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Three-year outcome of sirolimus-eluting versus bare-metal stents for the treatment of ST-segment elevation myocardial infarction (From the MISSION! intervention study)

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ABSTRACT

In order to compare long-term efficacy and safety of sirolimus-eluting stents (SES) to bare-metal stents (BMS) for ST-segment elevation myocardial infarction (STEMI), outcome was assessed in patients (n=310, age 59±11years, 78% male) included in the randomized MISSION!-intervention study after a median follow-up of 38 months. All patients were treated with aspirin (lifelong) and clopidogrel for 1 year after stent implantation. Except for a significant difference between reference vessel diameters (SES: 2.76mm vs. BMS: 2.92mm, p=0.02), there were no significant differences in baseline and angiographic characteristics between the treatment groups (158 SES, 152 BMS). A significant difference between SES and BMS patients for all revascularization endpoints was found after the first year of follow-up. However, at 3 years of follow-up, although there was still a trend towards a better clinical outcome in SES treated patients, differences were no longer significant [death (4.4% vs. 6.6%; p=0.41), target vessel related myocardial infarction (2.5% vs. 4.6%; p=0.32), target vessel revascularization (8.9% vs. 15.8%; p=0.06), target lesion revascularization (6.3% vs. 12.5%; p=0.06) and target vessel failure (12.0% vs. 19.7%; p=0.06)]. Three cases of very late (definite) stent thrombosis were observed in the SES group (1.9%) versus 0 in the BMS group (p=0.14).

In conclusion, the significant SES benefit (compared to BMS) in STEMI patients at 1 year follow-up in terms of target vessel revascularizations declined to some extent due to more similar target vessel revascularization rates during the 2 subsequent years. Rates of death and nonfatal recurrent MI remained comparable. (Current controlled trials number, ISRCTN628258620.)

INTRODUCTION

This randomized prospective study was designed to evaluate angiographic outcome and clinical efficacy of third-generation bare-metal stents (BMS) compared with that seen in sirolimus-eluting stents (SES) in ST-segment elevation myocardial infarction (STEMI) patients. Following the mid-term (12 months) angiographic and clinical results ¹, the present study evaluated clinical outcome after 3 years of follow-up from the index event.

METHODS

Study design

The MISSION! intervention study (Current Controlled Trials number, ISRCTN62825862 ¹) was a single-center, single-blind, randomized prospective study to evaluate clinical and 9-month angiographic 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 were blinded to the treatment assignment. During the study period, all patients were treated according to the institutional STEMI protocol, which included standardized outpatient follow-up ².

The study design, and methods have been described in detail previously ¹. In brief, consecutive patients with de novo coronary lesions were eligible for participation if symptoms of STEMI started <9 hours before arrival at the catheterization laboratory and the ECG demonstrated a STEMI. Exclusion criteria were detailed previously,¹ but in summary consisted of any "off-label" indication other than STEMI. 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.

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.

Follow-up and data collection

Both treatment groups received dual antiplatelet therapy for an equal treatment duration. Aspirin (100 mg/day) was prescribed indefinitely and clopidogrel (75 mg/day) for 12 months. Patients were seen at the outpatient clinic at 30 days, 3, 6, and 12 months according to the MISSION care program ². During follow-up, patients were treated with beta-blocking agents, statins, and angiotensin-converting enzyme inhibitors or angiotensin II blockers. Follow-up angiography was performed at 9 months. Long-term follow-up data of each patient was

documented prospectively in an electronic patient file and data management system (EPD-VISION 6.01) of the Leiden University Medical Center. Data was recorded after 3 years by patient visits at the out-patient clinic, or if not possible, by telephone inquiry. When a patient visit took place at another hospital, specific data inquiry was performed after written consent of the patient.

