Randomized Trial of Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction (SESAMI)

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Objectives	To confirm whether sirolimus-eluting stents (SES) safely reduce the incidence of restenosis in patients with ST-segment elevation acute myocardial infarction compared with bare-metal stents (BMS).
Background	In the setting of primary angioplasty, stent restenosis occurs in up to 27% of patients. The introduction of drug-eluting stents has drastically reduced the incidence of restenosis in clinically stable patients.
Methods	We conducted a randomized trial of 320 patients with acute ST-segment elevation myocardial infarction assigned to receive SES or BMS. The primary end point was binary restenosis at 1-year angiographic follow-up.
Results	At 1 year, the incidence of binary restenosis was lower in the SES group than in the BMS group (9.3% vs. 21.3%, respectively; p = 0.032), as were the rates of target lesion revascularization (4.3% vs. 11.2%; p = 0.02), target vessel revascularization (5% vs. 13.1; p = 0.015), major adverse cardiac events (6.8% vs. 16.8%; p = 0.005), and target vessel failure (8.7% vs. 18.7%; p = 0.007). The incidence of angiographically documented stent thrombosis was 1.2% (n = 2) in the SES group and 0.6% (n = 1) in the BMS group.
Conclusions	In patients with acute myocardial infarction, SES are superior to BMS, reducing the incidence of binary restenosis by 56%, target lesion revascularization by 61%, target vessel revascularization by 62%, adverse cardiac events by 59%, and target vessel failure by 53% at 1 year. (Sirolimus Eluting Stenting in Acute Myocardial Infarction; http://www.clinicaltrials.gov/ct/show/NCT00288210; NCT00288210) (J Am Coll Cardiol 2007;49: 1924–30) © 2007 by the American College of Cardiology Foundation

The treatment of acute myocardial infarction (MI) has evolved dramatically in the last decade. Primary coronary angioplasty with stent implantation is now considered the standard of care. However, in the setting of primary angioplasty, the incidence of stent restenosis remains high,

up to 27% (1,2), leading to rehospitalization and increased cost (3,4). In patients undergoing elective percutaneous coronary intervention (PCI), the use of drug-eluting stents has drastically reduced the incidence of restenosis compared with bare-metal stents (BMS) in patients with comparable stent thrombosis (5–9). However, it is not known if sirolimus-eluting stents (SES) increase event-free survival at mid-term follow-up after acute MI. To answer this question, we conducted a study in which patients with acute MI

eligible for primary angioplasty were randomized to receive SES or BMS.

Methods

The SESAMI (Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction) trial is a randomized trial conducted in a single center where patients with suspected acute MI are admitted directly to the cardiac catheterization laboratory. Percutaneous transluminal coronary angioplasty was performed by 6 experienced operators, each of whom performs 200 to 250 such elective procedures annually. The study was approved by our hospital ethics committee, and all randomized patients gave written informed consent. The trial was conducted in accordance with the ethical principles of the Helsinki Declaration regarding investigation in humans.

Study population. Patients were included if they were >18 years of age, had symptoms of acute MI for ≥30 min but ≤12 h, and had ≥1 mm ST-segment elevation in at least 2 contiguous leads or left bundle-branch block. The exclusion criteria were cardiogenic shock (systolic blood pressure <80

mm Hg for >30 min or need for intravenous pressors or intra-aortic balloon counterpulsation); a history of bleeding diathesis, leukopenia, thrombocytopenia, or severe hepatic or renal dysfunction; noncardiac illness associated with a life expectancy of <1 year; left main coronary artery or graft disease; participation in another study; or inability to give informed consent owing to prolonged cardiopulmonary resuscitation. Excluded patients received clinically appropriate treatment.

Catheterization and study procedure. The study protocol recommended that aspirin (500 mg intravenously) and beta-blockers (in the absence of contraindications) be administered in the emergency room. Patients were then taken immediately to the cardiac catheterization laboratory to undergo coronary angiography.

