conclusions*—**In patients with coronary total occlusions, everolimus-eluting stent is as effective as sirolimus-eluting stent.

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Key Words: chronic total coronary occlusion ■ restenosis ■ stent

Total coronary occlusion (TCO) represents one of the most challenging scenarios for interventional cardiologists. Even when recanalization is obtained and a coronary stent is placed, the risk of restenosis and even reocclusion frequently limits the initially successful result.[1] Large randomized trials on drug-eluting stents (DESs) frequently excluded patients with TCO, and only the sirolimus-eluting stent (SES) has been randomly compared with bare-metal stents in studies focused on TCO.[2–4]

Second-generation DESs have provided better platforms, new drugs, and new polymers, with the objective of improve deliverability and even safety of these devices. Among them,

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WHAT IS KNOWN

- Chronic coronary occlusions constitute one of the most challenging subsets for coronary interventions, and only sirolimus-eluting stents have been compared with bare-metal stents in randomized trials in this setting.
- Second-generation drug-eluting stents may provide some advantages over first-generation devices, mainly by improving acute stent performance, and potentially long-term safety.

WHAT THE STUDY ADDS

- The Coronary occlusion treated by EveroLimus-Eluting Stent (CIBELES) randomized trial has demonstrated that the everolimus-eluting stent is noninferior to the sirolimus-eluting stent in chronic coronary occlusions in terms of in-stent late loss values (primary end point).
- Moreover, everolimus-eluting stents showed a trend to lower risk of stent thrombosis.
- The results of the CIBELES trial support the use of everolimus-eluting stent as the first-choice device in successfully recanalized chronic coronary occlusions.

everolimus-eluting stents (EESs) with a cobalt-chromium stent platform have been shown to be associated with significantly lower rates of cardiac events and stent thrombosis in comparison with first-generation DESs in large randomized clinical trials[5–7] and are currently the most frequently used type of DES. However, this stent has not been randomly tested specifically in a population of patients with TCO. The randomized Chronic Coronary Occlusion Treated by Everolimus-Eluting Stent (CIBELES) trial was designed to demonstrate the efficacy of EES in treating TCO in a head-to-head comparison with SES.

Methods

Study Patients

The design and rationale of the study has been published previously in detail.[8] The CIBELES trial is a multicenter, controlled, single-blinded, randomized clinical trial. Thirteen centers from Spain and Portugal participated in the study. The study was sponsored by the Spanish Society of Cardiology, with an unrestricted grant from Abbott Vascular. Chiltern International monitored the trial.

Patients ≥18 years old with a TCO (thrombolysis in myocardial infarction flow grade 0 or 1) with an estimated time of occlusion >2 weeks were included. True chronic total occlusions are those with an estimated time since occlusion of >3 months. However, most randomized trials evaluating restenosis in TCO, such as the Primary Stenting of Totally Occluded Native Coronary Arteries II (PRISON-II), included patients with an estimated time since occlusion of >2 weeks. Consequently, we decided to include patients with TCOs with an estimated time since occlusion of >2 weeks.

Only patients with angina, silent ischemia, or viable myocardium at the area supplied by the target vessel were eligible for the trial. Exclusion criteria were as follows: (1) acute myocardial infarction (both ST-segment elevation and non–ST-segment elevation myocardial infarction) at the area supplied by the target vessel within 2 weeks before the inclusion in the study; (2) lesions not successfully crossed with the guide wire and dilated with balloon angioplasty; (3) lesions previously treated percutaneously; (4) lesions not suitable for 2.25- to 3.50-mm coronary stent implantation; (5) patients not willing to undergo angiographic follow-up; (6) contraindications for prolonged double (aspirin plus thienopyridine) antiplatelet therapy (eg, allergy to aspirin, need for chronic oral anticoagulation, or scheduled major surgical intervention within 12 months); (7) pregnancy or absence of a negative pregnancy test result in women of childbearing age; (8) chronic renal failure (creatinine plasma value >3.0 mg/dL); (9) plasma platelet count <100.000 mm^3 or >700.000 mm^3; (10) severe noncardiac diseases limiting life expectancy to <1 year; and (11) patients currently included in another clinical trial.

The ethics committees of all of the participating centers revised and approved both the protocol and the informed consent before the beginning of the study. Every patient gave a written informed consent for the study before the procedure. The first patient was included on November 17, 2008, and the last patient was randomized on September 9, 2010.

