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Randomized Comparison of Everolimus-Eluting Stents and Sirolimus-Eluting Stents in Patients With ST Elevation Myocardial Infarction

RACES-MI Trial

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ABSTRACT

OBJECTIVES The aim of the current study was to compare everolimus-eluting stents (EES) with sirolimus-eluting stents (SES) in patients undergoing primary angioplasty.

BACKGROUND Drug-eluting stents may offer benefits in terms of repeat revascularization. However, as shown for first-generation drug-eluting stents, they may be counterbalanced by a potential higher risk of stent thrombosis, especially among patients with ST-segment elevation myocardial infarction (STEMI). No data have been reported so far on the long-term benefits and safety of the new generation of drug-eluting stents in STEMI.

METHODS Consecutive STEMI patients admitted within 12 h of symptom onset and undergoing primary angioplasty and stent implantation at a tertiary center with 24-h primary percutaneous coronary intervention capability were randomly assigned to SES or EES. The primary endpoint was a major adverse cardiac event at 3-year follow-up. The secondary endpoints were death, reinfarction, definite or probable stent thrombosis, and target vessel revascularization at 3-year follow-up. No patient was lost to follow-up.

RESULTS From April 2007 to May 2009, 500 patients with STEMI were randomized to EES (n = 250) or SES (n = 250). No difference was observed in terms of baseline demographic and clinical characteristics between the groups. No difference was observed between the groups in terms of number of implanted stents per patient or total stent length. However, a larger reference diameter was observed with SES (3.35 ± 0.51 mm vs. 3.25 ± 0.51 mm, p = 0.001), whereas patients randomized to EES more often received glycoprotein IIb/IIIa inhibitors (54.4% vs. 42.4%, p = 0.006). Follow-up data were available in all patients (1,095 ± 159 days). No significant difference was observed between EES and SES in major adverse cardiac events (16% vs. 20.8%, adjusted hazard ratio [HR]: 0.75 [95% confidence interval (CI): 0.5 to 1.13], p = 0.17), cardiac death (4.4% vs. 5.6%, adjusted HR: 0.77 [95% CI: 0.35 to 1.71], p = 0.53), recurrent MI (6.4% vs. 10%, adjusted HR: 0.62 [95% CI: 0.33 to 1.16], p = 0.13), and target vessel revascularization (4.8% vs. 4.8%, adjusted HR: 1.00 [95% CI: 0.45 to 2.32], p = 0.99). However, EES was associated with a significant reduction in stent thrombosis (1.6% vs. 5.2%, adjusted HR: 0.3 [95% CI: 0.1 to 0.92], p = 0.035).

CONCLUSIONS This study shows that among STEMI patients undergoing primary angioplasty, EES has similar efficacy as SES, but is associated with a significant reduction in stent thrombosis. (Randomized Comparison of Everolimus Eluting Stents and Sirolimus Eluting Stent in Patients With ST Elevation Myocardial Infarction [RACES-MI]; NCT01684982) (J Am Coll Cardiol Intv 2014;7:849–56) © 2014 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stent(s)

CI = confidence interval

DES = drug-eluting stent(s)

EES = everolimus-eluting stent(s)

HR = hazard ratio

MACE = major adverse cardiac events

PCI = percutaneous coronary intervention

SES = sirolimus-eluting stent(s)

ST = stent thrombosis

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

TVR = target vessel revascularization

Several randomized trials have clearly shown the adjunctive benefits in terms of mortality from primary percutaneous coronary intervention (PCI) as compared with thrombolysis as reperfusion strategy in the treatment of patients with ST-segment elevation myocardial infarction (STEMI) (1,2). Even though stent implantation, compared with balloon angioplasty, has reduced the occurrence of restenosis in selected STEMI patients (3,4), the outcome of bare-metal stents (BMS) seem to be worse in unselected patients with a rate of target vessel revascularization (TVR) up to 20% (5,6). Several randomized trials have shown that drug-eluting stents (DES), compared with BMS, are associated with a significant reduction in restenosis and TVR in STEMI patients (7–17). However, concerns have emerged on the higher risk of stent thrombosis (ST) with first-generation DES (18). The new-generation DES with more biocompatible polymers may potentially provide benefits in both TVR and ST in the setting of STEMI (19). Therefore, the aim of the RACES-MI (Randomized Comparison of Everolimus Eluting Stents and Sirolimus Eluting Stent in Patients With ST Elevation Myocardial Infarction) trial was to compare everolimus-eluting stents (EES) with sirolimus-eluting stents (SES) in patients undergoing primary angioplasty for STEMI at short- and long-term follow-up.

