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Original Studies

Long-Term Clinical Outcomes After Sirolimus-Eluting Stent Implantation for Treatment of Restenosis Within Bare-Metal Versus Drug-Eluting Stents

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Background: Sirolimus-eluting stents have been increasingly used for treatment of restenosis after implantation of bare metal stents (BMSs) or drug-eluting stents (DESs), but little is known regarding their long-term outcomes. Methods: We compared long-term clinical outcomes in 295 patients treated with sirolimus-eluting stents for post-BMS (n = 224) vs. post-DES (n = 71) restenosis. All follow-ups were at least 12 months, and the primary endpoint was major adverse cardiac events (MACE), defined as cardiac death, nonfatal myocardial infarction (MI) or target lesion revascularization (TLR). Results: Baseline characteristics were similar between the two groups, except that mean lesion length (28.0 ± 16.2 vs. 19.5 ± 13.6, $P < 0.01$) and mean stented length (35.4 ± 19.2 vs. 25.7 ± 14.7, $P < 0.01$) were significantly longer in the post-BMS group. Major in-hospital complications occurred in 2 patients. During a mean follow-up of 31.3 ± 11.1 months, there were 9 deaths (4 cardiac, 5 noncardiac), 3 nonfatal MIs, and 25 TLRs. Late stent thrombosis was documented in 2 patients (1 in each group). There were no between group differences in cardiac or total deaths, but there were trends toward less frequent cardiac death/MI or TLR in the post-BMS group. The cumulative probability of MACE-free survival was significantly better for the post-BMS group (95.0% ± 1.5% vs. 87.3% ± 4.0% at 1 year; 93.0% ± 1.7% vs. 81.0% ± 5.2% at 2 years; Log Rank P = 0.016). In multivariate analysis, post-DES restenosis was the only significant predictor of MACE (OR 3.29, 95%CI 1.13–9.61, P = 0.029). Conclusions: Sirolimus-eluting stents were effective for treatment of in-stent restenosis, but post-DES restenosis was associated with poorer outcomes than post-BMS restenosis. © 2008 Wiley-Liss, Inc.

Key words: drug-eluting stents; long-term outcomes; restenosis; percutaneous coronary intervention

INTRODUCTION

Although restenosis is relatively rare after drug-eluting stent (DES) implantation, it can still affect a significant number of patients [1–4]. In-stent restenosis has been considered difficult to treat and these patients are at higher risk for recurrence [5,6]. Compared with brachytherapy, sirolimus-eluting stents have been shown to result in superior clinical outcomes for treatment of restenosis within bare-metal stents (BMS) [7,8]. The use of DESs has increased for treatment of post-BMS or post-DES restenosis, both because of the simplicity of the procedure and its dramatic effects [9–12]. Little is known, however, about the long-term outcomes of this approach, and the role of DESs in treating post-DES restenosis remains unclear. We therefore compared long-term clinical outcomes in patients treated with sirolimus-eluting stents for post-BMS vs. post-DES restenosis.

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METHODS

Study Patients

The study population consisted of 295 consecutive patients with a first episode of restenosis after BMS ($n = 224$) or DES ($n = 71$) who were treated with sirolimus-eluting stents at our institution between February 2003 and May 2006. During the study period, 3,718 patients with 5,308 lesions were treated with DES, and the overall rate of target lesion revascularization (TLR) was 4%.

Stenting Procedure

Patients were implanted with Cypher™ stents (Cordis Corporation, Miami Lakes, FL) according to standard techniques, with stent selection left to the discretion of the operator. Complete lesion coverage was recommended, as well as angiographic optimization with <20% residual stenosis by visual estimate. All patients were pretreated with aspirin and clopidogrel. During the procedure, each patient received an 8,000 U bolus of heparin, with a repeat bolus of 2,000 U to maintain the activated clotting time ≥300 sec. Patients took aspirin (100–200 mg/day) indefinitely and clopidogrel (75 mg/day) for at least 6 months.

Angiographic Analysis

Angiographic analysis was performed by two experienced angiographers unaware of the study goal. Percent diameter stenosis, minimal lumen diameter, and reference diameter using an on-line quantitative angiographic analysis system (Xcelera Cath 1.1, Philips, Netherlands) were measured before predilation and after the stenting procedure. Angiographic measurements were made during diastole after intracoronary nitroglycerin administration, using the guiding catheter for calibration of magnification. In-stent restenosis was defined as a diameter stenosis of ≥50% occurring in the segment inside the stent or a segment 5 mm proximal or distal to the stent.

