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Clinical and Angiographic Outcome After Sirolimus-Eluting Stent Implantation in Aorto-Ostial Lesions

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OBJECTIVES This observational study evaluated the clinical and angiographic outcomes of patients with aorto-ostial coronary artery disease treated with sirolimus-eluting stents (SESs) or with bare metal stents (BMSs).

BACKGROUND The safety and effectiveness of SESs for the treatment of aorto-ostial lesions have not been demonstrated.

METHODS We identified 82 consecutive patients who underwent percutaneous coronary interventions in 82 aorto-ostial lesions using the SES (32 patients) or BMS (50 patients) and compared the two groups of patients. The incidence of major adverse cardiac events (MACE), including death or Q-wave myocardial infarction (MI), target lesion revascularization (TLR), and target vessel revascularization (TVR), were recorded in-hospital and at a 10-month follow-up.

RESULTS All stents were implanted successfully. There were no statistically significant differences regarding major in-hospital complications between the two groups. At 10-month follow-up, two (6.3%) patients in the SES group and 14 (28%) patients in the BMS group underwent TLR ($p = 0.01$); MACE were less frequent in the SES group compared to the BMS group (19% vs. 44%, $p = 0.02$). Angiographic follow-up showed lower binary restenosis rates (11% vs. 51%, $p = 0.001$) and smaller late loss (0.21 ± 0.31 mm vs. 2.06 ± 1.37 mm, $p < 0.0001$) in the SES group.

CONCLUSIONS The main finding of our study is that, compared to the BMS, implantation of the SES in aorto-ostial lesions appears safe and effective, with no increase in major in-hospital complications and a significant improvement in restenosis and late event rates at 10-month follow-up. (J Am Coll Cardiol 2004;44:967–71) © 2004 by the American College of Cardiology Foundation

Previous studies with bare metal stents (BMSs) showed that aorto-ostial lesions have higher restenosis rates than non–aorto-ostial lesions (1–4). Traditionally, the presence of an aorto-ostial stenosis poses a special management problem for the interventionalist in that ostial lesions are the most likely to be associated with suboptimal angiographic results due to lesion rigidity and recoil (1,2,4,5). Although stents provide adequate scaffolding to prevent recoil, in-stent restenosis is mainly due to neointimal hyperplasia. Sirolimus-eluting stents (SESs) (Cypher, Cordis/Johnson & Johnson, Warren, New Jersey) have been shown to reduce neointimal hyperplasia and risk of restenosis (6,7). However, the issue of SES implantation in aorto-ostial lesions has not been adequately evaluated, because these patients were excluded or minimally represented in the multicenter randomized trials versus patients treated with BMSs. The purpose of this study was to evaluate the safety and effectiveness of the SES implantation in aorto-ostial lesions.

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METHODS

We evaluated retrospectively 32 consecutive patients who underwent percutaneous coronary interventions in 32 aorto-ostial lesions using the SES between April 2002 and March 2003. A control group for comparison was composed of 50 consecutive patients who underwent treatment of aorto-ostial lesions (50 lesions) with the BMS during the period immediately before the introduction of the SES. The following BMSs were used: BX Sonic or BX Velocity (Cordis/Johnson & Johnson) in 28%; JoMed polytetrafluoroethylene (PTFE)-covered stent (JoMed, Rangendingen, Germany) in 14%; Multi-Link Penta (Guidant Corp., Santa Clara, California) in 10%; Diamond-Flex (Phytis, Dreieich, Germany) in 10%; Multi-Link Tetra (Guidant Corp.) in 5%; Sorin Carbon (Sorin Biomedica, Saluggia, Italy) in 8%; and other stents in 27%.

All patients were pre-treated with ticlopidine or clopidogrel and aspirin at least three days before the procedure; a loading dose of 300 mg clopidogrel was administered to those who were not pre-treated. Aspirin was continued indefinitely and clopidogrel or ticlopidine for at least three months after SES and for one month following BMS

Abbreviations and Acronyms

BMS = bare metal stent
DS = diameter stenosis
MACE = major adverse cardiac events
MI = myocardial infarction
MLD = minimal lumen diameter
PTFE = polytetrafluoroethylene
SES = sirolimus-eluting stent
TLR = target lesion revascularization
TVR = target vessel revascularization

implantation. Stent implantation methods have been described previously (8). All stents were implanted with high-pressure (>12 atm) final balloon dilatation with an attempt to fully cover the angiographic lesion and to ensure complete stent apposition.

Glycoprotein IIb/IIIa inhibitors were administered at the operator's discretion.

