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Sirolimus-Eluting Stents Versus Bare-Metal Stents in Patients With ST-Segment Elevation Myocardial Infarction: 9-Month Angiographic and Intravascular Ultrasound Results and 12-Month Clinical Outcome

Results From the MISSION! Intervention Study

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Objectives Our purpose was to evaluate the efficacy and safety of drug-eluting stents in the setting of primary percutaneous coronary intervention for ST-segment elevation myocardial infarction (STEMI).

Background There is inconsistent and limited evidence about the efficacy and safety of drug-eluting stents in STEMI patients.

Methods A single-blind, single-center, randomized study was performed to compare bare-metal stents (BMS) with sirolimus-eluting stents (SES) in 310 STEMI patients. The primary end point was in-segment late luminal loss (LLL) at 9 months. Secondary end points included late stent malapposition (LSM) at 9 months as determined by intravascular ultrasound imaging and clinical events at 12 months.

Results In-segment LLL was 0.68 ± 0.57 mm in the BMS group and 0.12 ± 0.43 mm in the SES group with a mean difference of 0.56 mm, 95% confidence interval 0.43 to 0.68 mm ($p < 0.001$). Late stent malapposition at 9 months was present in 12.5% BMS patients and in 37.5% SES patients ($p < 0.001$). Event-free survival at 12 months was 73.6% in BMS patients and 86.0% in SES patients ($p = 0.01$). The target-vessel-failure-free survival was 84.7% in the BMS group and 93.0% in the SES group ($p = 0.02$), mainly because of a higher target lesion revascularization rate in BMS patients (11.3% vs. 3.2%; $p = 0.006$). Rates of death, myocardial infarction, and stent thrombosis were not different.

Conclusions Sirolimus-eluting stent implantation in STEMI patients is associated with a favorable midterm clinical and angiographic outcome compared with treatment with BMS. However, LSM raises concern about the long-term safety of SES in STEMI patients (MISSION!; ISRCTN62825862). (J Am Coll Cardiol 2008;51:618–26) © 2008 by the American College of Cardiology Foundation

Percutaneous coronary intervention (PCI) is the preferred revascularization strategy in patients presenting with ST-segment elevation myocardial infarction (STEMI) (1). Percutaneous coronary intervention is directed at restoring coronary flow, stabilizing the ruptured plaque, and reducing infarct size, thereby improving short- and long-term clinical outcome. Implantation of a bare-metal coronary artery stent (BMS) during primary PCI further improves outcome compared with balloon angioplasty alone by reducing the number of acute complications and the restenosis rate (2,3). Drug-eluting stents have been proven effective in reducing restenosis in patients with stable and unstable angina (4–7). Inconsistent and limited results have been presented about the efficacy and safety of drug-eluting stents in STEMI

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patients (8,9). In particular, stent thrombosis occurring late after implantation of drug-eluting stents, possibly related to late malapposition of the stent struts, has raised safety concerns (10,11). Therefore, this randomized prospective study was designed to evaluate midterm angiographic outcome and clinical efficacy of third-generation BMS compared with that seen in sirolimus-eluting stents (SES) in STEMI patients. To address the issue of late stent malapposition (LSM), intravascular ultrasound (IVUS) imaging was performed in both groups at 9-month follow-up.

Methods

Study design. This is a single-center, single-blind, randomized prospective noninferiority study to evaluate clinical, angiographic, and IVUS results in STEMI patients treated with either BMS or SES. The study protocol was approved by the institutional ethical committee. Written informed consent was obtained from all patients before enrollment and before the follow-up catheterization. Patients and operators performing the follow-up angiography were blinded to the treatment assignment. The study was conducted from February 2004 to October 2006. During the study period, all patients were treated according to the institutional STEMI protocol, which included standardized outpatient follow-up (12).

Patient selection. Patients were eligible if STEMI symptoms started <9 h before the procedure and the electrocardiogram (ECG) demonstrated STEMI (ST-segment elevation ≥0.2 mV in ≥2 contiguous leads in V_1 through V_3 or ≥0.1 mV in other leads, or [presumed] new left bundle branch block). Furthermore, the target lesion length should be ≤24 mm. Exclusion criteria were: 1) age <18 years or >80 years; 2) left main stenosis of ≥50%; 3) triple-vessel disease, defined as ≥50% stenosis in ≥3 major epicardial branches; 4) previous PCI or coronary artery bypass grafting of the infarct-related artery; 5) thrombolytic therapy for the index infarction; 5) target vessel reference diameter <2.25 mm or >3.75 mm; 6) need for mechanical ventilation; 7) contraindication to the use of aspirin, clopidogrel, heparin, or abciximab; 8) known renal failure; or 9) a life expectancy <12 months.

After crossing the target lesion with a guidewire and after visual estimation of the target vessel reference diameter, randomization to treatment with a BMS (Vision, Guidant Corp. Indianapolis, Indiana) or SES (Cypher, Cordis Corp., Miami Lakes, Florida) was performed in a 1:1 ratio.