Definitions and End Points

The primary end point was in-stent late loss (ISLL) at 9-month angiographic follow-up. Secondary angiographic end points included binary angiographic restenosis, vessel reocclusion, and in-segment late loss at 9 months. Secondary clinical end points included death, myocardial infarction, and new target vessel revascularization. ISLL was defined as the difference between minimum lumen diameter within the borders of the stent immediately after implantation and that measured at angiographic follow-up. Binary angiographic restenosis was defined as the presence of >50% in-stent diameter stenosis and vessel reocclusion as the presence of total vessel occlusion (100% diameter stenosis and thrombolysis in myocardial infarction flow 0 or 1) at angiographic follow-up.

Deaths during the study were classified as cardiac or noncardiac by the clinical events committee. All of the deaths were considered cardiac unless a clear noncardiac cause of death could be identified. The diagnosis of myocardial infarction was defined as described here. First, Q-wave myocardial infarction was the presence of new abnormal Q-waves, in association with a creatinine-phosphokinase elevation ≥2-fold the upper normal limit. Second, non-Q-wave acute myocardial infarction was the presence of creatinine-phosphokinase elevation ≥2-fold the upper normal limit associated with chest pain and/or ST-segment or T-wave abnormalities at the ECG. Episodes of stent thrombosis were classified following the Academic Research Consortium criteria.[9] New target vessel revascularizations were only recommended in the presence of >50% stenosis in association with angina and ischemia or myocardial viability demonstrated by noninvasive or invasive techniques. Any target vessel revascularization was considered target lesion revascularization when located at the stented segment and/or the 5 mm adjacent to the stent. Vascular complications included hematoma >5 cm, arteriovenous fistula, pseudoaneurysm, and retroperitoneal bleeding. Bleeding or vascular complications were considered severe when life threatening or requiring surgical repair and/or blood transfusion. Major adverse events included death, myocardial infarction, or new revascularization procedures.

Procedure and Follow-up

The antithrombotic treatment during percutaneous coronary intervention (PCI), approach (radial versus femoral), type of guiding catheter, guide wire, and other technical issues were left to the operator's preferences and local clinical practice. It was recommended that the entire segment dilated by the balloon be covered by the stent. As a recommendation, thienopyridines were withdrawn the day after angiographic follow-up, unless the patient needed a subsequent PCI.

A 12-lead ECG and blood sample, including determination of cardiac enzymes, were taken 24 hours after PCI. Angiographic follow-up was scheduled 9 months after PCI. In the presence of binary angiographic restenosis, a new percutaneous target vessel revascularization was recommended if clinically indicated (angina, silent ischemia, or myocardial viability) and technically suitable.

The 2 best angiographic views were used for the immediate angiographic results, as well as for the angiographic follow-up, after

administration of nitroglycerin 0.2 mg intracoronary. Quantitative coronary analysis was performed at a central core laboratory (Hospital Clínico, Madrid, Spain), by experienced physicians, blinded to the type of stent implanted, not participating in the trial and not involved in the treatment of the patients. The MEDIS quantitative coronary analysis software (MEDIS, Leiden, the Netherlands) was used for quantitative coronary analysis. The following angiographic variables were measured: reference vessel diameter, minimum lumen diameter, percentage of stenosis, lesion length, and thrombolysis in myocardial infarction flow at baseline, immediately after PCI, and at angiographic follow-up. Clinical events were evaluated and classified by a clinical events committee composed of 3 physicians not participating in the study and not involved in the treatment and follow-up of the patients.

Statistical Analysis

In the SPIRIT-I and II trials (Clinical Trial of the Abbott Vascular XIENCE V Everolimus Eluting Coronary Stent System), mean ISLLs for EES during follow-up were 0.10 and 0.11 mm, respectively.[10,11] For SES, different studies have shown ISLL ranging from 0.05 to 0.28 mm.[12] Therefore, it was assumed that both EES and SES had the same mean values of ISLL, and an SD of 0.45 mm was also assumed for both groups. The estimated number of patients per group needed to demonstrate the noninferiority of EES versus SES in terms of ISLL (expected difference in means for $ISLL_{SES} - ISLL_{EES} = 0$, with a noninferiority margin of 0.20 mm), with a 1-sided α error of 0.05 and β error of 0.10 (90% statistical power), was 88. Estimating that 15% of patients would not finally undergo angiographic follow-up, 104 patients were needed to be included in each group. Thus, the total number of patients to be included was 208.[8] One of the 208 patients signing the informed consent and was randomized but was not finally included in the study because of patient refusal before starting the procedure. Thus, 207 patients were finally included in the study (101 allocated to SES and 106 to EES).