METHODS

The RACES-MI trial is a prospective, single-center, randomized trial evaluating the benefits of EES versus SES implantation in patients undergoing primary angioplasty for acute STEMI. Individuals eligible for enrollment were consecutive patients presenting with STEMI who fulfilled all of the following inclusion criteria: 1) chest pain for more than 30 min; and 2) ST-segment elevation of ≥1 mm in ≥2 contiguous electrocardiograph leads or with presumably new left bundle branch block. Exclusion criteria included the following: 1) active internal bleeding or a history of bleeding diathesis within the previous 30 days; 2) contraindication to dual antiplatelet therapy for 12 months; 3) known allergy to sirolimus or everolimus; 4) a history of stroke within 30 days or any history of hemorrhagic stroke; 5) history, symptoms, or findings suggestive of aortic dissection; 6) pregnancy; 7) participation in other trials. No angiographic exclusion criteria were used.

The institutional review board of the Ospedale "S.G. Moscati" (Avellino, Italy) approved the protocol in 2007, and all patients gave written informed consent.

Open-label randomization was performed in the catheterization laboratory after initial angiography by the treating physician when eligibility criteria were met. A 1:1 computer-generated random sequence, without blocking or stratification, was used. Sealed envelopes indicated the treatment group to which the patients were assigned: SES or EES.

MEDICATIONS. All patients received a 70 U/kg intravenous bolus of unfractionated heparin, aspirin intravenously (500 mg), and clopidogrel (600-mg loading dose). Glycoprotein IIb/IIIa inhibitor administration, and the number and length of stents to be implanted were left to the operator's discretion. Postinterventional antiplatelet therapy for all patients consisted of aspirin (100 mg/day) indefinitely and clopidogrel (75 mg daily recommended for 12 months).

ANGIOPLASTY PROCEDURE. Stenting procedures were performed according to standard techniques. The number and length of stents to be implanted were

TABLE 1 Baseline Demographic and Clinical Characteristics of the 2 Groups of Patients

	SES (n = 250)	EES (n = 250)	p Value
Age, yrs	59 ± 12	59 ± 11	0.53
Male	62	67.6	0.19
Hypertension	41.2	42	0.86
Diabetes	27.2	25.6	
IDDM	9.6	10	0.69
NIDDM	17.6	15.6	
Smoking	34.4	33.6	0.85
Previous MI	12	14.4	0.43
Previous CABG	8	6.8	0.61
Previous PCI	12.4	9.6	0.32
Previous CVA	3.2	4	0.63
Family history of CAD	32.4	36	0.4
PAD	2.4	3.2	0.59
Chronic renal failure	8.4	10.4	0.45
Anemia	10.4	8.8	0.54
Heart rate at presentation, beats/min	65 ± 24	69 ± 24	0.25
Killip class >1	14.4	15.2	0.80
Anterior MI	45.2	42.4	0.53
Ejection fraction, %	47.4 ± 8.4	47.5 ± 8	0.9
Ischemia time, min	177 ± 148	182 ± 152	0.67
Door-to-balloon time, min	44 ± 17	46 ± 16	0.16

Values are mean ± SD or percentages.

CABG = coronary artery bypass graft; CAD = coronary artery disease; CVA = cerebrovascular accident; EES = everolimus-eluting stent(s); IDDM = insulin-dependent diabetes mellitus; MI = myocardial infarction; NIDDM = non-insulin-dependent diabetes mellitus; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; SES = sirolimus-eluting stent(s).

left to the operator's discretion. The operator was allowed to implant DES to cover the entire length of the lesion with coverage of the entire stented segment and of 5-mm proximal and distal segments. The use of intravascular ultrasound, adjunctive thrombectomy devices, distal protection devices, and intra-aortic balloon pump were left to the operator's discretion.