Study procedure. Before the procedure all patients received 300 mg of aspirin, 300 to 600 mg of clopidogrel, and an intravenous bolus of abciximab (25 μg/kg), followed by a continuous infusion of 10 μg/kg/min for 12 h. At start of the procedure, 5,000 IU of heparin was given. Lesions were treated according to current interventional practice. Direct stenting was allowed. If more than 1 stent was required, additional assigned study stents were used. Stent size and length selection was based on visual estimation. Before and immediately after the intervention, 2 angiograms in orthogonal projections were obtained. Intravascular ultrasound imaging was performed after stent implantation (motorized pull-back [0.5 mm/s]), starting >10 mm distal to the stent and ending at the coronary ostium, using a 2.9-F 20-MHz catheter and a dedicated IVUS console (Eagle Eye, Volcano Corp., Rancho Cordova, California) (13). Intravascular-ultrasound-guided stenting was not performed to reflect routine angiographic stent implantation. Each angiogram and ultrasound sequence was preceded by 200 to 300 μg of intracoronary nitroglycerin.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CI = confidence interval
HR = hazard ratio
IVUS = intravascular ultrasound
LLL = late luminal loss
LSM = late stent malapposition
MI = myocardial infarction
MLD = minimal luminal diameter
PCI = percutaneous coronary intervention
QCA = quantitative coronary angiography
SES = sirolimus-eluting stent(s)
STEMI = ST-segment elevation myocardial infarction

Follow-up and data collection. Patients were seen at the outpatient clinic at 30 days, 3, 6, and 12 months (12). Aspirin (80 to 100 mg/day) was prescribed indefinitely and clopidogrel (75 mg/day) for 12 months. Patients were treated with beta-blocking agents, statins, and angiotensin-converting enzyme inhibitors or angiotensin II blockers. Follow-up angiography and IVUS imaging was performed at 9 months.

Quantitative coronary angiography (QCA) and IVUS analysis. Angiograms were analyzed off-line by analysts blinded for the assigned treatment using validated QCA systems (CMS version 6.1, Medis, Leiden, the Netherlands). Measurements were made in a single projection showing the most severe stenosis following standardized operating procedures (14). The minimal lumen diameter (MLD) was measured, and the percentage diameter stenosis was calculated using the interpolated reference diameter approach. Late luminal loss (LLL) was defined as the difference between the post-procedural MLD and follow-up MLD. Angiographic restenosis was defined as ≥50% diameter stenosis at 9-months, follow-up.

Intravascular ultrasound images were analyzed off-line, using quantitative IVUS analysis software (QCU-CMS version 4.14, Medis). The stented segment (+5 mm proximally and distally to the stent) was analyzed. The stent and lumen boundaries were determined in all individual frames. In case of malapposition, the stent boundaries were used as lumen boundaries. The volume within the stent and the luminal volume were calculated applying Simpson's rule (15). Stent malapposition was defined as a separation of at least 1 stent strut, not overlapping a side branch, from the intimal surface with IVUS evidence of blood speckles behind the strut (16,17). The site of malapposition was classified as: 1) the body of the stent; 2) the proximal stent edge; or 3) the distal stent edge. Malapposition was persis-

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tent if it was present immediately after stent implantation and at follow-up, and acquired if it was present at follow-up only.

Study end points. The primary end point of the study was in-segment LLL at 9-month follow-up angiography. Secondary end points were angiographic restenosis and LSM at 9 months. Additional secondary end points were death, myocardial infarction (MI), target vessel revascularization, target lesion revascularization, target vessel failure, stent thrombosis, procedural success, and clinical success. All deaths were defined as cardiac, unless it was unequivocally proven noncardiac. Myocardial infarction during follow-up was defined as a troponin-T rise >0.03 μg/l with symptoms or PCI, a rise of troponin-T >0.15 μg/l after coronary artery bypass grafting, or a rerise of troponin-T >25% after recent MI in the presence of symptoms or re-PCI, or the development of new Q waves on ECG (18,19). All infarctions were categorized as spontaneous or procedure related (nonindex procedure) (18,19). Procedural success was defined as the achievement of <50% diameter stenosis by QCA with achievement of Thrombolysis In Myocardial Infarction flow grade 3. Clinical success was defined as procedural success without death or reinfarction during the index hospitalization. Target vessel and target lesion revascularization were defined as any revascularization procedure of the target vessel or target lesion (from 5 mm distally to the stent up to 5 mm proximally to the stent), respectively. Clinically driven target lesion revascularization was defined as repeated revascularization procedure of the target lesion (showing ≥50% diameter stenosis) driven by clinical symptoms at rest in conjunction with electrocardiographic evidence of ischemia or a positive stress test (in the presence or absence of clinical symptoms). Target vessel failure was defined as the composite of cardiac death or recurrent MI attributable to the target vessel or any revascularization procedure of the target vessel. If events could not unequivocally be attributed to a nonculprit vessel, they were considered culprit vessel related. Stent thrombosis was defined as angiographically documented thrombus within the stent and/or typical chest pain with recurrent ST-segment elevation in the territory of the infarct-related vessel in combination with a significant rise of troponin levels and/or the presence of new Q waves in the territory of the infarct-related vessel. Stent thrombosis was classified as acute if it occurred <24 h after the index procedure, as subacute if it occurred between 1 to 30 days, and as late if it occurred >30 days (9). All clinical events were adjudicated by a clinical events committee whose members were blinded for the assigned stent type.