Once blood flow was established (spontaneously or by balloon inflation), the operator determined if the patient qualified for randomization. The infarct-related vessel had to be a native coronary artery with a visually estimated reference diameter >2.5 and ≤4.0 mm. Sealed sequentially numbered opaque allocation envelopes were used for randomization. The allocation schedule was based on computer-generated random numbers (block size 20). Patients were assigned in equal numbers to receive SES (Cypher, Cordis, Miami Lakes, Florida) or BMS (BX stent, Cordis) of the same diameter as the reference vessel. Clopidogrel, an inhibitor of adenosine diphosphate–induced platelet aggregation, was given as a bolus of 4 tablets immediately after the procedure and was continued for 1 year in both groups. Dilatation after stent placement was at the operator's discretion.

Myocardial perfusion was graded as in the Thrombolysis In Myocardial Infarction (TIMI) trial; flow grade 3 within the vessel was considered to be normal (10). The glycoprotein IIb/IIIa receptor inhibitor abciximab (ReoPro, Eli Lilly, Indianapolis, Indiana; Centocor, Horsham, Pennsylvania) was administered as a 0.25 mg/kg bolus followed by a 12-h infusion (0.125 μg/kg/min; maximum, 10 μg/min) (11–14). If it was not started in the emergency room, abciximab therapy was initiated in the catheterization laboratory before coronary angiography. The heparin dose was calculated to achieve an activated clotting time of 200 to 250 s. Plasma levels of creatine kinase-myocardial band and troponin I were measured in samples obtained at baseline and 8 and 24 h after the index procedure.

Angiographic analysis. Cineangiograms were obtained immediately after the procedure, according to standard guidelines. Standard morphologic criteria were used to characterize the complexity of the lesions at baseline and to identify angiographic complications (15).

Successful stent implantation was defined as <20% residual stenosis by visual assessment over the entire stent length, with TIMI flow grade 3 and no more than National Heart, Lung, and Blood Institute type A peristent dissection. Angiographic readers were blinded to the type of stent implanted. The projection that best

showed the stenosis was used for all of the analyses. The contrast-filled nontapered tip of the catheter was used for calibration. Digital angiograms were analyzed with an automated edge-detection system (CAAS II, Pie Medical Imaging, Maastricht, the Netherlands) (16). The minimal luminal diameter and extent of stenosis were measured before and after the procedure and at follow-up. Binary restenosis was defined as ≥50% reduction of the initial lumen diameter in the target lesion inside or at the proximal and distal 5 mm of the stent.

End points. The primary end point for the trial was binary restenosis at the 1-year angiographic follow-up. All serious clinical events, including stent thrombosis, were reviewed by 2 authors (A.G. and D.A.), who were unaware of stent assignment. The secondary end points were target lesion revascularization (TLR), target vessel revascularization (TVR), major adverse cardiovascular events (MACE), and target vessel failure (TVF) at 1 year.

Target lesion revascularization was defined as repeated PCI or bypass grafting of the target vessel driven by clinical symptoms of myocardial ischemia, a positive stress test attributable to the target vessel, or an in-lesion stenosis >70% of the reference luminal diameter. Target vessel failure was defined as the combination of TVR, recurrent infarction, and target vessel-related death within 1 year. Reinfarction was defined as recurrent ischemic symptoms or electrocardiographic changes, accompanied by a creatine kinase level more than twice the upper limit of the normal range (and an elevated myocardial band isoform level) or more than 50% higher than the previous value during hospitalization.

To capture all possible adverse events attributable to stent thrombosis, we used the new Academic Research Consortium definitions for thrombosis. Stent thrombosis was defined as definite (angiographic confirmation), probable (heart attack attributable to the treated vessel without angiographic confirmation), or possible (unexplained sudden death not attributed to another cause such as car accident or cancer).

Statistical analysis. To determine the effect of SES on binary restenosis in patients with acute MI, we calculated that 160 patients would be required to undergo angiographic follow-up at 1 year. To detect with 90% power a reduction in the primary end point, using a 2-sided test for differences in independent binomial proportions, we set significance at the 0.025 level, given expected restenosis rates of 27% (1,2) after BMS and 7% after SES. To

accommodate patient loss at the angiographic follow-up, we enrolled 200 patients. To have more information about the secondary clinical end points (TLR, TVR, MACE, and TVF) at 1 year, we increased this number to 320 patients.