Statistical analysis was performed with the SPSS 12.0 statistical package (SPSS Inc, Chicago, IL). The primary end point (ISLL) was assessed by a 1-sided test for noninferiority using the Student *t* test (comparison of a continuous variable in 2 groups). Other comparisons of continuous variables between both SES and EES groups were performed using 2-sided unpaired *t* tests. Categorical variables between patients allocated to SES and EES were compared with the χ^2 test (Fisher exact test when necessary). Figures of subgroup analysis (incidence of major adverse cardiac events) accordingly to age, sex, diabetes mellitus, and estimated time since occlusion are provided with the odds ratios and their 95% confidence intervals. Clinical events were evaluated by the Kaplan–Meier survival curves, and the log-rank test was used to compare outcomes between groups. All of the analyses were conducted on an intent-to-treat basis. Differences were considered statistically significant when $P<0.05$, although all of the *P* values are provided.

Results

Baseline Characteristics and Procedural Results

Most clinical characteristics were not statistically different between both groups of patients, except for a significantly higher prevalence of previous PCI in patients allocated to SES. The proportion of diabetic patients was higher in patients allocated to EES (40.6% versus 31.7%), but differences were not statistically significant (Table 1). The estimated time since occlusion was >3 months in 165 patients (80%), without significant differences between both groups. Reference vessel diameter was also similar between both groups of patients (3.1±0.7 mm in SES in comparison with 2.9±0.6 mm in EES patients; $P=0.164$).

Procedural details were similar in both groups of patients (Table 2). The majority of procedures (>75%) were performed by femoral approach, and retrograde techniques were used only in 5% of procedures. The mean total stent length was ≈48 mm, without significant differences in both groups.

One patient allocated to SES had a coronary perforation. Severe coronary dissection during the procedure occurred in 4 patients allocated to SES and 5 allocated to EES. Final angiographic result was successful in 98% of patients in both groups. Two patients in each group underwent coronary stent implantation, but final distal flow was thrombolysis in myocardial infarction 0 or 1, thus being considered to have an unsuccessful angiographic result.

Clinical Outcomes

During the 12-month clinical follow-up, 28 patients experienced major adverse cardiac events (death, myocardial infarction, or new revascularization procedures of the target vessel),

Table 1. Baseline Characteristics

Characteristic	SES	EES	*P* Value
Age	63±11	65±10	0.094
Female, %	13.9	19.8	0.254
Diabetes mellitus, %	31.7	40.6	0.184
Insulin dependent diabetes mellitus, %	5.9	9.4	0.347
Hypertension, %	67.3	68.9	0.812
Hypercholesterolemia, %	77.2	66.0	0.075
Smoking, %	61.4	50.0	0.099
No. of coronary risk factors			0.381
0	2.0	4.7	
1	11.9	18.9	
2	39.6	33.0	
3	38.6	33.0	
4	7.9	10.4	
Previous PCI, %	42.6	25.5	0.012
Previous CABG, %	4.0	4.7	1.000
Previous infarction	42.6	33.0	0.202
Time of occlusion >3 mo	83.2	76.4	0.227
Peripheral artery disease, %	7.9	15.1	0.107
Clinical indication, %			0.324
Angina	66.3	72.6	
Persistent ischemia	33.7	27.4	
Noninvasive test performed, %	56.4	62.3	0.393
Left ventricular ejection fraction	54±14	52±13	0.305
Creatinine value, mg/dL	1.0±0.3	1.0±0.4	0.622
Plasmatic glucose, mg/dL	118.2±52.1	121.0±47.8	0.743
No. of vessels diseased			0.980
1	44.6	43.4	
2	29.7	30.2	
3	25.7	26.4	
Multivessel disease, %	55.4	56.6	0.867
Collateral circulation, %	90.1	91.5	0.812
Moderate-severe calcification, %	34.7	41.5	0.310
Moderate-severe tortuosity, %	13.9	13.2	0.616
Bifurcation, %	23.8	25.5	0.775

CABG indicates coronary artery bypass grafting; EES, everolimus-eluting stent; PCI, percutaneous coronary intervention; and SES, sirolimus-eluting stent.