Angiographic analysis. Cineangiograms were analyzed using a validated edge detection system (Version 5.2, CMS, MEDIS, The Netherlands). Standard qualitative and quantitative definitions and measurements were used. Using the contrast-filled catheter as the calibration standard, minimal lumen diameter (MLD), reference diameter, and percent diameter stenosis (DS) before and after coronary intervention were obtained from the single "worst" and least foreshortened view. Aorto-ostial lesions were defined as lesions involving the junction between the aorta and the orifice of the right coronary artery, left main, or a saphenous vein graft within 3 mm of the vessel ostia.

Angiographic success was defined as a final residual stenosis less than 30%. Angiographic restenosis was defined as >50% DS by quantitative coronary angiography within a previously stented vessel segment. Late lumen loss was defined as the difference between the MLD at the completion of the stenting procedure and that measured at follow-up. These are standard qualitative and quantitative analyses and definitions, and they have been published previously (9).

Clinical definitions and follow-up. Pre-specified clinical and laboratory demographic information was obtained from hospital charts that were reviewed by independent research personnel; data were entered prospectively into a dedicated database. Standard definitions included: 1) Q-wave myocardial infarction (MI): the presence of new pathological Q waves in the electrocardiogram associated with an elevation of cardiac enzyme ≥2 times the upper normal value, and 2) non–Q-wave MI: creatine kinase-MB enzyme elevation ≥3 times the upper normal value without new Q waves.

Clinical follow-up was performed by either telephone contact or office visit. Major adverse cardiac events (MACE) were recorded, including death (all-cause), Q-wave MI, and target lesion revascularization (TLR) and

Table 1. Baseline Clinical and Angiographic Characteristics

	SES	BMS	p Value
Patient characteristics			
Patients (n)	32	50	
Male gender, n (%)	27 (84)	41 (82)	0.7
Age (yrs)	62 ± 10	63 ± 11	0.9
Unstable angina, n (%)	8 (25)	22 (44)	0.06
Diabetes, n (%)	3 (9.4)	6 (12)	0.7
Hypertension, n (%)	22 (69)	21 (42)	0.02
Hypercholesterolemia, n (%)	22 (69)	20 (40)	0.01
Family history of coronary artery disease, n (%)	11 (34)	11 (22)	0.2
Current smoking, n (%)	5 (15)	14 (22)	0.2
Previous MI, n (%)	11 (36)	27 (54)	0.1
Previous PCI, n (%)	22 (69)	38 (76)	0.4
Previous bypass surgery, n (%)	10 (31)	21 (42)	0.3
Multivessel disease, n (%)	22 (69)	39 (77)	0.7
Left ventricular ejection fraction, n (%)	51 ± 8	55 ± 9	0.04
Lesion characteristics			
Lesions (n)	32	50	
Vessels treated			0.4
Left main artery, n (%)	10 (31)	10 (20)	
Right coronary artery, n (%)	17 (53)	28 (56)	
Saphenous vein graft, n (%)	5 (16)	12 (24)	
Lesion characteristics			
Calcium, n (%)	4 (13)	6 (12)	0.9
Eccentric, n (%)	16 (67)	32 (64)	0.8
In-stent restenosis, n (%)	12 (38)	11 (22)	0.2
Pre-intervention TIMI flow grade 0 to 2, n (%)	8 (25)	6 (12)	0.2
Total occlusion, n (%)	2 (6)	1 (2)	0.3
Thrombus, n (%)	0	3 (6)	0.1

Values are presented as numbers, (relative percentages), or mean ± SD.
BMS = bare metal stent; MI = myocardial infarction; PCI = percutaneous coronary intervention; SES = sirolimus-eluting stent; TIMI = Thrombolysis In Myocardial Infarction.

Table 2. Procedural Data and In-Hospital Outcome

	SES	BMS	p Value
Procedural characteristics			
Procedures (n)	32	50	
Maximum balloon diameter (mm)	3.50 ± 0.40	3.82 ± 0.49	0.003
Maximum balloon inflation (atm)	17.84 ± 3.12	18.28 ± 3.94	0.6
Stent length per lesion (mm)	24.81 ± 16.25	13.71 ± 5.57	<0.0001
Stents per lesion	1.18 ± 0.47	1.02 ± 0.33	0.07
Debulking, n (%)	1 (3.1)	3 (6)	0.9
Cutting balloon, n (%)	7 (22)	12 (24)	0.9
Glycoprotein IIb/IIIa inhibitors, n (%)	10 (31)	11 (22)	0.5
Procedural complications			
Intra-aortic balloon pump, n (%)	1 (3.1)	1 (2)	0.7
Acute stent thrombosis, n (%)	0	0	0
TIMI flow grade 0 to 2, n (%)	0	1 (2)	0.8
Dissection after stent, n (%)	0	1 (2)	0.8
Perforation, n (%)	0	0	
In-hospital outcome			NS
Angiographic success, n (%)	32 (100)	50 (100)	1.0
Death, n (%)	0	0	NS
Q-wave MI, n (%)	1 (3.1)	0	0.1
Non–Q-wave MI, n (%)	3 (9.3)	7 (14)	0.7
Stroke, n (%)	0	0	NS
Emergency bypass surgery, n (%)	0	0	NS
Repeat PCI, n (%)	0	0	NS

Values are presented as numbers (relative percentages), or mean ± SD.
Abbreviations as in Table 1.

target vessel revascularization (TVR) (whether percutaneous or surgical).