Categoric variables were compared with the likelihood ratio chi-square test or the Fisher exact test. Continuous variables are presented as median and interquartile range and were compared with 1-way analysis of variance or the Mann-Whitney test; for pairwise analyses, the Wilcoxon 2-sample test was used.

Event-free composites during the 1-year follow-up were analyzed with the Kaplan-Meier method. Differences in the 2 event-free curves were analyzed with the log-rank test; a 2-sided probability of <0.05 was considered to be significant. The treatment groups were compared on an intent-to-treat basis. All statistical tests were performed with SPSS for Windows, version 14 (SPSS Inc., Chicago, Illinois). All data were analyzed by a professional statistician.

Results

Baseline characteristics. Over a 30-month enrollment period, 423 patients with acute MI were screened. Of these, 320 were randomly assigned to 1 of the 2 treatment groups: 160 to SES and 160 to BMS. A total of 103 patients were excluded because they had left main disease (n = 3), graft disease (n = 15), or cardiogenic shock (n = 32), presented more than 12 h after the onset of pain (n = 34), or refused to give informed consent (n = 19) (Fig. 1). The 2 groups were well matched (Table 1). However, a higher percentage of patients in the BMS group had a previous MI (5.6% vs. 12.5%; p = 0.047). Angioplasty was performed with thrombolysis in 17.8% of the patients and without in 82.2% (Table 1).

Procedural results. The procedural results are summarized in Table 2. Two patients randomized to the SES group had tortuous calcific vessels that prevented implantation of the SES. Both patients received a new-generation BMS
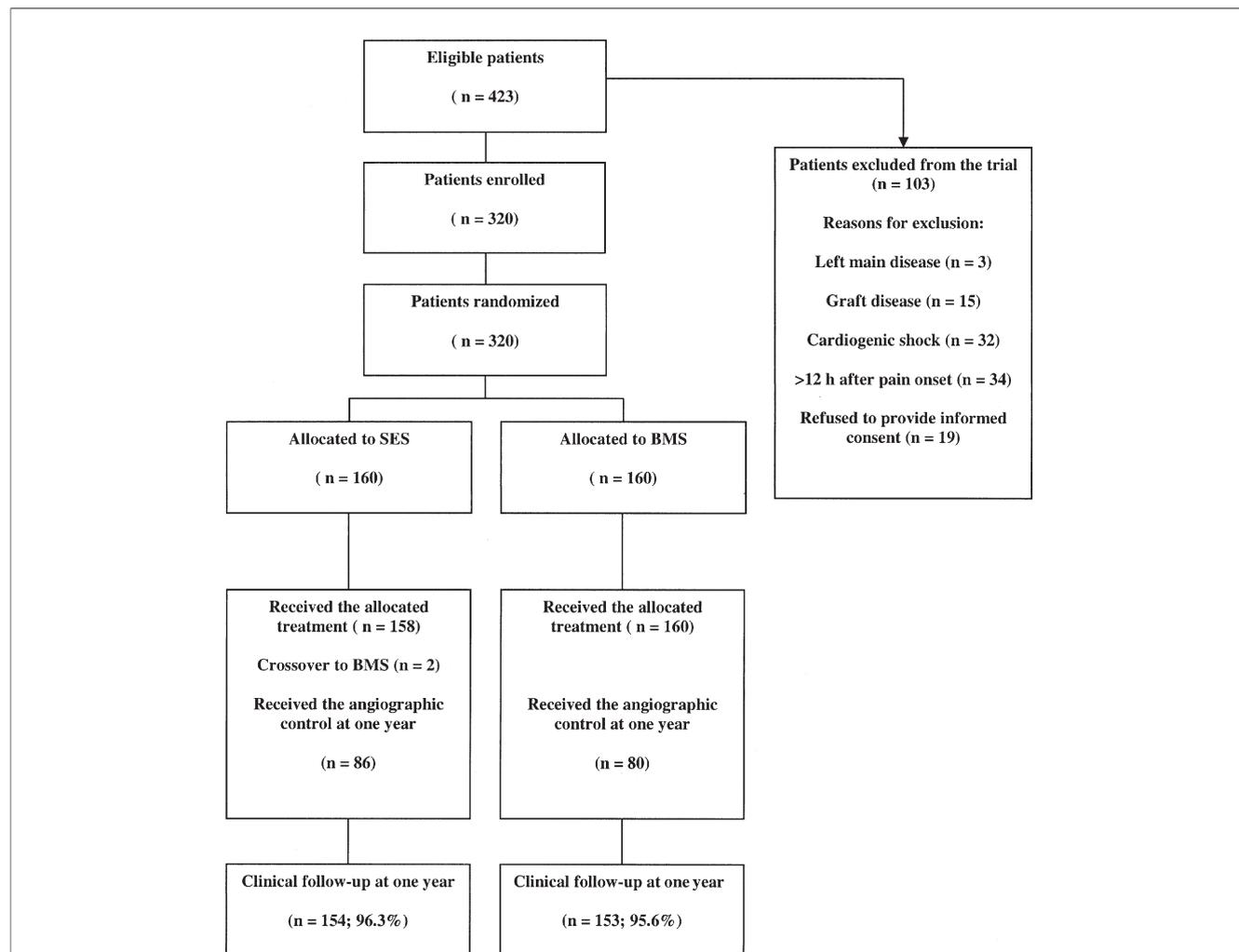