ANGIOGRAPHIC ANALYSIS. TIMI (Thrombolysis In Myocardial Infarction) flow grade 3 coronary flow in the treated vessel and a residual stenosis <30% were the criteria used to define a successful PCI. Quantitative angiographic analyses (Integris Allura, Philips, Amsterdam, the Netherlands) were performed online and off-line by 2 experienced technicians who were unaware of treatment assignment. The average value was finally considered for each measured parameter.

DATA COLLECTION AND FOLLOW-UP. As per protocol, patients were reviewed at our outpatient clinic or by telephone interview at 6, 12, 24, and 36 months after stent implantation. For patients who died during follow-up, hospital records and necropsy data were reviewed, when possible. No patient was lost to follow-up.

TABLE 2 Angiographic and Procedural Characteristics of the 2 Groups of Patients

	SES (n = 250)	EES (n = 250)	p Value
IRA			
LM	3.2	2.4	
LAD	42.4	45.2	
LCX	20.0	16.8	0.69
RCA	32.0	34.8	
SVG	1.6	0.8	
Pre-procedural TIMI flow			
0–1	62.0	69.6	
2	26.8	18.0	0.063
3	11.2	12.4	
Post-procedural TIMI flow			
0–1	6.6	8.8	
2	8.0	7.6	0.48
3	86.0	83.6	
Vessel disease			
1	50.4	53.8	
2	39.2	34.1	0.48
3	10.4	12.0	
RD, mm	3.35 ± 0.51	3.25 ± 0.51	0.001
Stent diameter, mm	3.16 ± 0.39	3.09 ± 0.45	0.071
Total stent length, mm	22.0 ± 7.7	22.3 ± 8.0	0.72
Stents, n	1.12 ± 0.35	1.11 ± 0.35	0.8
GP IIb/IIIa inhibitors	42.4	54.4	0.006
Thrombectomy devices	23.2	21.2	0.59

Values are % or mean ± SD.

GP = glycoprotein; IRA = infarct-related artery; LAD = left anterior descending artery; LCX = left circumflex artery; LM = left main artery; RCA = right coronary artery; RD = reference diameter; SVG = saphenous vein graft; TIMI = Thrombolysis In Myocardial Infarction.

TABLE 3 Medical Therapy of the 2 Groups of Patients at Discharge and Clopidogrel Therapy at Follow-Up

	SES (n = 250)	EES (n = 250)	p Value
Aspirin	100	100	1.0
Beta-blockers	96	92.8	0.12
ACE inhibitors	90.4	91.2	0.76
Statins	99.6	100	0.5
Clopidogrel	100	100	1.0
Clopidogrel at 6 months	98.0	98.8	0.89
Clopidogrel at 12 months	96.0	96.4	0.9

Values are percentages.

ACE = angiotensin-converting enzyme; other abbreviations as in Table 1.

STUDY ENDPOINTS AND DEFINITIONS. The primary endpoint was major adverse cardiac events (MACE) at 3-year follow-up, defined as combined cardiac death, reinfarction, definite or probable ST, and TVR. Secondary endpoints were cumulative occurrence of the following: 1) cardiac death; 2) reinfarction; 3) definite or probable ST; and 4) TVR at 3-year follow-up. All deaths were considered cardiac unless an unequivocal noncardiac cause could be identified. Recurrent MI was defined as recurrence of angina symptoms with typical electrocardiographic changes and increase above the upper limit of normal of creatine kinase-myocardial band or troponin. The indication

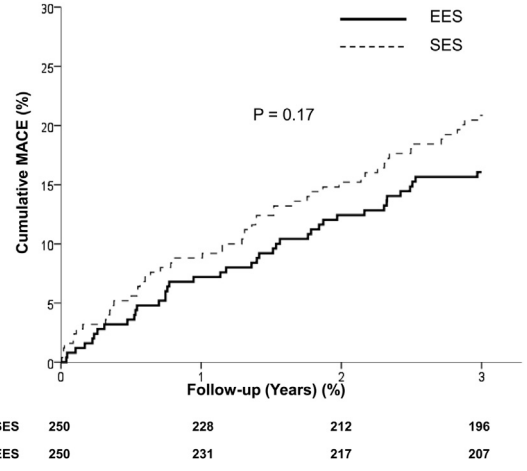

FIGURE 1 MACE in SES Versus EES

Kaplan-Meier curves showing the occurrence of major adverse cardiac events (MACE) in sirolimus-eluting stents (SES) versus everolimus-eluting stents (EES).