Statistical design and analysis. The study objective was to assess whether the outcome of treatment with BMS was noninferior to the outcome of treatment with SES. To prove noninferiority, a difference of ≤0.35 mm angiographic in-segment LLL at 9 months was considered clinically insignificant. The sample size to demonstrate noninferiority of BMS was 244 patients (1-sided) based on the following assumptions: 1) angiographic in-segment LLL at 9 months is 0.40 mm in the SES group and 0.60 mm in the BMS group, with a common within-group standard deviation of 0.40 mm (power 0.90, alpha error of 0.05). To compensate for unsuccessful interventions, crossovers, and losses to follow-up, the sample size was increased to a total of 316 patients. All analyses were conducted according to the intention-to-treat principle. Analysis of post-procedural and follow-up angiographic and IVUS data was conducted according to the number of patients for which complete data were available. All continuous variables were compared between the treatment groups with a *t* test or, in case of non-normality as tested by Shapiro-Wilk's statistics, with an equivalent nonparametric test. Categorical variables were compared with Pearson's chi-square test or Fisher exact test in case of 1 or more cells in the contingency table with expectation <5. Event-free and target-vessel-failure-free survival were computed using Kaplan-Meier estimates and compared between treatment groups with the log-rank test. The hazard ratio (HR) was calculated by Cox regression with treatment group as sole covariate. To correct for differences in baseline characteristics, the appropriate multivariate analysis was performed. All p values were 2-sided, and a p value of less than 0.05 was considered statistically significant. All analyses were conducted with SPSS version 12.0.1 statistical analysis software (SPSS Inc., Chicago, Illinois).

Results

Patients. A total of 316 STEMI patients were enrolled in the study (Table 1, Fig. 1). Six patients were subsequently excluded because the assigned study stent was not available, and 310 patients (152 assigned to BMS and 158 assigned to SES) were included in the analysis. With exception of a larger reference diameter in the BMS group, the groups were comparable. One patient crossed over from SES to BMS because of the inability to cross the lesion with the SES. Procedural characteristics are summarized in Table 2.

Angiographic results. Post-procedural and follow-up angiographic data were available for 124 BMS patients (81.6%) and 131 SES patients (82.9%). Patients with and without follow-up angiography had similar baseline characteristics. Six patients without follow-up angiography died during follow-up (4 BMS and 2 SES patients). The median time to angiographic follow-up was 272 days (10th to 90th percentiles: 268 to 295 days) in the BMS group and 272 days (10th to 90th percentiles: 270 to 290 days) in the SES group (p = 0.66). Post-procedural and follow-up QCA results are summarized in Table 3. The mean difference between BMS and SES patients in in-segment LLL was 0.56 mm (95% confidence interval [CI] 0.43 to 0.68, p < 0.001) at 9 months. This difference remained

Table 1 Baseline Clinical and Angiographic Characteristics

Characteristic	SES (n = 158)	BMS (n = 152)	p Value
Age (yrs)	59.2 ± 11.2	59.1 ± 11.6	0.99
Male gender	118 (74.7)	123 (80.9)	0.19
Diabetes mellitus	20 (12.7)	10 (6.6)	0.07
Current smoker	84 (53.2)	85 (55.9)	0.63
Hypercholesterolemia	37 (23.4)	25 (16.4)	0.13
Hypertension	48 (30.4)	39 (25.7)	0.36
Family history of CAD	73 (46.2)	60 (39.5)	0.23
Prior myocardial infarction	7 (4.4)	5 (3.3)	0.60
Prior PCI	4 (2.5)	1 (0.7)	0.37*
Prior CABG	1 (0.6)	1 (0.7)	1.00*
Time, min: median (interquartile range)			
Symptoms onset to first ECG	88 (47–153)	106 (71–151)	0.11*
Symptoms onset to balloon inflation	183 (133–258)	195 (153–257)	0.19*
Target vessel			
LAD	87 (55.1)	83 (54.6)	
RCA	40 (25.3)	51 (33.6)	0.09
LCX	31 (19.6)	18 (11.8)	
Multivessel disease	56 (35.4)	50 (32.9)	0.64
TIMI flow grade before			
0	96 (60.8)	90 (59.2)	
1	18 (11.4)	15 (9.9)	0.87
2	20 (12.6)	24 (15.8)	
3	24 (15.2)	23 (15.1)	
Maximal creatinine phosphokinase, U/l			
Median	1,844	2,079	0.25*
Interquartile range	863–3,413	1,012–3,792	
QCA before procedure			
Lesion length, mm	13.9 ± 5.6	15.0 ± 8.6	0.47
Reference diameter, mm	2.76 ± 0.54	2.92 ± 0.56	0.02
Minimal luminal diameter, mm	0.21 ± 0.35	0.27 ± 0.41	0.19*
Stenosis, % of luminal diameter	91.0 ± 13.6	92.5 ± 12.4	0.35*