Figure 1   CONSORT Diagram of the Study

BMS = bare-metal stents; CONSORT = Consolidated Standards of Reporting Trials; SES = sirolimus-eluting stents.

Table 1	Baseline Characteristics of the SES Study Patients and BMS Control Patients		
Characteristic	SES (n = 160)	BMS (n = 160)	p Value
Age (yrs)			0.81
Median	63	62	
Interquartile range	54–70	52–72	
Male gender	128 (80%)	128 (80%)	
Diabetes mellitus	28 (17.5%)	37 (23.7%)	0.13
Hypertension	87 (54.3%)	98 (58.7%)	0.20
Current smoker	91 (56.8%)	83 (51.7%)	0.10
Prior myocardial infarction	9 (5.6%)	20 (12.5%)	0.047
Prior PTCA	15 (9.4%)	17 (10.6%)	0.38
Prior coronary bypass	1 (0.6%)	1 (0.6%)	0.75
Killip class >2	13 (8.1%)	15 (9.3%)	0.38
ST-segment elevation	157 (98.1%)	158 (98.7%)	0.5
PTCA only	132 (82.5%)	131 (81.8%)	0.53
PTCA + thrombolysis	28 (17.5%)	29 (18.2%)	0.54
Time from symptom onset to PTCA (h)			
PTCA only			0.65
Median	4	4	
Interquartile range	3–7	3–6	
PTCA + thrombolysis			0.64
Median	6.0	6.2	
Interquartile range	2.6–9.5	3.0–8.5	
Angiographic features			
Single-vessel disease	94 (58.7%)	92 (57.5%)	0.92
Double-vessel disease	41 (25.6%)	42 (26.2%)	0.92
Triple-vessel disease	25 (15.6%)	42 (26.2%)	0.88
Infarct-related vessel			
Left anterior descending artery	75 (46.8%)	84 (52.5%)	0.29
Left circumflex artery	21 (13.1%)	20 (12.5%)	0.54
Right coronary artery	64 (40.1%)	56 (35.0%)	0.46
Enzymes			
CK-MB (peak)			
Median	147.5	138	0.88
Interquartile range	66–276	61–264	
Troponin I (peak)			
Median	55	47.5	0.87
Interquartile range	15–80	16–80	

Data are presented as number (%), median, or interquartile range.

BMS = bare-metal stent; CK-MB = creatine kinase-myocardial band; PTCA = percutaneous coronary angioplasty; SES = sirolimus-eluting stent.