Statistical analysis. Statistical analysis was performed using SPSS, version 11 (SPSS Inc., Chicago, Illinois). Continuous variables are expressed as mean ±1 SD and categorical variables as frequency (%). Continuous variables were compared using independent samples *t* test. Categorical variables were compared with chi-square statistics.

RESULTS

Baseline patient and lesion characteristics. The baseline clinical and lesion characteristics of the patient population were similar between the two groups, except for a higher incidence of hypertension and hypercholesterolemia and a lower mean ejection fraction in the SES group (Table 1). Patients with the BMS had a trend toward higher incidence of unstable angina. Out of the 20 left main coronary artery lesions, 9 (45%) were unprotected; 5 in the SES and 4 in the BMS group.

Procedural data and in-hospital outcome. The procedural data and in-hospital outcome are shown in Table 2. All stents were deployed successfully. The SES group, compared to the BMS, had a smaller mean maximum balloon diameter (3.50 vs. 3.82 mm, p = 0.003) and a longer mean stent length per lesion (24.81 vs. 13.71 mm, p < 0.0001).

There were no statistically significant differences regarding procedural and major in-hospital complications. All procedures except one (2%) of the BMS group resulted in Thrombolysis In Myocardial Infarction (TIMI) flow grade 3. There were no cases of acute stent thrombosis, perforations, or residual dissections. One (3.1%) patient in the SES group suffered a nonfatal, in-hospital Q-wave MI. Non–Q-wave MI occurred in three (9.3%) SES patients compared to seven (14%) of the BMS group (p = 0.7).

Clinical outcome. One-month follow-up was available in all patients, and no additional events (including subacute thrombosis) were recorded (data not shown). Ten-month cumulative clinical follow-up was available in all patients and is shown in Figure 1. Patients with the SES had lower TLR compared to patients with the BMS (6.3% vs. 28%, p = 0.03). One patient of the SES group suffered late-stent thrombosis presented as an acute MI and died four months post-procedure after discontinuation of antiplatelet therapy. There was a trend toward less frequent TVR in the SES group (16% vs. 34%, p = 0.06). In addition, the incidence

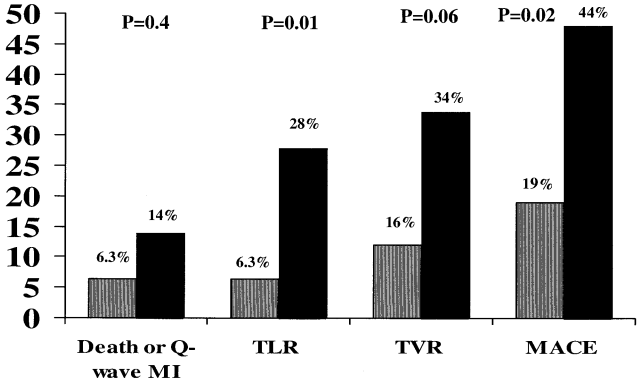

Figure 1. Cumulative clinical outcome at 10-month follow-up. **Black bars** = bare metal stent; **lined bars** = sirolimus-eluting stent. MACE = major adverse cardiac events; MI = myocardial infarction; TLR = target lesion revascularization; TVR = target vessel revascularization.

Table 3. Quantitative Coronary Angiography at Baseline, After Intervention, and at Follow-Up

Quantitative Coronary Angiography	SES	BMS	p Value
Lesions (n)	32	50	
Pre-intervention			
RVD (mm)	3.17 ± 0.59	3.47 ± 0.74	0.1
MLD (mm)	1.09 ± 0.69	1.48 ± 0.74	0.07
DS (%)	66 ± 19	58 ± 17	0.1
Lesion length (mm)	10.20 ± 7.27	8.47 ± 4.01	0.1
Post-intervention			
RVD (mm)	3.59 ± 0.52	3.97 ± 0.51	0.01
MLD (mm)	3.18 ± 0.55	3.66 ± 0.53	0.005
DS (%)	11 ± 7	9 ± 7	0.2
Follow-up			
Angiography done, n (%)	28 (88%)	35 (70%)	0.1
RVD (mm)	3.61 ± 0.43	3.50 ± 0.83	0.6
MLD (mm)	3.13 ± 0.59	1.60 ± 1.36	<0.0001
DS (%)	15 ± 13	55 ± 34	<0.0001
Late loss (mm)	0.21 ± 0.31	2.06 ± 1.37	<0.0001
Restenosis, n (%)	3 (11)	18 (51)	0.001

Values are presented as numbers, (relative percentages), or mean ± standard deviation.
DS = diameter stenosis; MLD = minimal lumen diameter; RVD = reference vessel diameter; other abbreviations as in Table 1.

of 10-month MACE was significantly lower in the SES compared to the BMS group (19% vs. 44%, p = 0.02).