Endpoint definition

Endpoints of the current study were death, myocardial infarction (MI), target vessel revascularization, target lesion revascularization, target vessel failure and stent thrombosis. All deaths were defined as cardiac, unless it was unequivocally proven noncardiac. Myocardial infarction during follow-up was defined as a troponin-T rise $>0.03 \mu\text{g/l}$ with symptoms or PCI, a rise of troponin-T $>0.15 \mu\text{g/l}$ after coronary artery bypass grafting, or a rise of troponin-T $>25\%$ after recent MI in the presence of symptoms or re-PCI, or the development of new Q waves on ECG^{3,4}. Infarctions were categorized as spontaneous or procedure related (non-index procedure)^{3, 4}.

Target vessel and target lesion revascularization were defined as any revascularization procedure of the target vessel or target lesion, respectively. Target vessel failure was defined as the composite of cardiac death or recurrent nonfatal 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 definite, probable and possible stent thrombosis (the composite of these being total stent thrombosis), further subdivided into acute (≤ 1 day), subacute (>1 day - ≤ 1 month), late (>1 month - ≤ 1 year) and very late (>1 year) stent thrombosis, according to the Academic Research Consortium definition⁵. All clinical events were adjudicated by a clinical events committee whose members were blinded for the assigned stent type.

Statistical Analysis

Since this study was planned as follow-up investigation of the MISSION! intervention study, sample size calculations were done for the original purpose only. Analyses were conducted according to the intention-to-treat principle. Continuous data are expressed as mean (\pm standard deviation) or as median (interquartile range (IQR) 25th/75th percentile); dichotomous data are presented as numbers and percentages. All continuous variables were compared between the treatment groups with a *t* test or, in the case of a non-Gaussian distribution, with a nonparametric test. Categorical variables were compared with Pearson's chi-square test or Fisher exact test as appropriate. Event rates over time were analyzed by method of Kaplan-Meier with corresponding log-rank test for differences in distribution between the curves.

Effect of a reference diameter $\geq 3\text{mm}$ on the risk of stent thrombosis was estimated by multivariate Cox regression analysis with treatment group as sole covariate. The rationale to conduct analysis this way was as follows: Other potential (known and unknown) confounders have already been accounted for due to the randomized design of this study. Adding variables to the multivariate analysis after randomization may reduce comparability between the treatment groups. Therefore, only variables that were known to be different from baseline, such as stent type and (see also baseline characteristics table) reference vessel diameter were entered into the multivariate model. All p values were 2-sided, and a p value < 0.05 was considered statistically significant. All analyses were conducted with SPSS version 16.0 statistical analysis software (SPSS Inc., Chicago, Illinois).

RESULTS

Baseline characteristics

A total of 316 STEMI patients were enrolled in the study (Figure 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 ¹. Baseline characteristics of the study population are reported in Table 1.

With exception of a slightly 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

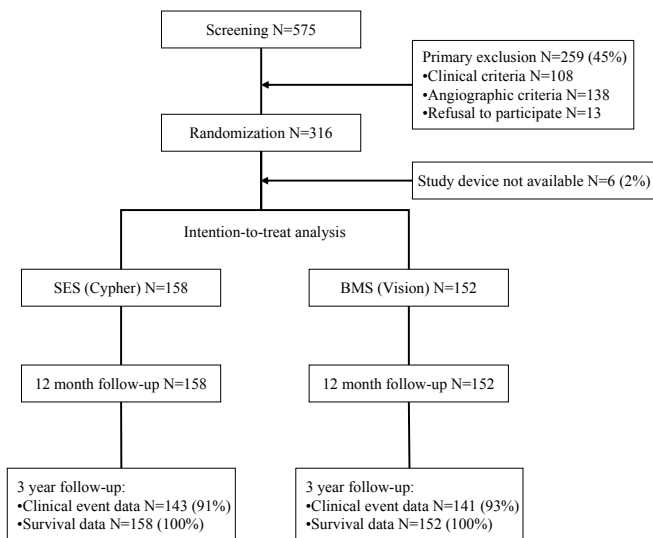


Figure 1. Patient Flow Chart, Enrollment and Follow-up. BMS = bare-metal stent; SES = sirolimus-eluting stent.

the lesion with the SES. No patients were lost for follow-up and all patients were contacted (Figure 1). Complete clinical data were available for 91% of the patients assigned to the SES group and for 93% of the patients assigned to the BMS group.