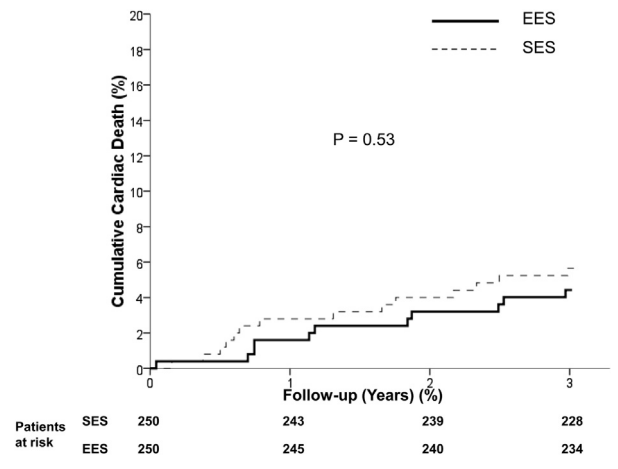

FIGURE 2 Cardiac Death in SES Versus EES

Kaplan-Meier curves showing the occurrence of cardiac death in SES versus EES. Abbreviations as in Figure 1.

for a second intervention had to be substantiated by symptoms or by electrocardiographic or scintigraphic evidence of ischemia at rest or during exercise. Subsequent revascularization of other coronary arteries did not constitute an endpoint. All events were reviewed by 2 cardiologists blinded to treatment assignment.

STATISTICAL ANALYSIS. Continuous data were expressed as mean ± SD and categorical data as percentages. The analysis of variance was appropriately used for continuous variables. The chi-square test or the Fisher exact test was used for categorical variables. The difference in event rates between groups during the follow-up period was assessed by the Kaplan-Meier method with the log-rank test. Furthermore, Cox regression analysis was performed to correct the results from any difference in baseline demographic, clinical, angiographic, or procedural characteristics that were different between the 2 groups. A probability value of $p < 0.05$ was considered significant.

Sample size calculation. According to our previous reports (4,5), we estimated a rate of target vessel failure at 3 years of 20% in the SES. With an anticipated 2-sided test for differences in independent binomial proportions at the 5% significance level, with a power of 80%, 220 patients per group were required to detect a reduction in a primary endpoint of 50% (from 20% to 10%) with EES versus SES. The number of patients was extended to 250 per group. Data were analyzed according to intention-to-treat analysis. Statistical analysis was performed using SPSS version 17.0 (SPSS, Inc., IBM, Armonk, New York).

RESULTS

PATIENT CHARACTERISTICS AND PROCEDURAL RESULTS. From April 2007 to May 2009, 563 consecutive STEMI patients were assessed for eligibility, and 63 patients were excluded because of exclusion criteria and/or refusal to participate. Therefore, our final population is represented by 500 STEMI patients who were randomized to EES (n = 250) or SES (n = 250). As reported in Tables 1 and 2, no difference was observed in terms of baseline demographic, clinical, and angiographic characteristics between the groups. No difference was observed between the groups in terms of number of implanted stents per patient (1.12 ± 0.35 vs. 1.11 ± 0.35, p = 0.8). As shown in Table 2, no difference was observed in terms of angiographic and procedural characteristics. Almost 50% of patients underwent PCI of the left anterior descending artery. Glycoprotein IIb/IIIa inhibitors were more often administered among patients randomized to EES. Procedural success was obtained in 93% to 95% of patients. No difference was observed in medical therapy at discharge (Table 3).

CLINICAL OUTCOME AT FOLLOW-UP. Follow-up data were available in all patients (1,095 ± 159 days). No difference was observed in terms of duration of dual antiplatelet therapy between the 2 groups (Table 3).