Data are expressed as number (%) or mean ± standard deviation. All comparisons between groups were performed with *t* test (continuous variables) or Pearson's chi-square test (categorical variables) except as indicated (*).

BMS = bare-metal stent; CABG = coronary artery bypass grafting; CAD = coronary artery disease; ECG = electrocardiogram; LAD = left anterior descending coronary artery; LCX = left circumflex artery; PCI = percutaneous coronary intervention; QCA = quantitative coronary angiography; RCA = right coronary artery; SES = sirolimus-eluting stent; TIMI = Thrombolysis In Myocardial Infarction.

significant after adjustment for baseline characteristics as listed in Table 1 (mean difference 0.60 mm, 95% CI 0.48 to 0.72, $p < 0.001$). The in-segment angiographic restenosis rate was 22.6% in the BMS group and 3.8% in the SES group (relative risk 5.92, 95% CI 2.36 to 14.84). The cumulative percentage diameter stenosis distribution after the procedure and at follow-up angiography is shown in Figure 2.

IVUS results. Follow-up IVUS results were available for 93 (61.2%) BMS patients and 115 (72.8%) SES patients ($p = 0.03$). Inability to cross the stented segment with the IVUS catheter in patients with significant restenosis was an important reason for the lower number of IVUS studies in BMS patients. Quantitative IVUS data are summarized in Table 4. At follow-up, the minimal luminal area was 4.01 ± 1.38 mm^2 in the BMS group and 5.67 ± 1.59 mm^2 in the SES group ($p < 0.001$). The percentage neointimal volume was 27.0 ± 11% in the BMS group and 3.3 ± 5.0% in the SES group ($p < 0.001$). Late stent malapposition was present in 12.5% BMS patients and 37.5% SES patients. Late stent malapposition was persistent in 11.3% BMS patients and 18.3% SES patients ($p = 0.19$). Late stent malapposition was acquired in 5.0% BMS patients and in 25% SES patients ($p < 0.001$). Acquired LSM within the body of the stent occurred almost exclusively in SES patients (20.2% vs. 1.3% in BMS patients, $p < 0.001$).

Clinical outcome. No patients were lost to follow-up. Adverse events during follow-up are listed in Table 5. The event-free survival was 73.6% in BMS patients and 86.0% in SES patients (HR 1.96, 95% CI 1.17 to 3.30) (Fig. 3A). During follow-up 6 patients died (1.9%), 4 BMS patients and 2 SES patients ($p = 0.44$). Recurrent MI occurred in 9.2% of BMS patients and 5.7% of SES patients ($p = 0.24$); in 7.2% and in 4.4% of the patients this was related to a re-PCI procedure, respectively ($p = 0.29$). Spontaneous MI, all related to stent thrombosis, occurred in 2.0% of BMS patients and in 1.3% of SES patients ($p = 0.68$). Target lesion revascularization rate was 11.2% in BMS