Table 1. Clinical and angiographic characteristics

Characteristics	SES (n = 158)	BMS (n = 152)	p value
Age (mean years \pm SD)	59.2 \pm 11.2	59.1 \pm 11.6	0.99
Men	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 coronary artery disease	73 (46.2%)	60 (39.5%)	0.23
Prior myocardial infarction	7 (4.4%)	5 (3.3%)	0.60
Prior percutaneous coronary intervention	4 (2.5%)	1 (0.7%)	0.37
Prior coronary artery bypass grafting	1 (0.6%)	1 (0.7%)	1.00
Symptoms onset to first electrocardiogram (median min [interquartile range])	88 (47–153)	106 (71–151)	0.11
Symptoms onset to balloon inflation (median min [interquartile range])	183 (133–258)	195 (153–257)	0.19
Target coronary artery			
Left	87 (55.1%)	83 (54.6%)	
Right	40 (25.3%)	51 (33.6%)	0.09
Left circumflex	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	
Quantitative coronary angiography pre-procedure			
Lesion length (mean mm \pm SD)	13.9 \pm 5.6	15.0 \pm 8.6	0.47
Reference diameter (mean mm \pm SD)	2.76 \pm 0.54	2.92 \pm 0.56	0.02*
Minimal luminal diameter (mean mm \pm SD)	0.21 \pm 0.35	0.27 \pm 0.41	0.19
Stenosis (mean % of luminal diameter \pm SD)	91.0 \pm 13.6	92.5 \pm 12.4	0.35

*p < 0.05

† Total cholesterol \geq 190 mg/dl or previous pharmacological treatment.

‡ Blood pressure \geq 140/90 mm Hg or previous pharmacological treatment.

Long-term follow-up

Clopidogrel was used up to 12 months by 93% (147/158; with 156 patients alive at follow-up) of patients in the SES group and by 96% (146/152; 148 patients alive at follow-up) of patients in the BMS group ($p = 0.24$). Aspirin treatment was continued by all patients during the entire follow-up of 3 years except when oral anticoagulation was indicated ($n=39$). Twenty-one patients (11 BMS, 10 SES) used clopidogrel >1 year. Reasons for prolongation of clopidogrel treatment were in most cases ($n=17$) the occurrence of an in-stent restenosis or stent thrombosis, and in 4 cases because of patient/doctor miscommunication. All patients who experienced target lesion revascularization and/or stent thrombosis <1 year post-MI used clopidogrel at the time the first event took place. This was true for patients of both treatment groups.

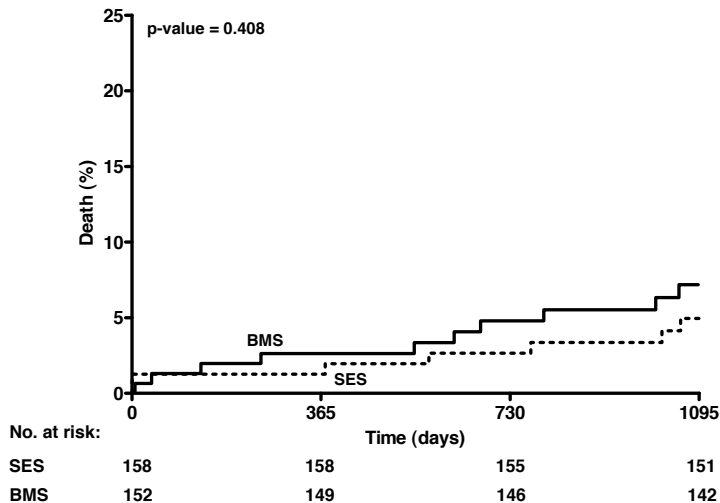


Figure 2. Kaplan-Meier estimates of the cumulative incidence of all-cause death. Abbreviations as in figure 1.