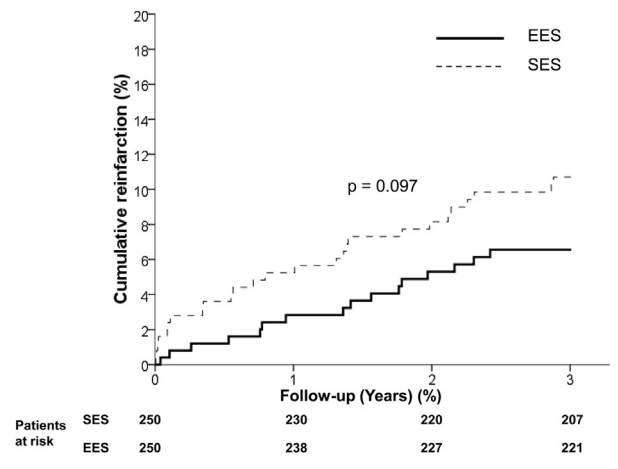

FIGURE 3 Reinfarction in SES Versus EES

Kaplan-Meier curves showing the occurrence of reinfarction in SES versus EES. Abbreviations as in Figure 1.

PRIMARY STUDY ENDPOINT. Major adverse cardiac events (MACE). MACE were observed in a total of 92 patients (18.4%). As shown in Figure 1, no significant difference was observed between EES and SES (16% vs. 20.8%, hazard ratio [HR]: 0.75 [95% confidence interval (CI): 0.5 to 1.13], p = 0.17; adjusted HR: 0.73 [95% CI: 0.48 to 1.10], p = 0.13).

SECONDARY STUDY ENDPOINTS. Cardiac mortality. A total of 28 patients had died at follow-up. Cardiac death was observed in 25 patients. As shown in Figure 2, no difference was observed in cardiac death between EES and SES (4.4% vs. 5.6%, HR: 0.77 [95% CI: 0.35 to 1.71], p = 0.53; adjusted HR: 0.75 [95% CI: 0.34 to 1.67], p = 0.48).

Repeat MI. Recurrent MI was observed in 41 patients (8.2%). As shown in Figure 3, no difference was observed between EES and SES (6.4% vs. 10%, HR: 0.62 [95% CI: 0.33 to 1.16], p = 0.13; adjusted HR: 0.57 [95% CI: 0.3 to 1.07], p = 0.08). Similar rates of reinfarction were observed after the exclusion of cases of definite or probable ST (adjusted HR: 0.92 [95% CI: 0.42 to 2.01], p = 0.84).

Stent thrombosis. ST was observed in 17 patients (3.4%). As shown in Figure 4, EES was associated with a significant reduction in ST (1.6% vs. 5.2%, HR: 0.3 [95% CI: 0.1 to 0.92], p = 0.035; adjusted HR: 0.26 [95% CI: 0.08 to 0.80], p = 0.019). None of the ST events was related to premature discontinuation during the first year of follow-up, whereas in case of very late ST, no patient was on dual antiplatelet therapy because it was stopped at 1 year after primary PCI. Time distribution of all types of ST events is shown in Table 4. Landmark analysis showed benefits with EES within and later than 1-year follow-up as compared to benefits associated with SES (Fig. 5).

Target-vessel revascularization. TVR was observed in 24 patients (4.8%). As reported in Figure 6, no difference was observed in terms of TVR between EES and SES (4.8% vs. 4.8%, HR: 1 [95% CI: 0.45 to 2.32], p = 0.99; adjusted HR: 1.0 [95% CI: 0.44 to 2.25], p = 0.99).

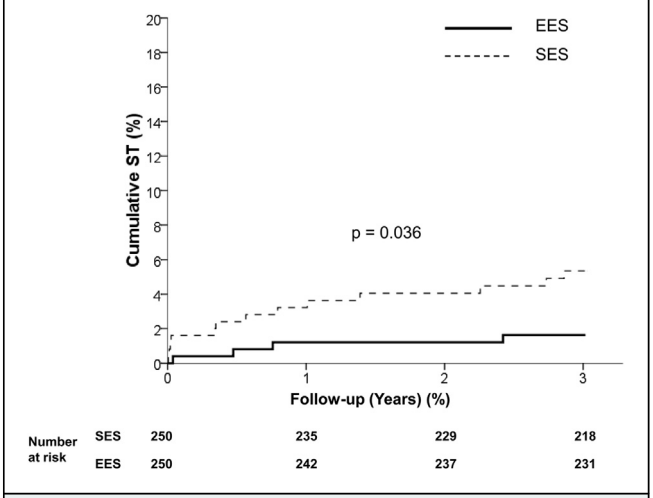

FIGURE 4 ST in SES Versus EES

Kaplan-Meier curves showing the occurrence of stent thrombosis (ST) in SES versus EES. Abbreviations as in Figure 1.