Quantitative coronary angiography. Quantitative coronary angiographic analysis is shown in Table 3. The mean reference vessel diameter was 3.17 mm for the SES and 3.47 mm for the BMS group (p = 0.1). The SES group had a trend (p = 0.07) toward smaller MLD compared to the BMS group. Post-intervention reference vessel diameter and MLD were significantly larger in the BMS group.

Angiographic follow-up was available in 88% of the SES patients versus 70% of the BMS patients (p = 0.1). The mean time to angiographic follow-up did not differ significantly between the two groups (7.4 vs. 6.3 months, p = 0.08). The rate of restenosis for the lesions treated with PTFE stents was 50% (three of six lesions with available angiographic follow-up) and did not differ significantly from the restenosis rate of the other stents of the BMS group (52%, p = 0.7). Binary restenosis occurred less frequently in the SES group (11% vs. 51%, p = 0.001). All three restenotic lesions in the SES group were focal (≤10 mm in length). Conversely, only 9 (50%) of the 18 restenotic lesions in the BMS group were focal. In addition, late loss was significantly smaller in the SES compared to the BMS group (0.21 ± 0.31 mm vs. 2.06 ± 1.37 mm, p < 0.0001).

DISCUSSION

The main finding of our study is that, compared to the BMS, implantation of the SES in aorto-ostial lesions appears safe and effective, with no increase in major in-hospital complications and a significant improvement in restenosis and late event rates at 10-month follow-up.

The findings of the current study are similar to the results of the major drug-eluting stent randomized trials, which invariably showed dramatic decrease in restenosis rates with the use of the SES (6,7). As expected, late loss in the SES group was significantly smaller compared to the BMS group. However, the mean late loss of 0.21 mm was slightly larger than the respective values of the landmark randomized trials of the SES versus the BMS. More specifically, the mean late loss was −0.01 mm in the RAVEL (Randomized study with the sirolimus-eluting Bx VELocity balloon-expandable stent) and 0.17 mm in the SIRIUS (A U.S. multicenter, randomized, double-blind study of the SIRolImUS-eluting stent in de novo native coronary lesions) (6,7). Lesion rigidity might be a possible explanation for this finding. Histologic data from pathologic series (10) and atherectomy specimens (11) showed that ostial lesions are frequently heavily calcified, fibrotic, and sclerotic. It has also been suggested that there may be more elastic recoil even after stent implantation at ostial sites because of the highly elastic tissue in the adjacent aortic wall (1,10). Therefore, stenting at ostial site may respond differently than other segments of the coronary artery. Furthermore, the nonavailability of 3.5-mm SES (seven-cell stent) in our center at the time of patient enrollment for the present study may have resulted in a slight mismatch of the vessel size and the stent diameter and thus to stent overexpansion or less homogeneous drug distribution in the SES group.

In our study, the SES group had significantly smaller post-intervention MLD compared to the BMS group; thus it consisted of lesions more prone to restenosis. Furthermore, 38% of the SES lesions were restenotic compared to 22% of the BMS lesions (p = 0.2). The discrepancy in the SES group between the TLR rate of 6.3% and the TVR rate of 16% is due to treatment of other lesions distal to the stented segments which were not stented at the time of the index procedure.

Study limitations. The major limitations of this study are the small sample size, the different percentages of angiographic follow-up in the two groups, and some imbalance in

risk factors for restenosis. The lack of randomization is a problem difficult to solve in view of the proven efficacy of drug-eluting stents. The discrepancy in angiographic follow-up between the two groups (88% for SES vs. 70% for BMS) might have skewed the results in favor of the BMS group, because it is well known that angiographic follow-up triggers repeat interventions (12). However, this difference was statistically significant, nor was the difference in the mean time to angiographic follow-up (7.4 ± 3.0 months vs. 6.3 ± 2.7 months, p = 0.08 for SES and BMS, respectively). It is worth noting that the majority of the patients who had restenosis were symptomatic or had evidence of ischemia (72% of the BMS vs. 67% of the SES group, p = 0.6). Among the variables affecting restenosis, diabetes and unstable angina were present more frequently in the BMS group, whereas other lesion variables associated with restenosis were slightly more frequent in the SES group.

CONCLUSIONS

The main finding of our study is that, compared to the BMS, implantation of the SES in aorto-ostial lesions appears safe and effective, with no increase in major in-hospital complications and a significant improvement in restenosis and late event rates at 10-month follow-up.

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