Deaths

Clinical outcome data at long-term follow-up are reported in Table 2. As compared to the previously reported mid-term results¹, 11 additional deaths occurred of which 5 in the SES group and 6 in the BMS group ($p=NS$). About half of these additional deaths were noncardiac (6/11, 55%, all cancer related). A Kaplan-Meier estimates of the cumulative incidence of all-cause death for the SES and BMS group is shown in Figure 2. Both treatment groups demonstrate a similar probability of all-cause death over the years (log-rank test $p=0.41$).

Myocardial infarction

Table 2 furthermore shows that most of the (6/7) additional recurrent spontaneous myocardial infarctions after the first year were target vessel related. There was no significant difference

Table 2. Clinical outcome at 12 months and at 3-year follow-up.

Event	12-month outcomes			3-year outcomes		
	SES (n = 158)	BMS (n = 152)	p value	SES (n = 158)	BMS (n = 152)	p-value
Death	2 (1.3%)	4 (2.6%)	0.44	7 (4.4%)	10 (6.6%)	0.41
Noncardiac	—	2 (1.3%)	0.24	3 (1.9%)	5 (3.3%)	0.68
Cardiac	2 (1.3%)	2 (1.3%)	1.00	4 (2.5%)	5 (3.3%)	0.95
Recurrent myocardial infarction†	9 (5.7%)	14 (9.2%)	0.24	12 (7.6%)	17 (11.2%)	0.28
Spontaneous	2 (1.3%)	3 (2.0%)	0.68	5 (3.2%)	7 (4.6%)	0.51
Target vessel related	2 (1.3%)	3 (2.0%)	0.68	4 (2.5%)	7 (4.6%)	0.32
Procedure related	7 (4.4%)	11 (7.2%)	0.29	7 (4.4%)	11 (7.2%)	0.29
Target vessel related	2 (1.3%)	6 (3.9%)	0.17	2 (1.3%)	6 (3.9%)	0.17
Revascularization procedure†	19 (12.0%)	35 (23.0%)	0.01*	28 (17.7%)	39 (25.7%)	0.09
PCI	17 (10.8%)	30 (19.7%)	0.03*	26 (16.5%)	33 (21.7%)	0.24
CABG	2 (1.3%)	5 (3.3%)	0.28	3 (1.9%)	8 (5.3%)	0.11
Target vessel revascularization†	8 (5.1%)	20 (13.2%)	0.01*	14 (8.9%)	24 (15.8%)	0.06
PCI	6 (3.8%)	17 (11.2%)	0.01*	11 (7.0%)	20 (13.2%)	0.07
CABG	2 (1.3%)	3 (2.0%)	0.68	3 (1.9%)	6 (3.9%)	0.46
Target lesion revascularization†	5 (3.2%)	17 (11.2%)	0.006*	10 (6.3%)	19 (12.5%)	0.06
PCI	3 (1.9%)	14 (9.2%)	0.005*	7 (4.4%)	15 (9.9%)	0.06
CABG	2 (1.3%)	3 (2.0%)	0.68	3 (1.9%)	6 (3.9%)	0.46
Clinically driven	4 (2.5%)	12 (7.9%)	0.03*	9 (5.7%)	14 (9.2%)	0.28
Target vessel failure	11 (7.0%)	23 (15.1%)	0.02*	19 (12.0%)	30 (19.7%)	0.06
Stent thrombosis						
Definite	1 (0.6%)	1 (0.7%)	1.00	4 (2.5%)	1 (0.7%)	0.39
Probable	1 (0.6%)	2 (1.3%)	0.97	1 (0.6%)	2 (1.3%)	0.97
Possible	—	—	—	1 (0.6%)	1 (0.7%)	1.00

*p <0.05. † The first event per patient was counted.