(Driver, Medtronic, Fridley, Minnesota) but were analyzed with the SES group according to the intent-to-treat principle. The rate of success according to angiographic criteria (<20% residual stenosis, TIMI flow grade 2 or 3) was similar in the 2 groups: 98.1% (SES) and 98.8% (BMS) (p = 0.47). Total stent length was significantly greater in the SES group. Stent diameter, however, was significantly larger in the BMS group.

Angiographic results. The binary restenosis rate at 1 year was 56% lower in the SES group than in the BMS group (9.3% vs. 21.3%, respectively; p = 0.032) (Table 3).

Risk factor and treatment effect analysis. No significant treatment interactions were detected that would suggest a lack of clinical benefit of SES in subsets of patients, including those with diabetes mellitus or variations in vessel diameter or lesion length.

Major adverse cardiac events. In-hospital adverse events were infrequent, with no significant difference between groups (Table 4). In-hospital death occurred in 4 BMS patients and 1 SES patient (2.5% vs. 0.6%, respectively; p = 0.375). Two patients (1.2%) in each group had a reinfarction. Angiographically documented stent thrombosis occurred in 1 BMS patient and 2 SES patients. There was no statistical difference in the combined outcome of death and MI between the 2 groups. Sirolimus-eluting stent implantation resulted in reductions of 61% in TLR (4.3% vs. 11.2%; p = 0.02), 62% in TVR (5% vs. 13.1%; p = 0.015), 59% in MACE (6.8% vs. 16.8%; p = 0.005), and 53% in TVF (8.7% vs. 18.7%; p = 0.007) (Fig. 2).

Discussion

This study shows that use of SES resulted in a significantly lower rate of angiographic binary restenosis than BMS in

Table 2	Procedural Results		
Value	**SES (n = 160)**	**BMS (n = 160)**	**p Value**
Procedural success	157 (98.1)	158 (98.8)	0.47
No. of stents implanted			
Mean	1	1	
Interquartile range	1–1	1–1	
Stent length (mm)	16.9 ± 4.1	19.4 ± 4.8	0.001
Stent diameter (mm)	3.14 ± .034	3.02 ± 0.28	0.001
Abciximab therapy			
Started in emergency room	26 (16.2%)	34 (21.2%)	0.25
Started in catheterization laboratory	98 (61.2%)	84 (52.5%)	0.32
TIMI flow			
PTCA only			
Before procedure	28 (17.5%)	31 (19.3%)	0.75
After procedure	150 (93.8%)	137 (85.6%)	0.40
PTCA + thrombolysis			
Before procedure	15 (9.4%)	42 (26.2%)	0.16
After procedure	139 (83.9%)	137 (85.6%)	0.89
Minimal lumen diameter (mm)			
Before procedure			0.38
Median	0	0	
Interquartile range	0–7	0–7	
Final			0.41
Median	2.7	2.7	
Interquartile range	2.4–2.95	2.4–2.90	
Extent of stenosis			
Before procedure			0.45
Median	100	100	
Interquartile range	73–100	72.1–100	
Final			0.14
Median	10.5	8.9	
Interquartile range	4.1–18.3	4.5–16.1	

Data are presented as number (%), mean ± SD, median, or interquartile range.
TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

patients with acute ST-segment elevation MI who underwent angioplasty with or without thrombolysis. Sirolimus-eluting stents also led to a higher rate of 1-year event-free survival.

These findings extend and confirm the positive finding of SES in stable patients to patients with ST-segment elevation MI. In the STRATEGY (Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent vs. Abciximab and Bare-Metal Stent in Myocardial Infarction) trial (2), 175 patients with ST-segment elevation MI were randomized to receive single high-dose bolus of tirofiban plus SES or abciximab plus BMS. However, the randomization design was primarily based on economic considerations, with the hope that the lower cost of tirofiban would offset the cost of SES, and binary stent restenosis was not the primary end point, which it was in our study.