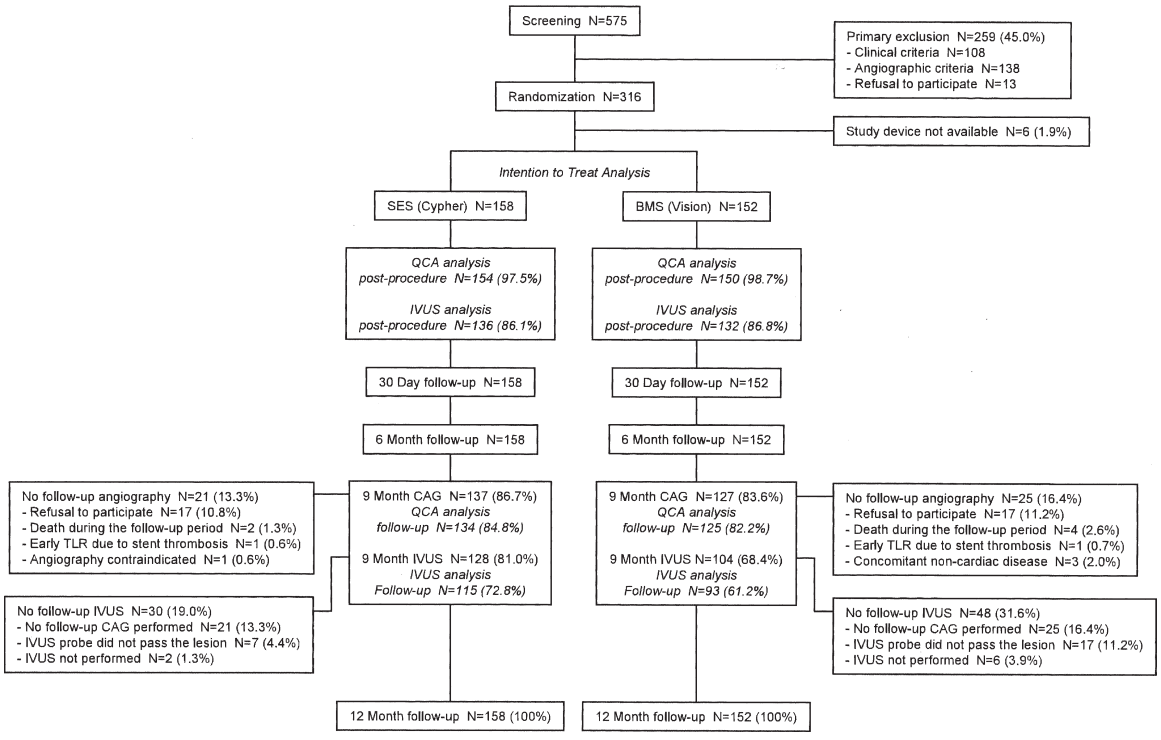

Figure 1 **Patient Flow Chart, Enrollment, and Outcomes**

BMS = bare metal stent; CAG = coronary angiography; IVUS = intravascular ultrasound; QCA = quantitative coronary angiography; SES = sirolimus-eluting stent; TLR = target lesion revascularization.

patients and 3.2% in SES patients (p = 0.006). The clinically driven target lesion revascularization rate was 7.9% in BMS patients and 2.5% in SES patients (p = 0.03). Target-vessel-failure-free survival was 84.7% in the BMS group and 93.0% in the SES group (HR 2.24, 95% CI 1.09 to 4.60) (Fig. 3B). Clinical event rates were not significantly different between patients who underwent follow-up angiography and patients who did not.

Table 2 **Procedural Characteristics**

Characteristic	SES (n = 158)	BMS (n = 152)	p Value
Direct stenting	57 (36.1)	59 (38.8)	0.62
Number of stents in the culprit lesion	1.34 ± 0.61	1.38 ± 0.63	0.57*
Implanted stent length, mm	26.5 ± 12.8	26.4 ± 11.1	0.95*
Maximum stent diameter, mm	3.31 ± 0.26	3.37 ± 0.35	0.05
Maximum balloon diameter, mm	3.37 ± 0.31	3.40 ± 0.30	0.30
Maximal balloon pressure, bar	12.3 ± 2.5	12.2 ± 3.0	0.70
Maximal balloon-to-artery ratio	1.17 ± 0.17	1.15 ± 0.19	0.26
TIMI flow grade after			
0	1 (0.6)	0 (0.0)	
1	1 (0.6)	1 (0.7)	1.00*
2	10 (6.4)	10 (6.6)	
3	146 (92.4)	141 (92.7)	
Abciximab therapy	158 (100.0)	151 (99.3)	0.49*
Multivessel intervention during the index procedure	10 (6.3)	8 (5.3)	0.69
Procedural success	146 (92.4)	141 (92.8)	0.90
Clinical success	146 (92.4)	140 (92.1)	0.92

Data are expressed as number (%) or mean ± standard deviation. All comparisons between groups were performed with *t* test (continuous variables) or Pearson's chi-square test (categorical variables) except as indicated (*).
Abbreviations as in Table 1.

Table 3 Results of Quantitative Coronary Angiography Post-Procedure and at Follow-Up