CABG = Coronary artery bypass grafting; PCI = percutaneous coronary intervention.

in the number of patients with spontaneous target vessel related myocardial infarction at three year follow-up (p=0.32). No additional procedure related myocardial infarctions were observed in the second and third year of follow-up. The Kaplan-Meier and landmark incidence estimates of the cumulative incidence of the combined endpoint target vessel related death/nonfatal MI demonstrates that the distribution of this combined endpoint over time was similar in both SES and BMS groups from beginning to end of follow-up (first year: log-rank test p=0.28; three years: log-rank test p=0.19) (Figure 3).

Revascularization

An additional 13 patients underwent revascularization procedures after the first year of follow-up (Table 2). Most were target vessel related (10/13, 77%) and approximately half were target lesion related (7/13, 54%). Though a significant difference was observed between SES and BMS groups for the number of patients undergoing a revascularization procedure (target vessel or target lesion related) during the first year of follow-up, this difference was no longer statistically significant after three year follow-up. This was due to the fact that relatively more SES patients underwent a revascularization procedure during the next 2 years of follow-up reducing the magnitude of the benefit of SES over BMS: an additional 9 patients in the SES group and another 4 patients in the BMS group. The same trend was observed for target

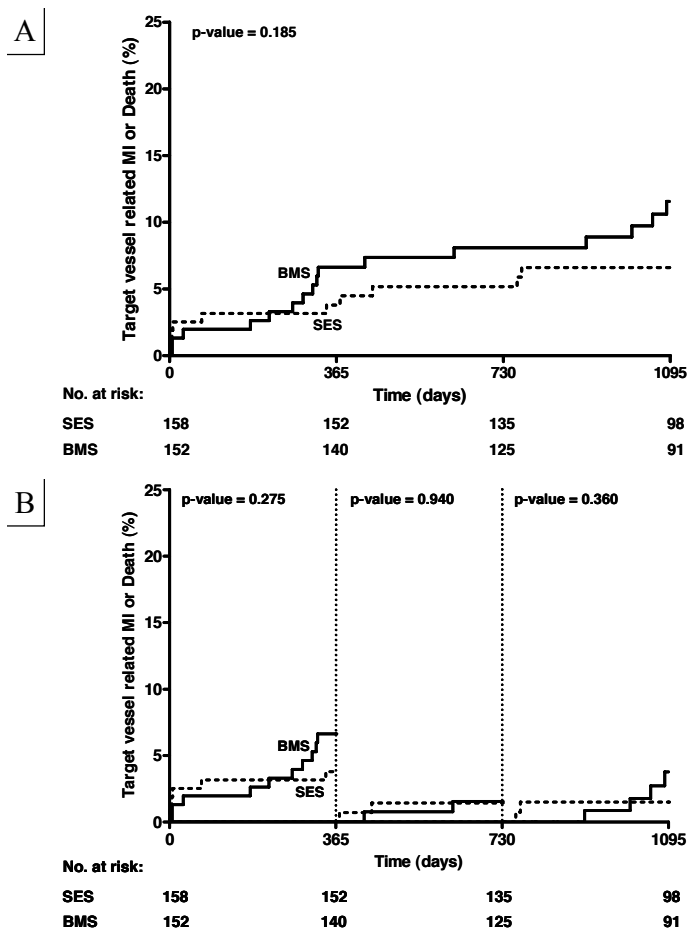


Figure 3. Kaplan-Meier (panel A) and landmark incidence (panel B) estimates for the combined endpoint target vessel related nonfatal MI or death. MI = myocardial infarction. Other abbreviations as in figure 1.

vessel related revascularizations and for target lesion related procedures. Figure 4 shows the cumulative incidence of target lesion revascularization procedure over the complete follow-up period (panel A) and for each year separately (panel B). The cumulative incidence of patients undergoing target lesion revascularization was significantly lower in the SES group during the first year of follow-up compared to the BMS group (log-rank test $p=0.006$). A more similar cumulative incidence was observed during the next years of follow-up (3 years: log-rank test $p=0.05$).