Table 3	Angiographic Results at 1-Year Follow-Up		
Outcome	**SES (n = 86)**	**BMS (n = 80)**	**p Value**
Binary restenosis (%)	9.3	21.3	0.03
Angiographic occlusion (%)	2.5	3.7	0.42
Mean diameter stenosis (%)	14	34	0.001
Late luminal loss (mm)	0.18	0.85	0.001

Abbreviations as in Table 1.

| Table 4	Clinical Outcome at Hospital Discharge and at 1 Year		
Outcome	**SES**	**BMS**	**p Value**
At hospital discharge			
Death (%)	1 (0.6%)	4 (2.5%)	0.19
Reinfarction (%)	2 (1.2%)	2 (1.2%)	
Target vessel revascularization (%)	1 (0.6%)	1 (0.6%)	
At 1 yr			
Death (%)	3 (1.8%)	7 (4.3%)	0.36
Reinfarction (%)	3 (1.8%)	3 (1.8%)	
Stent thrombosis (%)			
Definite	2 (1.2%)	1 (0.6%)	
Probable/possible	5 (3.1%)	6 (3.7%)	0.43
Target lesion revascularization	7 (4.3%)	18 (11.2%)	0.02
Target vessel revascularization	8 (5.0%)	22 (13.1%)	0.015
Major adverse coronary events	11 (6.8%)	27 (16.8%)	0.005
Target vessel failure	13 (8.7%)	29 (18.7%)	0.007

Abbreviations as in Table 1.
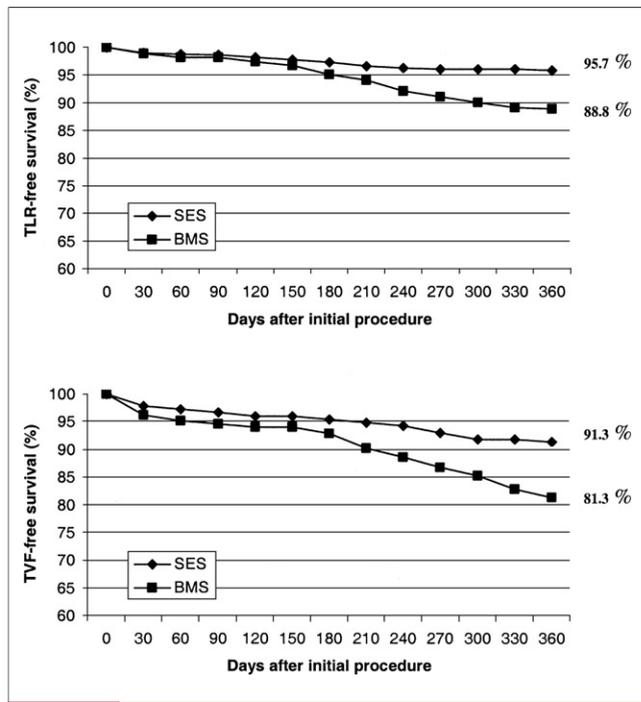
Figure 2 | **Actuarial Rate of Survival Free From TLR and TVF Among Patients Who Received an SES or a BMS**

The rate of event-free survival was significantly higher in the sirolimus-eluting stent (SES) group. BMS = bare-metal stent; TLR = target lesion revascularization; TVF = target vessel failure.

Recently, 2 randomized trials specifically studied the efficacy and safety of SES and paclitaxel-eluting stents in patients with acute MI. In TYPHOON (Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treatment With Balloon Angioplasty) (17), the rate of repeated revascularization procedures was significantly lower in the SES group than in the BMS control group. In the PASSION (Paclitaxel-Eluting Stent versus Conventional Stent in Myocardial Infarction With ST-Segment Elevation) trial (18), the reduction in the need for TLR with paclitaxel-eluting stents did not reach statistical significance.

The present study was designed to ascertain whether an SES is associated with a significantly lower rate of binary restenosis (our primary end point) compared with BMS. In contrast, the primary end points were TVF in the TYPHOON trial and MACE in the PASSION trial. In the present study, restenosis was evaluated angiographically at 1 year in all 160 prespecified patients required by power calculation. Angiographic follow-up was performed at 8 months in the TYPHOON trial and was not performed in the PASSION trial. In addition, the inclusion criteria were broader in the present study than in the TYPHOON trial, which excluded patients who had a previous MI, received a fibrinolytic agent for the index infarction, had an ejection fraction <30%, or had ostial, bifurcation, or excessively tortuous lesions. Therefore, the present results in the SESAMI trial confirm and extend the findings of the TYPHOON trial, showing that SES markedly reduces

clinical events at 1-year follow-up, primarily because fewer repeated revascularization procedures are required.