Characteristic	SES (n = 131)	BMS (n = 124)	p Value
Post-procedure			
Stented segment length, mm	22.3 ± 10.0	22.6 ± 8.4	0.77*
Reference diameter, mm	2.94 ± 0.49	3.02 ± 0.53	0.20
Minimal luminal diameter, mm			
In-segment	2.36 ± 0.50	2.41 ± 0.52	0.44
In-stent	2.67 ± 0.38	2.71 ± 0.37	0.33
Proximal margin	2.84 ± 0.52	2.95 ± 0.58	0.15
Distal margin	2.35 ± 0.53	2.40 ± 0.56	0.49
Stenosis, % of luminal diameter			
In-segment	20.0 ± 8.2	20.4 ± 9.1	0.67
In-stent	11.1 ± 6.9	12.4 ± 7.2	0.14
Proximal margin	11.4 ± 9.4	10.8 ± 9.7	0.64
Distal margin	15.1 ± 10.9	14.9 ± 10.8	0.91
Follow-up			
Reference diameter, mm	2.96 ± 0.47	2.92 ± 0.50	0.59
Minimal luminal diameter, mm			
In-segment	2.24 ± 0.55	1.74 ± 0.59	<0.001
In-stent	2.48 ± 0.52	1.77 ± 0.59	<0.001
Proximal margin	2.64 ± 0.58	2.60 ± 0.62	0.67
Distal margin	2.33 ± 0.57	2.24 ± 0.60	0.26
Late luminal loss, mm			
In-segment	0.12 ± 0.43	0.68 ± 0.57	<0.001
In-stent	0.19 ± 0.39	0.95 ± 0.55	<0.001
Proximal margin	0.20 ± 0.33	0.34 ± 0.48	0.01
Distal margin	0.03 ± 0.31	0.16 ± 0.45	0.007
Stenosis, % of luminal diameter			
In-segment	24.3 ± 12.7	40.8 ± 17.5	<0.001
In-stent	16.2 ± 13.0	39.7 ± 18.0	<0.001
Proximal margin	16.0 ± 11.8	16.6 ± 12.7	0.71
Distal margin	15.0 ± 11.4	17.4 ± 14.5	0.16
Angiographic restenosis			
In-segment	5 (3.8)	28 (22.6)	<0.001
In-stent	3 (2.3)	28 (22.6)	<0.001
Proximal margin	1 (0.9)	2 (1.9)	0.61
Distal margin	1 (0.8)	2 (1.7)	0.61

Data are expressed as number (%) or mean ± standard deviation. All comparisons between groups were performed with a *t* test except as indicated (*).

Abbreviations as in Table 1.

Discussion

Compared with treatment with BMS, both in-segment LLL and target vessel failure rates were significantly lower after treatment with SES in patients with acute MI. However, after SES implantation LSM was seen more often than after implantation of BMS.

Angiographic results. Angiographic in-segment LLL at 9-months' follow-up was chosen as the primary end point, since it reflects the luminal response of the treated segment, including the segments just outside the stent. Late luminal loss is a surrogate but powerful end point to compare the efficacy of stents for the prevention of restenosis (20). In-segment LLL in the SES group was comparable to the LLL found in the angiographic subgroup of the recently published TYPHOON (Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated With Angioplasty) (9). The SES LLL was in fact comparable to the LLL in stable angina patients and superior to LLL achieved with BMS in other STEMI studies (2,5,6). The rate of LLL in the BMS group was slightly higher than in the TYPHOON study, which may be explained by the longer implanted stent length in our study.

IVUS results. As in patients with stable angina, SES treatment in STEMI patients is associated with negligible neointimal hyperplasia, whereas BMS treatment is associated with significant hyperplasia at follow-up (21). This finding explains the low angiographic in-stent restenosis rate in the SES group. However, despite excellent angiographic results, a significant rate of LSM (37.5%) was observed in the SES group. The majority of these malappositions was not present immediately after implantation but developed during follow-up, predominantly along the body of the stent (20.2%). The rate of LSM after SES in STEMI patients is even higher than observed in the

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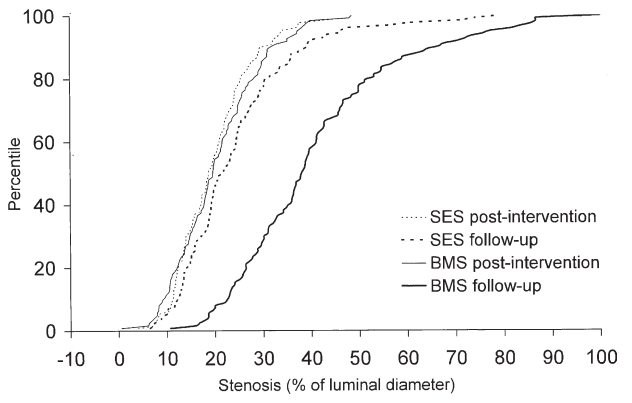

Figure 2 Cumulative Rate of In-Segment Percentage Diameter Stenosis

Abbreviations as in Figure 1.

SIRIUS (Sirolimus-Eluting Stent in Coronary Lesions) (16.3%) and RAVEL (A Randomized Comparison of a Sirolimus-Eluting Stent With a Standard Stent for Coronary Revascularization) (21%) studies, both comparing SES with BMS in patients with stable and unstable angina