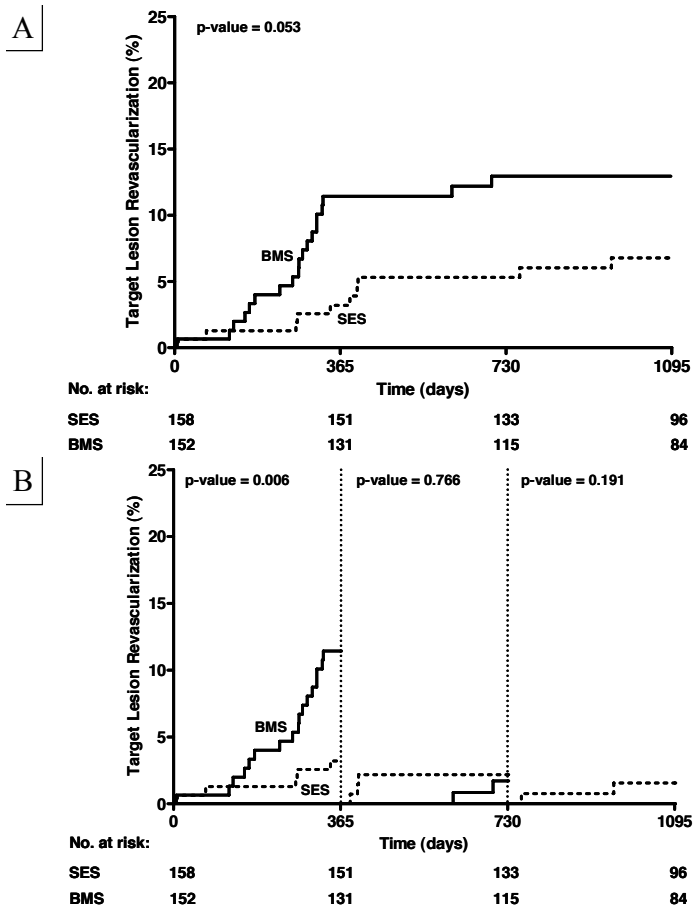


Figure 4. Kaplan-Meier (panel A) and landmark incidence estimates (panel B) for target lesion revascularization. Abbreviations as in figure 1.

Target vessel failure

Table 2 shows that the combined endpoint target vessel failure (death/MI/revascularization related to target vessel) occurred overall less frequently in the SES group than in the BMS group, particularly due to the difference in events occurring during the first year (first year: 7.0% vs. 15.1% of patients respectively, $p=0.02$; three year total: 12.0% vs. 19.7%, $p=0.06$). Correspondingly, figure 5 demonstrates that a statistically significant difference in the cumulative incidence of target vessel failure between SES and BMS patients was observed only in the first year after the index procedure (first year: log-rank test $p=0.02$; three years: log-rank test $p=0.06$).