Table 2. Procedural Details

Variable	SES	EES	*P* Value
Treated vessel, %			0.420
Left main	1.0	0.0	
Anterior descending	41.6	40.6	
Left circumflex	20.8	17.0	
Right coronary artery	35.6	42.5	
2 vessels (RCA and LCX)	1.0	0.0	
Approach, %			0.395
Femoral	74.3	79.2	
Radial	25.7	20.8	
Retrograde approach, *n*/%	5.0	4.7	1.000
No. of stents (range, 1–4 for both)	2.0±1.0	2.1±1.0	0.278
Total stent length, mm	47.5±24.6	49.8±23.2	0.483
Maximum stent diameter, mm	2.9±0.4	2.9±0.4	0.874
Minimum stent diameter, mm	2.6±0.4	2.6±0.4	0.889

EES indicates everolimus-eluting stent; LCX indicates left circumflex; RCA, right coronary artery; and SES, sirolimus-eluting stent.

including 16 patients allocated to SES and 12 allocated to EES (Table 3). The cumulative incidence of major adverse cardiac events at 12 months was 15.9% and 11.1% in patients allocated to SES and EES, respectively (log-rank: *P*=0.335; Figure 1). Figure 2 shows the influence of the type of stent on the incidence of major adverse cardiac events in different subgroups of patients.

There were 2 deaths in patients allocated to SES, both of them because of cardiac failure (1 and 6 months after the index procedure). One patient allocated to EES had a sudden death 8 months after the inclusion in the study. There were 3 patients allocated to SES that experienced a myocardial infarction (all of them non-Q-wave myocardial infarction). One of them experienced a postprocedure myocardial infarction, and the other 2 cases of myocardial infarction were related to stent thrombosis. In patients allocated to EES, no myocardial infarctions were diagnosed.

There were 20 patients who underwent a new revascularization of the target vessel, including 11 patients allocated to SES and 9 allocated to EES (incidence at 1 year, 11.6% versus 7.9%, respectively; *P*=0.526). Of these 20 new revascularization procedures of the target vessel, 13 (65%) were target lesion revascularizations, including 8 in patients allocated to SES and 5 in those allocated to EES (incidence of target lesion revascularization 7.5% and 6.0% for patients allocated to SES and EES, respectively; *P*=0.676). In addition, 5 patients underwent a new revascularization for a nontarget vessel (2 patients allocated to SES and 3 allocated to EES).

Three patients allocated to SES experienced a definitive or probable stent thrombosis. One patient experienced a definitive stent thrombosis 117 days after the index procedure. This patient was admitted with a non-ST elevation acute myocardial infarction, and coronary angiography showed a thrombotic occlusion of the target vessel that was subsequently treated with a new percutaneous coronary intervention. Other patient experienced a non-Q wave myocardial infarction 9 days after the index procedure, which was managed conservatively. This patient underwent the scheduled angiographic follow-up, and a total occlusion of the target vessel was documented. It was considered that a stent thrombosis was the most probable cause of the non-Q wave myocardial infarction (probable stent thrombosis) in this patient. A third patient allocated to SES received 3 SESs and also a paclitaxel-eluting stent at a distal level. This patient had a thrombosis of the distally implanted paclitaxel-eluting stent 24 hours after the index procedure. Although there was no evidence of SES thrombosis, this patient was codified to have experienced a definitive stent thrombosis in an intention-to-treat analysis. No probable or definitive stent thrombosis (neither early nor late stent thrombosis) was documented in patients allocated to EES. Thus, the cumulative incidence of probable or definitive stent thrombosis at 12 months was 3% and 0% in patients allocated to SES and EES, respectively (log-rank: *P*=0.075; Figure 3).

Severe vascular or bleeding complications occurred in 2 patients allocated to SES and 1 allocated to EES. Figure 4 shows the proportion of patients on double antiplatelet therapy at each time of follow-up in both groups of patients.

Angiographic Results

Because there were 3 deaths before angiographic follow-up and 4 patients had an angiographic unsuccessful result, there were 200 patients eligible for angiographic follow-up. There were 181 patients undergoing angiographic follow-up (90.5% of eligible patients and 87.4% of the overall study population).

Table 3. Clinical Events at 12 Months

	Patients With Events			Probability of Being Free From Events		
Variable	SES	EES	*P* Value	SES	EES	*P* Value (Log-Rank)
Cardiac events at 365 d, *n*/%	16 (15.8)	12 (11.3)	0.335	84.1±3.6	88.1±3.1	0.324
Death	2 (2.0)	1 (0.9)	0.523	98.0±1.4	99.0±1.0	0.523
Myocardial infarction	3 (3.0)	0 (0.0)	0.076	97.0±1.7	100.0	0.075
Target vessel revascularization	11 (11.6)	9 (7.9)	0.526	86.7±3.4	90.1±3.0	0.415
Stent thrombosis, *n*/%	3 (3.0)	0 (0.0)	0.075	97.0±1.7	100.0	0.075
Early	2	0				
Late	1	0				
Stroke, *n*/%	1 (1.0)	1 (0.9)	0.736	99.0±1.0	98.6±1.4	0.964

EES indicates everolimus-eluting stent; and SES, sirolimus-eluting stent. Table shows the proportion of patients experiencing each event at this follow-up compared with the χ^2 test. The probability of being free from events was calculated with the Kaplan–Meier survival curves and compared with the log-rank test.