Table 4 Results of Coronary Ultrasound Analysis at Follow-Up

Characteristic	SES (n = 115)	BMS (n = 93)	p Value
Area, mm^2			
Minimal stent area	6.05 ± 1.56	6.54 ± 1.41	0.02
In-stent MLA	5.67 ± 1.59	4.01 ± 1.38	<0.001
Proximal margin MLA	6.81 ± 2.15	6.57 ± 2.53	0.55
Distal margin MLA	5.77 ± 2.09	5.52 ± 2.10	0.45
Volume, mm^3			
Stent volume	188 ± 86	199 ± 77	0.32
Lumen volume	181 ± 81	145 ± 60	<0.001
Neointimal volume	7 ± 12	54 ± 31	<0.001*
Percentage neointimal volume	3.3 ± 5.0	27.0 ± 11.0	<0.001*
Late stent malapposition†			
Number evaluated	104	80	
Any site‡	39 (37.5)	10 (12.5)	<0.001
Persistent	19 (18.3)	9 (11.3)	0.19
Acquired	26 (25.0)	4 (5.0)	<0.001*
Proximal stent edge	17 (16.3)	7 (8.8)	0.13
Persistent	14 (13.5)	7 (8.8)	0.32
Acquired	3 (2.9)	0 (0.0)	0.26*
Stent body	27 (26.0)	2 (2.5)	<0.001*
Persistent	6 (5.8)	1 (1.3)	0.14*
Acquired	21 (20.2)	1 (1.3)	<0.001*
Distal stent edge	13 (12.5)	4 (5.0)	0.08*
Persistent	6 (5.8)	2 (2.5)	0.47*
Acquired	7 (6.7)	2 (2.5)	0.30*

Data are expressed as number (%) or mean ± standard deviation. All comparisons between groups were performed with *t* test (continuous variables) or Pearson's chi-square test (categorical variables) except indicated (*); †Data are presented for patients with paired (post-procedural and follow-up) intravascular ultrasound results; ‡Some patients had both persistent and acquired late stent malapposition (6 SES, 3 BMS).

MLA = minimal luminal area; other abbreviations as in Table 1.

Table 5 Clinical Events During 12-Months Follow-Up

Event	SES (n = 158)	BMS (n = 152)	p Value
Death	2 (1.3)	4 (2.6)	0.44*
Noncardiac	—	2 (1.3)	0.24*
Cardiac	2 (1.3)	2 (1.3)	1.00*
Target vessel related	2 (1.3)	2 (1.3)	1.00*
Recurrent myocardial infarction	9 (5.7)	14 (9.2)	0.24
Spontaneous	2 (1.3)	3 (2.0)	0.68*
Target vessel related	2 (1.3)	3 (2.0)	0.68*
Procedure related	7 (4.4)	11 (7.2)	0.29
Target vessel related	2 (1.3)	6 (3.9)	0.17*
Revascularization procedure†	19 (12.0)	35 (23.0)	0.01
PCI	17 (10.8)	30 (19.7)	0.03
CABG	2 (1.3)	5 (3.3)	0.28*
Target vessel revascularization†	8 (5.1)	20 (13.2)	0.01
PCI	6 (3.8)	17 (11.2)	0.01
CABG	2 (1.3)	3 (2.0)	0.68*
Target lesion revascularization†	5 (3.2)	17 (11.2)	0.006
PCI	3 (1.9)	14 (9.2)	0.005
CABG	2 (1.3)	3 (2.0)	0.68*
Clinically driven	4 (2.5)	12 (7.9)	0.03
Any event	22 (13.9)	40 (26.3)	0.01‡
Target vessel failure	11 (7.0)	23 (15.1)	0.02‡
Stent thrombosis	2 (1.3)	3 (2.0)	0.68*
Acute (<24 h)	—	—	—
Subacute (1 day to 30 days)	2 (1.3)	2 (1.3)	1.00*
Late (>30 days)	—	1 (0.7)	0.49*
Angiographically documented	1 (0.6)	1 (0.7)	1.00*

Data are expressed as number (%). All comparisons between groups were performed with Pearson's chi-square test (categorical variables), except as indicated (Fisher exact test*; log-rank test‡); †If the patient underwent more than 1 procedure, for every type of revascularization procedure (revascularization, target vessel revascularization, or target lesion revascularization) the first event per patient was counted.

Abbreviations as in Table 1.

(5,22). In line with our findings, acquired LSM in the SIRIUS study was also mainly located alongside the body of stent (22). There are only limited data about LSM after stenting in STEMI patients. Hong et al. (23) reported an LSM rate of 11.5% after BMS implantation. In contrast, LSM after drug-eluting stent implantation was present in 31.8% in an observational study of the same group (24). Late stent malapposition may be caused by 3 different factors: 1) insufficient stent deployment during implantation; 2) resolution of thrombus and/or plaque behind the stent; or 3) positive remodeling of the vessel wall. Persistent LSM, mainly involving the proximal or distal edges of the stents, may be caused by insufficient stent deployment and is thought to be of minor clinical importance (23). In contrast, acquired LSM, especially when located along the body of the stent, may be due to an adverse effect of the drug on the vessel wall resulting in positive remodeling. This type of LSM cannot be avoided during stent implantation and raises concern about long-term safety, as LSM has been related to very late (>1 year) stent thrombosis (11,25).