Although significantly lower than in the BMS group, the incidence of angiographically confirmed binary restenosis in the SES group was not negligible (9.3%). Saia et al. (19) reported a binary restenosis rate of 0% in patients with ST-segment elevation MI. However, the difference may reflect, in part, the shorter angiographic follow-up time (6 months) in that study. The incidence of angiographic restenosis in the BMS arm (21.3%) was comparable with that in other studies (11,14,20).

Although efficacy in reducing restenosis has been demonstrated, the safety of SES in the setting of acute MI had not been resolved. Laboratory data suggested that SES could induce endothelial dysfunction (21), delay vascular healing (22), and increase agonist-induced platelet aggregation (23), potentially resulting in greater risk of stent thrombosis than with BMS. In a clinical study, vessel segments adjacent to SES showed paradoxic exercise-induced coronary vasoconstriction, a sign of dysfunctional endothelium (24). In a postmortem study, several procedural and pathologic risk factors for stent thrombosis were identified, such as a local hypersensitivity reaction, ostial or bifurcation stenting, malapposition or incomplete apposition, restenosis, and strut penetration into a necrotic core (25). Meanwhile, in a prospective observational cohort study of 2,229 consecutive "real-world" patients who underwent successful implantation of SES or paclitaxel-eluting stents, the cumulative incidence of stent thrombosis at 9 months was substantially higher than the rate reported in clinical trials (26). Premature discontinuation of antiplatelet therapy, renal failure, bifurcation lesions, diabetes, and low ejection fraction were identified as predictors of thrombotic events; all of these potentially increase the risk of thrombotic complications and worsen the outcome after SES implantation, especially in vulnerable patients such as those treated during the acute phase of MI.

In the present study, such concerns did not translate into clinical events. Using the new Academic Research Consortium definitions for thrombosis, we identified only 2 episodes of definite stent thrombosis in the SES group. One episode occurred 20 h after the procedure in a patient with bleeding problems who could not receive abciximab. The other occurred 8 months after the index procedure. This low incidence of stent thrombosis confirms the safety of SES in the setting of acute MI reported in a large registry study, in which the cumulative incidence of stent thrombosis was 0.87% at 1 year (27). However, that study did not have sufficient power to detect a difference in stent thrombosis rates between the 2 stents. In addition, although the low rate of angiographically proven stent thrombosis in the present study might appear reassuring, larger dedicated studies with a long-term follow-up are needed to answer this question definitively. Furthermore, the role of long-term dual antiplatelet therapy in patients with acute MI treated with DES remains to be defined.

Study limitations. Several potential limitations of our study should be mentioned. First, ~20% of screened patients were excluded because of cardiogenic shock, left main coronary disease, and bypass grafts. However, these exclusions reflect the daily practice in the real world of interventional cardiology. Second, although the angiographic readers were blinded to the type of stent implanted, an independent core-lab analysis would have been preferable. Third, although we found no differences in the rates of death, MI, or stent thrombosis, the study did not have sufficient power to show a difference in those clinical events. To do so would require a study of thousands of patients, which would not be feasible in a small, single-center study such as ours. Fourth, the BMS used in the control group was a BX stent, not a new-generation stent. However, using 2 stents based on the same platform helped to reveal the difference in antirestenotic efficacy of the sirolimus elution. Moreover, although new-generation stents may have reduced the restenosis rate, as shown by Pache et al. (28), the restenosis rate in the BMS group was not particularly high and was in line with previous primary angioplasty trials.

Conclusions

We have demonstrated that an SES reduces the incidence of restenosis and the secondary end points of TLR, TVR, MACE, and TVF in a broadly selected population with ST-segment elevation MI treated with primary angioplasty. Only 2 episodes of definite stent thrombosis occurred, indicating that routine SES implantation in the setting of ST-segment elevation MI is safe.

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