DISCUSSION

This is among the first randomized studies comparing EES and SES in patients undergoing primary angioplasty for STEMI. The main finding of the current study is that at 3-year follow-up, EES and SES are equally effective, whereas EES, as compared to SES, is associated with a significant reduction in definite/probable ST. After initial safety concerns, numerous studies and randomized trials have demonstrated the safety and efficacy of stenting in the setting of STEMI (3,5,6). A recent comprehensive meta-analysis in patients undergoing primary PCI has shown the benefits of stenting versus balloon angioplasty alone in terms of reducing TVR, although no definite impact on death and reinfarction was present (4). However, restenosis rates after BMS in STEMI patients are still high, especially in unselected patients with complex lesion morphology (5,6). Many randomized trials have been conducted, therefore, on the use of DES (7–17). However, recent concerns have emerged regarding the risk of late ST and death associated with DES. As most episodes of ST result in MI, this increase

TABLE 4 Timing of ST According to ARC Definition of Definite, Probable, and Possible

	SES (n = 250)	EES (n = 250)	p Value
Acute definite	0	0	1.0
Acute probable	0	0	1.0
Acute possible	0	0	1.0
Subacute definite	4 (1.6)	1 (0.4)	0.22
Subacute probable	0	0	1.0
Subacute possible	0	0	1.0
Late definite	4 (1.6)	1 (0.4)	0.17
Late probable	1 (0.4)	1 (0.4)	1.0
Late possible	0	0	1.0
Very late definite	3 (1.2)	0	0.089
Very late probable	2 (0.8)	1 (0.4)	0.54
Very late possible	0	0	0

Values are n (%).

ARC = Academic Research Consortium; ST = stent thrombosis; other abbreviations as in Table 1.

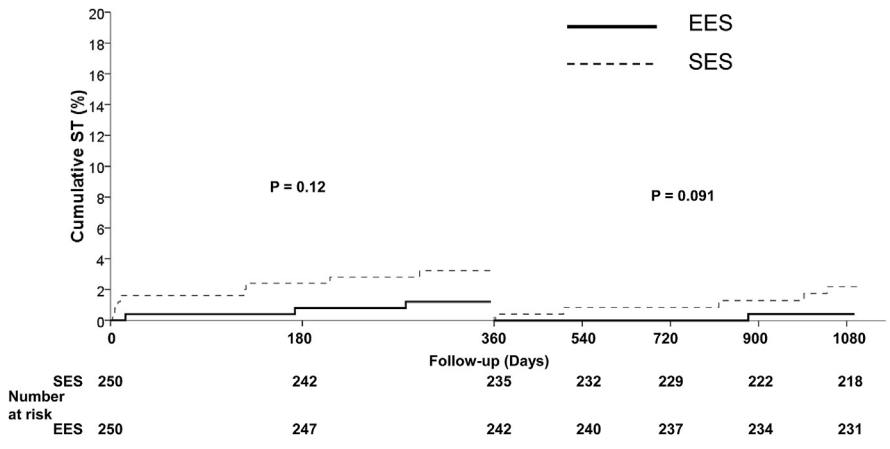

FIGURE 5 ST Within or Later Than 1-Year Follow-Up in SES Versus EES

Landmark analysis showing the occurrence of ST within or later than 1-year follow-up in SES versus EES. Abbreviations as in Figures 1 and 4.

with DES may affect mortality, particularly after primary angioplasty, as reinfarction is a major determinant of survival (20,21). In fact, a recent individual-patient data meta-analysis including >6,000 patients has shown that first-generation DES, as compared with BMS, are associated with a significant reduction in TVR, but higher rates of late ST (18). Therefore, the attention of research has been focused on new DES technologies with more biocompatible or bioabsorbable polymers. Among elective patients, those stents have been shown to further improve outcome as compared with the outcomes of BMS and first-generation DES (19). Few studies have so far investigated the new generation of DES in the setting of STEMI.