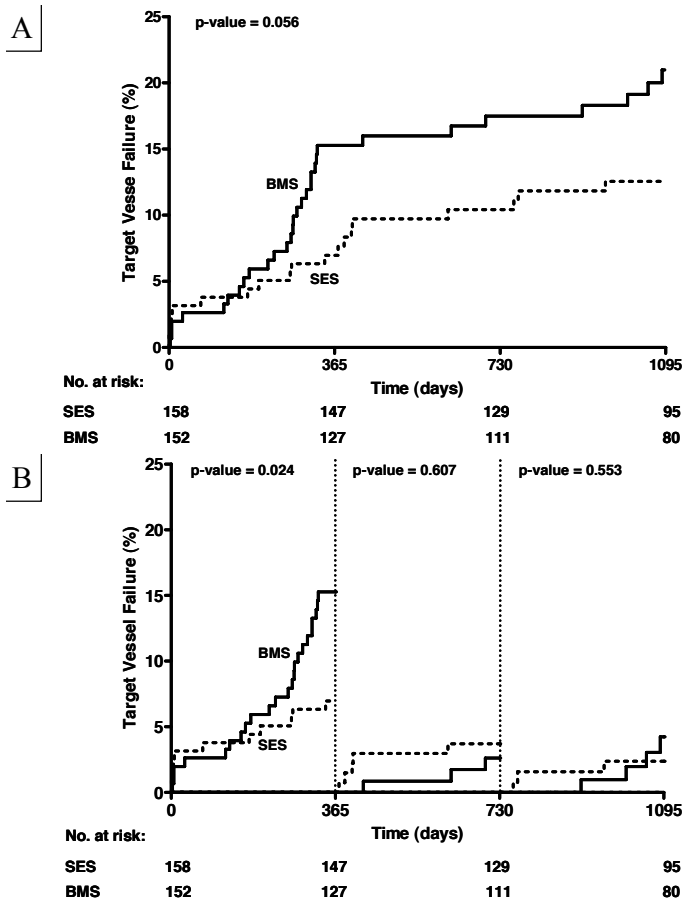


Figure 5. Kaplan-Meier (panel A) and landmark incidence (panel B) estimates for the combined endpoint target vessel failure. Abbreviations as in figure 1.

Stent thrombosis

In table 2 the number of patients experiencing definite, probable or possible stent thrombosis is reported for SES and BMS groups ⁵. Three cases of very late (definite) stent thrombosis were seen in the SES group (1.9%) versus none in the BMS group (p=NS). Figure 6 demonstrates the cumulative incidence of total stent thromboses (total of definite, probable and possible) for both stent type groups during 3 years of follow-up. Comparison of the cumulative incidence of stent thrombosis for the entire follow-up period, showed that the event rate was similar in the SES and BMS groups (Figure 6, log-rank test p=0.56).

Despite the low incidence of stent thrombosis, results of the multivariate analysis suggest that a reference diameter of ≥ 3 mm was related to an increased hazard of definite stent thrombosis in the overall patient population (adjusted: HR 10.2, 95%CI 1.1-92.5; p=0.039), independent of stent type.

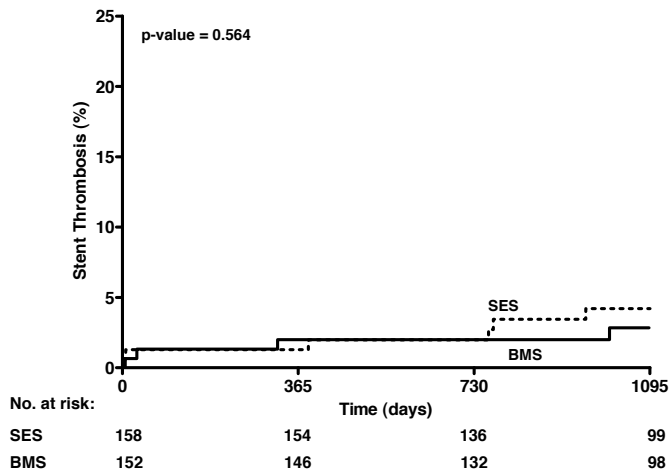


Figure 6. Kaplan-Meier estimates of the cumulative incidence of stent thrombosis. Abbreviations as in figure 1.

DISCUSSION

Key findings of this randomized study were: (1) Clinical outcome at three year follow-up was comparable for STEMI patients treated with either SES or BMS, and (2) the overall benefit of SES offered over BMS reflected mostly the advantage achieved during one year of follow-up. Although the total number of events was relatively lower in the SES treated group compared to the BMS treated group, the statistical advantage in terms of target vessel revascularizations gradually declined during three year follow-up due to more similar event rates after one year.

Drug-eluting vs. bare-metal stents in STEMI patients

Though primary PCI has been shown to be superior to medical therapy alone in patients presenting for acute myocardial infarction, particularly for STEMI patients⁶⁻⁸, data regarding efficacy and safety of DES use in these patients is still relatively scarce. Randomized studies investigating DES use for off-label indications often excluded patients with acute myocardial infarction^{9;10}. In addition, observational studies investigating DES use in patients with acute myocardial infarction had varying and sometimes conflicting results, or were unable to correct for dissimilar duration of dual antiplatelet therapy¹¹⁻¹⁴. Most randomized studies thus far including this study reported DES (including SES) to be superior to BMS at 12 months follow-up when comparing DES with BMS treatment for primary PCI in STEMI patients^{1;15-21}. In these studies DES mainly reduced the need for repeat revascularization procedures, but did not significantly reduce 12 month rates of death or myocardial infarction.