Clinical outcome. The reduction of target vessel failure rate after SES implantation in STEMI patients was in line with the results of the TYPHOON study (9). In contrast,

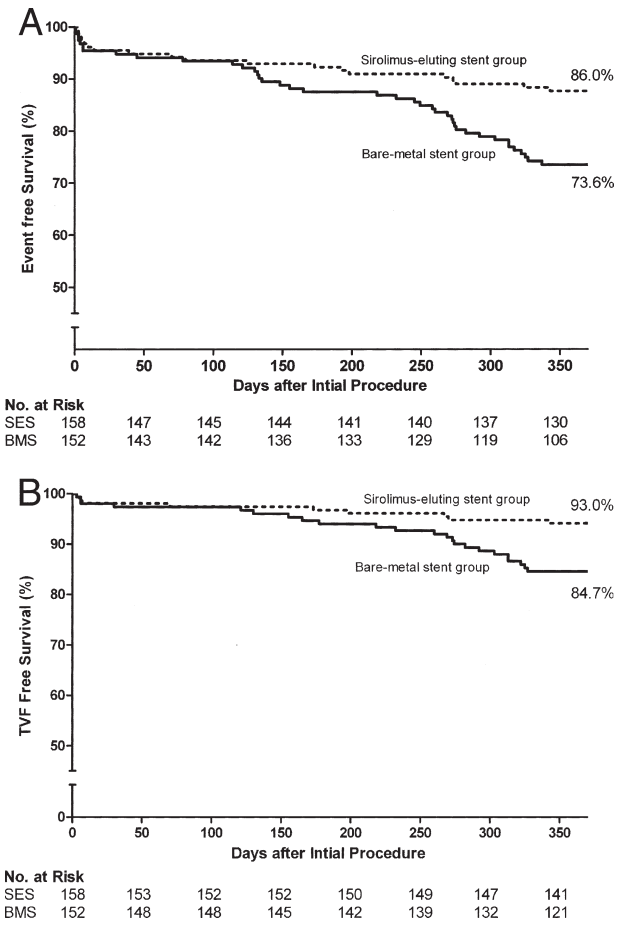

Figure 3 Event Free and TVF Free Survival

(A) Kaplan-Meier estimates of survival free from any events among patients treated with BMS and those treated with SES. The event-free survival was significantly higher in the SES group than the BMS group ($p = 0.01$). **(B)** Kaplan-Meier estimates of survival free from target vessel failure (TVF) among patients treated with BMS and those treated with SES. The TVF free survival was significantly higher in the SES group than the BMS group ($p = 0.02$). Abbreviations as in Figure 1.

the PASSION (Paclitaxel Eluting Stent Versus Conventional Stent in ST-Segment Elevation Myocardial Infarction) study, comparing paclitaxel-eluting stents and BMS in STEMI patients, failed to demonstrate a reduction in the target vessel failure rate in the paclitaxel-eluting stent group (8). This difference may be explained by differences in baseline characteristics such as a larger reference diameter and shorter implanted stent length, differences in stent design and drug efficacy, or the lack of angiographic follow-up in the PASSION study (26).

Mortality and MI rates were low in both groups. The MI rate was slightly higher than in the TYPHOON study, possibly because of the strict definitions used in our study. Of interest, the stent thrombosis rate at 12 months was lower and comparable to the results of the STRATEGY (Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent vs. Abciximab and Bare-Metal Stent in Myocardial Infarction) study (comparing SES with tirofiban and BMS with abciximab in STEMI patients) (27). There were no cases of acute stent thrombosis (<24 h), possibly because of the intensive antithrombotic regimen applied, including the administration of abciximab in all patients. Late stent thrombosis (>30 days) occurred in 1 BMS patient (0.7%).

Study limitations. With regard to the outcome, the non-inferiority design of the study is a relative limitation (28). At the time of conception of the study, only limited information about the efficacy of SES and third-generation BMS in STEMI patients was available. It was assumed that, despite limited differences in late loss, third-generation BMS were not inferior to drug-eluting stents with regard to efficacy, whereas adverse effects of drug-eluting stents such as LSM and delayed re-endothelialization could be avoided by using BMS (11). Another limitation is that the angiographic and clinical results of this study cannot be translated into general daily clinical practice, as this was a single-center study in selected patients, and patients were followed using a strict guideline-based follow-up protocol, which is not common practice yet. Moreover, this study was underpowered to detect differences in safety events such as death, recurrent MI, or stent thrombosis. Since IVUS follow-up was not possible in some BMS patients because of restenosis, we cannot exclude that LSM was underestimated in the BMS group, although this is unlikely since these patients had more neointimal growth. Finally, we cannot exclude that the routine angiographic follow-up did result in additional revascularization procedures, magnifying the difference in clinical outcome between BMS and SES.

Conclusions

The SES implantation in STEMI patients is associated with superior midterm clinical and angiographic results compared with BMS implantation. However, LSM is frequently observed in STEMI patients treated with SES, raising concern about long-term safety warranting long-term clinical follow-up. Therefore, based on this study, we cannot recommend or discourage SES use in STEMI patients.

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