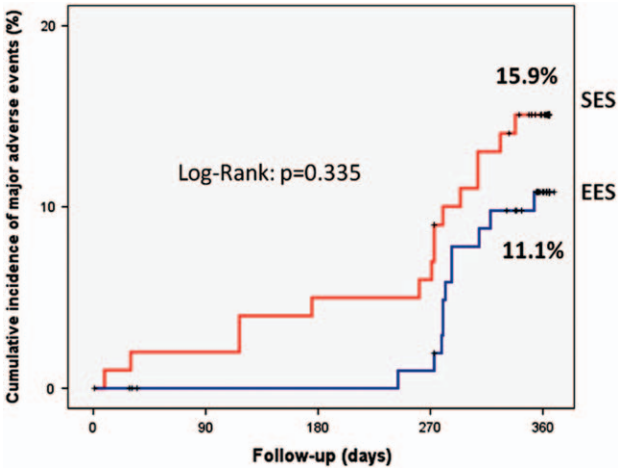

Figure 1. Cumulative incidence of major adverse cardiac events and Kaplan–Meier curves in patients allocated to sirolimus-eluting stent (SES) and everolimus-eluting stent (EES).

Table 4 shows the angiographic data at baseline, immediately after PCI, and at angiographic follow-up. ISLL was 0.29±0.60 mm in patients allocated to SES and 0.13±0.69 mm in those allocated to EES (P=0.116). Thus, the observed difference in ISLL between both groups was –0.16 mm (95% 2-sided confidence interval, 0.04 to –0.36 mm; 95% 1-sided confidence interval, –0.06 to –∞). Because the margin for noninferiority was 0.20 mm, the primary end point of noninferiority of ISLL was met (P<0.01; Figure 5A and 5B). The rate of binary angiographic restenosis was 10.8% and 9.1% in patients allocated to SES and EES, respectively (P=0.709), whereas the rate of vessel reocclusion at follow-up was 3.2% and 1.1%, respectively (P=0.339). Overall, 18 patients experienced in-stent restenosis, including 10 allocated to SES and 8 allocated to EES. The angiographic pattern of in-stent restenosis was focal in 5 patients in each group of patients, whereas it was diffuse in 5 SES patients (total occlusion in 3 of them) and in 3 EES patients (total occlusion in 1 patient).[12]

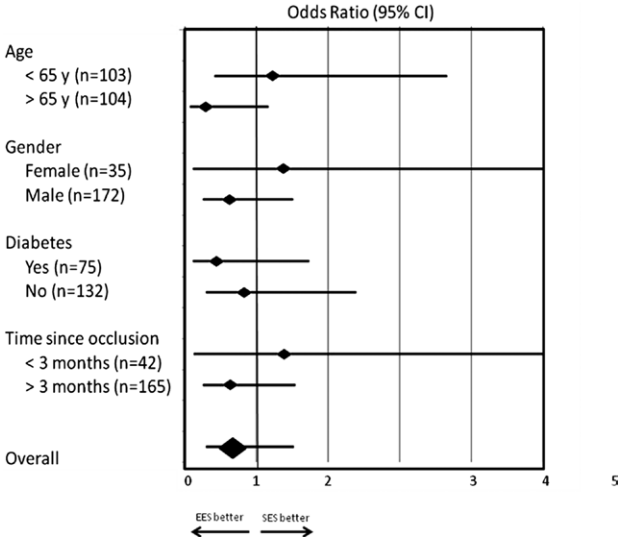

Figure 2. Influence of the type of stent on the clinical outcome (incidence of major adverse cardiac events) in different subgroups of patients.