Drug-eluting vs. bare-metal stents: Short vs. long-term

Recent results of the current randomized trial suggest that the maximum benefit of SES over BMS, in terms of repeat revascularizations, is reached within the first year after index-intervention. This is supported by data from investigators of large registry studies such as the study from Mauri et al¹⁴ who reported that drug-eluting stents were associated with reduced rates of death and repeat revascularization at 2-years follow-up as compared to bare-metal stents. The significant difference of event rates consisted chiefly of the markedly reduced cumulative event rates of DES in the first year of follow-up, after which event rates were comparable between DES and BMS. Other studies reached the same conclusion²²⁻²⁴.

Similarly, at an update of the Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty (TYPHOON) presented at EuroPCR 2009, investigators reported that at 4 years, SES were able to maintain their initial advantage in terms of revascularization rates over BMS. Though it is perhaps questionable whether the trial's follow-up was complete enough to draw definitive conclusions (only 70% of original cohort), again the same time-dependent trend was observed as demonstrated by equal increases in the rate of target vessel revascularizations in SES and BMS groups (4% each) after the first year of follow-up¹⁸. Moreover, the recently published short- and long-term data of the Paclitaxel- or Sirolimus-Eluting Stent Versus Bare Metal Stent in Primary Angioplasty (PASEO) Trial further confirms this pattern²¹.

Results of the present study were also remarkably similar to the 3-year outcome of a large observational study by Applegate et al, who investigated DES versus BMS for "off-label" indications (not restricted to patients with myocardial infarction) in 1246 DES treated patients and 1147 BMS treated patients²². DES benefit seemed to occur entirely within the first year, with similar rates of target vessel revascularization, death and nonfatal MI in the second and third years. Abovementioned examples including results of the current study confirm a consistent pattern of time-dependent benefit of DES over BMS that decreases

in magnitude after the first year. Newer stents with better long term performance have not been tested in this study, but may potentially have a significantly better long-term performance.

Limitations

The clinical results of this study cannot be seamlessly translated into general daily clinical practice, as this was a single-center study in a selected group of patients and patients were followed in a strict-guideline based out-patient protocol², which is not common practice yet. Event rates in daily clinical practice can be expected to be in general higher than in this study. Furthermore, the follow-up study was not designed to detect small differences in the incidence of stent thrombosis between the groups. It is possible that with a larger sample size, the borderline non-significant differences of target vessel related events between SES and BMS groups may still have been significant after 3 years. A trend toward a “catch up phenomenon” is visible, but the results should be interpreted with caution. It deserves mentioning that the power calculation for sample size of the main MISSION! intervention study¹ was based on angiographic late luminal loss which was not an endpoint in this 3-year follow-up study. In addition, complete clinical follow-up was not available for all patients. However, it is highly unlikely that patients lost to follow-up experienced a serious clinical event such as revascularization or MI, as this would probably have led to admission at the PCI center and therefore would not have gone unnoticed. Finally, the original study design dictated angiographic follow-up at 9-months which was discussed in a previous publication¹. We cannot exclude that the routine angiographic follow-up did result in additional revascularization procedures, perhaps magnifying differences between BMS and SES in the first year of follow-up. It did however not influence the long-term event rates. Furthermore, the 1-year MISSION treatment program included regular visits and ischemia detection by stress/rest myocardial perfusion scanning at 3 months after STEMI, which facilitated in treatment decision-making.

CONCLUSION

The significant SES benefit (compared to BMS) in STEMI patients at 1 year follow-up in terms of target vessel revascularizations declined to some extent due to more similar target vessel revascularization rates during the 2 subsequent years. Rates of death and nonfatal recurrent MI remained comparable.

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