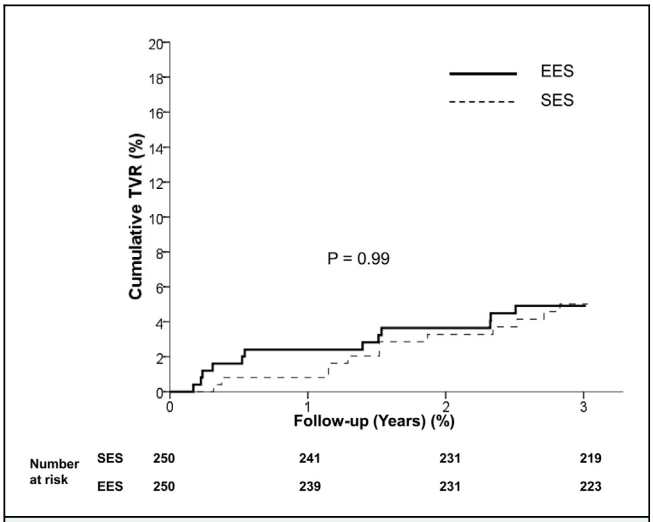

FIGURE 6 TVR in SES Versus EES

Kaplan-Meier curves showing the occurrence of target vessel revascularization (TVR) in SES versus EES. Abbreviations as in Figure 1.

The CONFORTABLE-AMI (Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction) trial (22) compared a biolimus-eluting stent with biodegradable polymer versus BMS in 1,500 patents. At 1-year follow-up, MACE occurred in 24 patients (4.3%) receiving biolimus-eluting stents and 49 patients (8.7%) receiving BMS ($p = 0.004$). The difference was driven by a lower risk of target vessel-related reinfarction (0.5% vs. 2.7%, $p = 0.01$) and ischemia-driven target lesion revascularization (1.6% vs. 5.7%, $p < 0.001$) in patients receiving biolimus-eluting stents versus BMS.

In the EXAMINATION (Clinical Evaluation of Xience-V Stent in Acute Myocardial Infarction) trial (23), 1,498 STEMI patients were randomly assigned to receive EES or BMS. At 1-year follow-up, the primary endpoint (patient-oriented combined endpoint of all-cause death, any recurrent MI, and any coronary revascularization) was similar in both groups (11.9% in the EES group vs. 14.2% in the BMS group; $p = 0.19$). However, EES was associated with significantly lower rates of target lesion and vessel revascularization (2.1% vs. 5.0%, $p = 0.003$, and 3.7% vs. 6.8%, $p = 0.0077$) and ST (0.5% vs. 1.9% for definite and 0.9% vs. 2.5% for combined definite or probable, both $p = 0.019$).

In the XAMI (XienceV Stent vs Cypher Stent in Primary PCI for Acute Myocardial Infarction) (24)

trial, 625 patients with acute MI were randomized (2:1) to receive EES or SES. The primary endpoint was MACE at 1 year consisting of cardiac death, nonfatal acute MI, or any TVR. EES was associated with a significant reduction in the primary endpoint (4% vs. 7.7%, p = 0.048), whereas no difference was observed in terms of cardiac mortality (1.5% vs. 2.7%, p = 0.36), and definite and/or probable ST (1.2% vs. 2.7%, p = 0.21).

This is the first study comparing EES and SES in STEMI with available 3-year follow-up data. Whereas EES and SES performed equally in terms of efficacy (similar TVR rates), EES was associated with a significant reduction in ST.

Together, these data support the preserved efficacy but improved safety of new-generation as compared to first-generation DES in the setting of STEMI.

STUDY LIMITATIONS. Despite long-term follow-up data, due to the relatively small sample size, the study is underpowered to evaluate mortality and other secondary endpoints. Furthermore, a larger use of thrombectomy devices, by reducing the thrombotic burden, might have potentially affected the results of our study (25).

CONCLUSIONS

This study shows that among STEMI patients undergoing primary angioplasty, at 3-year follow-up EES and SES are equally effective, whereas EES is associated with a significant reduction in definite/probable ST. Therefore, while waiting for the results of additional large studies with long-term follow-up data, EES may be safely considered for use in STEMI patients undergoing primary angioplasty.

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