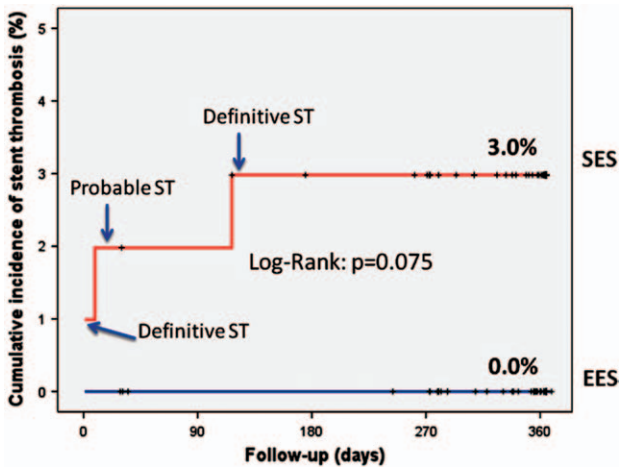

Figure 3. Cumulative incidence of stent thrombosis (definitive or probable) and Kaplan–Meier curves in patients allocated to sirolimus-eluting stent (SES) and everolimus-eluting stent (EES).

Comparison of Patients With More and Less Than 3 Months After Occlusion

Of the 207 patients included, 42 (20.3%) had an estimated time since occlusion <3 months. These patients had a lower frequency of moderate or severe lesion calcification (23.8% versus 41.8%; P=0.032) and higher mean values of the minimum lumen diameter (2.3±0.6 versus 2.1±0.5 mm, respectively; P=0.014) and reference vessel diameter (2.9±0.6 versus 2.7±0.5 mm, respectively; P=0.048) after the procedure.

There were no statistically significant differences between patients with >3 months and <3 months in the incidence of major adverse cardiac events at 12 months (probability of being free from events, 85.8±2.7% versus 92.3±4.3%; log-rank, P=0.256). Also, there were no statistically significant differences in the rates of binary angiographic restenosis (9.7% versus 2.4%; P=0.234) and vessel reocclusion (1.8% versus 2.0%, respectively; P=0.469).

Discussion

The CIBELES trial compared the second-generation cobalt-chromium everolimus-eluting coronary stent Xience-V (EES)

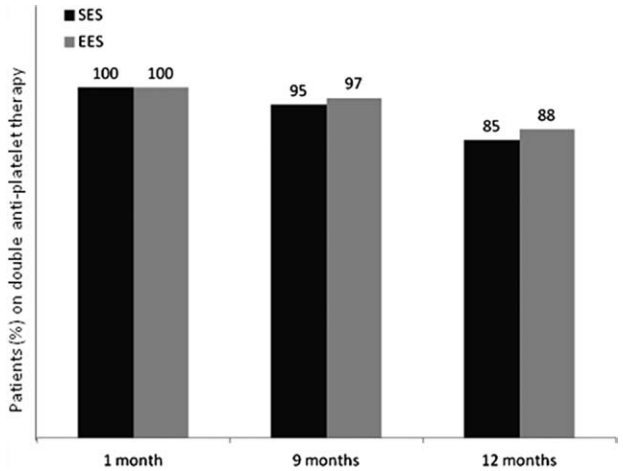

Figure 4. Proportion of patients on double antiplatelet therapy at each time of follow-up (P=not significant in all).

Table 4. Angiographic Data (Quantitative Coronary Analysis)

Variable	SES (n=101)	EES (n=106)	*P* Value
Preprocedure			
RVD (proximal), mm	3.1±0.7	2.9±0.6	0.164
Lesion length, mm	19.1±17.6	18.7±18.1	0.840
Postprocedure			
In-stent RVD, mm	2.8±0.5	2.7±0.5	0.119
In-stent MLD, mm	2.2±0.5	2.1±0.5	0.089
In-stent % stenosis	20.1±10.7	21.4±9.6	0.393
In-segment RVD, mm	2.6±0.6	2.5±0.6	0.552
In-segment MLD, mm	1.8±0.5	1.7±0.6	0.461
In-segment % stenosis	31.0±12.7	32.2±14.0	0.574
TIMI flow, %			1.000
0 or 1	2.0	1.9	
2	3.0	2.8	
3	95.0	95.3	
Follow-up			
In-stent RVD, mm	2.8±0.6	2.7±0.6	0.333
In-stent MLD, mm	2.0±0.6	2.0±0.7	0.939
In-stent % stenosis	30.0±18.1	28.9±18.7	0.700
In-stent late loss, mm*	0.29±0.60	0.13±0.69	0.116
In-segment RVD, mm	2.8±0.5	2.7±0.6	0.249
In-segment MLD, mm	1.8±0.5	1.7±0.7	0.224
In-segment % stenosis	33.1±16.1	37.9±22.9	0.140
In-segment late loss, mm	0.0±0.6	0.1±0.7	0.258
BAR, %	10.8	9.1	0.709
Reocclusion, %	3.2	1.1	0.339

BAR indicates binary angiographic restenosis; EES, everolimus-eluting stent; MLD, mimimum lumen diameter; RVD, reference vessel diameter; SES, sirolimus-eluting stent; and TIMI, thrombolysis in myocardial infarction. Table shows the proportion of patients experiencing each event at this follow-up compared with the χ_2 test. The probability of being free from events was calculated with the Kaplan–Meier survival curves and compared with the log-rank test.

*All data are shown as 2-sided unpaired *t* test comparisons. For in-stent late loss, 1-sided *t* test *P* value is <0.01.

with the first-generation stainless-steel sirolimus-eluting coronary stent Cypher (SES) in patients with TCO, with this being, to the best of our knowledge, the largest randomized trial performed with DESs in this subset of patients. The primary end point was met, because ISLL was found to be noninferior to SES in terms of ISLL. In the era of DESs, ISLL has demonstrated to be a valid parameter to evaluate the clinical efficacy of a given DES, and because of that it has been adopted as a parameter to compare different types of DESs.[13]

Among patients undergoing coronary angiography, 13% to 18% of them have a TCO.[14,15] TCO constitutes one of the most difficult scenarios for interventional cardiologists. Apart from the difficulties in obtaining a recanalization of the vessel, patients with TCO and an initially successful angiographic result have very high rates of restenosis, reocclusion, and new revascularization procedures in comparison with non-CTO patients.[16,17] For all of these reasons, only a minority of TCOs are attempted to be treated by percutaneous coronary interventions, whereas most of them are left on medical treatment or sent for coronary artery bypass grafting.[14,18] However, given the apparent benefit of successfully treating this type of patients,[19,20] TCO is one of the fields of major interest for interventional cardiologists.

Several registries showed a rate of restenosis and new revascularization procedures in patients with TCO lower than expected when treated with sirolimus- or paclitaxel-eluting stents.[21,22] However, only the SESs have been randomly compared with bare-metal stents (BMSs) in this type of patient. In the PRISON-II trial, treatment with SESs significantly reduced the rates of binary angiographic restenosis (from 41% to 11%), vessel reocclusion (from 13% to 4%), and the need for new revascularization procedures (from 22% to 8%) in comparison with BMSs. Similar data were found in the Gruppo Italiano di Studio sullo Stent nelle Occlusioni Coronariche Societá Italiana di Cardiologia Invasiva (GISSOC-II-GISE) study (*n*=152), in which patients allocated to SES showed, in comparison with BMS, lower values of mean ISLL (0.20±0.49 versus 1.57±0.85 mm), binary angiographic restenosis (8% versus 68%), and reocclusion (0% versus 17%).[3] Using a bioabsorbable coating and including a lower number of patients, the CORACTO trial showed better results with SES in comparison with BMS (ISLL, 0.77 versus 1.8 mm; binary angiographic restenosis, 17% versus 60%; and vessel reocclusion, 0% versus 16% in patients allocated to DES versus BMS, respectively).[4]

Currently, the most frequently used DES is the EES, which has demonstrated to be superior to paclitaxel-eluting stents and similar to SESs in terms of antirestenotic effect (late loss and binary angiographic restenosis).[5–7] Moreover, in comparison with first-generation DES, the EES has 2 important advantages. First, the device has a more flexible platform, mainly because of its thinner struts and cobalt-chromium alloy, providing better periprocedural results.[23] Second, the polymer present in EES seems to be more biocompatible and has a lower thickness in comparison with the polymer that is present in the first-generation DES.[24] These 2 characteristics are probably related to the lower incidence of clinical events

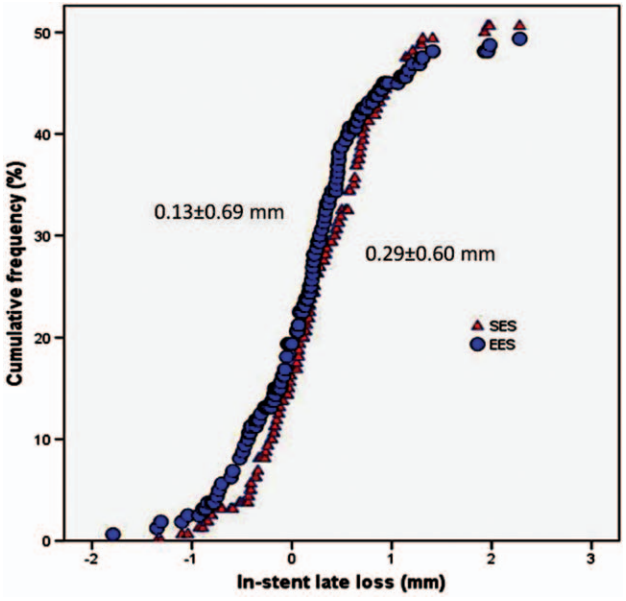

Figure 5. In-stent late loss in patients allocated to sirolimus-eluting stent (SES) and everolimus-eluting stent (EES) shown as cumulative frequency of in-stent late loss.

(mainly stent thrombosis) in patients treated with EES in comparison with paclitaxel-eluting stents and SESs.[5–7]

In the CIBELES trial, the primary noninferiority end point was met, because EES was noninferior to SES in terms of ISLL. However, ISLL was lower in patients allocated to EES, although differences were not statistically significant. The rate of binary angiographic variables and clinical end points were not significantly different between both groups of patients, but were numerically lower in patients allocated to EES. Very importantly, no definitive or probable stent thrombosis occurred in patients allocated to EES in comparison with 3 patients allocated to SES. All of these data indicate that EES is at least as effective as SES in the treatment of TCO.

Study Limitations

Although randomized and multicenter, this study may have some limitations. First, true chronic total occlusions are those with an estimated time since occlusion >3 months. However, the CIBELES trial included patients with an estimated time since occlusion >2 weeks. This is justified because most randomized trials evaluating restenosis in TCO, such as the PRISON-II, included patients with an estimated time since occlusion of >2 weeks because in TCOs, estimated time since occlusion has an impact on the probability of obtaining a successful recanalization rather than on the risk of subsequent restenosis. Second, the study was powered to compare in-stent late loss between SES and EES but not to a rare event such as stent thrombosis. Because of that, despite the fact that all 3 stent thrombosis cases observed in the study were in the SES group because of the modest number of patients enrolled, we cannot draw any conclusion about the safety profile of SES versus EES in this high-risk population.

APPENDIX (LIST OF INVESTIGATORS)

Principal investigator: Raul Moreno. **Co-principal investigator:** Eulogio Garcia. **Clinical Events Committee:** Esteban Lopez de Sa, Carlos Macaya, Jose-Luis Lopez-Sendon. **List of investigators:** Hospital Universitario La Paz, Madrid, Spain: Raul Moreno, Guillermo Galeote, Angel Sanchez-Recalde, Santiago Jimenez-Valero, Luis Calvo, Ignacio Plaza, Angela Portela (42 patients). Hospital de Santa Cruz, Lisbon, Portugal: Rui Campante Teles, Manuel Almeida, Luis Raposo, and Pedro Araujo Goncalves (34 patients). Hospital de Galdakao, Bilbao, Spain: Jose-Ramón Rumoroso, Mario Sabada Sagredo, Asier Subinas Elorriaga (28 patients). Hospital de Santo Antonio, Porto, Portugal: Henrique Cyrne Carvalho, Joao Silveira, and André Luz (21 patients). Hospital Puerta de Hierro, Majadahonda, Spain: Francisco Javier Goicolea, and Jose Antonio Fernández Díaz (17 patients). Hospital Virgen de la Salud, Toledo, Spain: José Moreu, and Tomás Cantón (15 patients). Hospital German Trias I Pujol, Badalona, Spain: Fina Mauri, and Oriol Rodriguez (14 patients). Hospital Santa Creu I Sant Pau, Barcelona, Spain: Antonio Serra, Manel Sabate (12 patients). Hospital General, Alicante, Spain: Vicente Mainar and Javier Pineda (9 patients). Hospital de Santa Marta, Lisboa, Portugal: Lino Patricio, and Rui Ferreira (7 patients). Hospital Virgen de la Arrixaca, Murcia, Spain: Mariano Valdés, Javier Lacunza (5 patients). Complejo Hospitalario de León, Spain: Felipe Fernández-Vázquez, Armando Pérez de Prado (2 patients). Hospital García de Orta, Lisboa, Portugal: Helder Pereira (1 patient).

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Disclosures

None.

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Randomized Comparison of Sirolimus-Eluting and Everolimus-Eluting Coronary Stents in the Treatment of Total Coronary Occlusions: Results From the Chronic Coronary Occlusion Treated by Everolimus-eluting Stent Randomized Trial

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