Definitions and Follow-up

All demographic, clinical, angiographic, and procedural characteristics were prospectively entered into a dedicated database. Follow-up information was obtained by chart reviews or telephone calls, and all patients were followed up for >12 months. The primary end-point was major adverse cardiac events (MACE), defined as cardiac death, nonfatal myocardial infarction (MI) or TLR.

MI was diagnosed when CK-MB was elevated >3-fold with chest pain ≥30 min or with the appearance of new electrocardiographic changes. TLR was defined as either surgical or percutaneous reintervention driven by significant (≥50%) luminal narrowing, within or 5 mm proximal or distal to the stent, together with angina symptoms or objective evidence of ischemia. Stent thrombosis was defined as acute coronary syndrome and angiographic confirmation of thrombus or occlusion within the peri-stent region.

TABLE I. Clinical Characteristics

Characteristics	Post-BMS group ($n = 224$)	Post-DES group ($n = 71$)
Age (years)	59.9 ± 10.6	58.7 ± 10.9
Men	171 (76.3)	47 (66.2)
Current smoker	50 (22.3)	14 (19.7)
Diabetes mellitus	71 (31.9)	16 (22.5)
Hypercholesterolemia (≥200 mg/dl)	17 (7.6)	7 (9.9)
Hypertension	112 (50)	34 (47.9)
Clinical presentation		
Stable angina pectoris	131 (58.5)	44 (62.0)
Unstable angina pectoris	85 (37.9)	22 (31.0)
Acute myocardial infarction	8 (3.6)	5 (7.0)
Multi-vessel coronary disease (≥2)	94 (41.9)	25 (35.2)
Previous myocardial infarction	7 (3.1)	2 (2.8)
Previous bypass surgery	10 (4.5)	1 (1.4)
Left ventricular ejection fraction (%)	57.4 ± 9.5	59.2 ± 7.6

Values in parentheses indicate the percentages.

Statistical Analysis

Data were expressed as mean ± SD for continuous variables and frequencies for categorical variables. Continuous variables were compared by unpaired Student's t tests and categorical variables by χ^2-tests. The cumulative incidence of MACE was estimated according to the Kaplan-Meier method, and the log-rank test was used to compare survival curves of the two groups. A two-sided P-value <0.05 was required for statistical significance.

RESULTS

Baseline clinical and angiographic data are summarized in Tables I and II. The patient characteristics of the two groups were similar. In the post-BMS group; however, there were more complex lesions with a longer lesion length, as well as more frequent use of longer stents. The proportion of nonfocal restenosis was also significantly higher in the post-BMS than in the post-DES group (79.9% vs 36.6%, $P < 0.01$). The overall procedural success rate (<30% residual diameter stenosis and absence of in-hospital complications) was 99.3%. There were 2 major in-hospital complications in the post-BMS group (1 cardiac death and 1 stent thrombosis), but none in the post-DES group.

During a mean follow-up of 31.3 ± 11.1 months (median 31.9 months; 34.4 months in post-BMS group, 24.6 months in post-DES group), there were 9 deaths (4 cardiac, 5 noncardiac), 3 nonfatal MIs, and 25

TABLE II. Angiographic Characteristics

Characteristics	Post-BMS group (n = 224)	Post-DES group (n = 71)
No. of restenotic lesions	234	73
Lesions treated with Cypher stents	232	73
Lesions treated with balloon angioplasty	2	
Target coronary vessel		
Left anterior descending	136 (58.1)	47 (64.4)
Left circumflex	21 (9.4)	10 (13.7)
Right	63 (26.9)	14 (19.7)
Left main	15 (6.7)	2 (2.7)
In-stent restenosis pattern*		
Focal	47 (20.1)	47 (64.4)
Diffuse	144 (61.5)	16 (21.9)
Proliferative	22 (9.4)	3 (4.1)
Total	21 (9.0)	7 (9.6)
Procedural characteristics		
Balloon to artery ratio	1.25 ± 0.20	1.20 ± 0.19
Maximal inflation pressure (atm)	16.3 ± 3.6	15.9 ± 3.5
Cypher stents per lesion	1.42 ± 0.67	1.16 ± 0.41*
Cypher stent length per lesion (mm)	35.4 ± 19.2	25.7 ± 14.7*
Quantitative coronary angiography		
Lesion length (mm)	28.0 ± 16.2	19.5 ± 13.6*
Reference vessel diameter (mm)	2.88 ± 0.48	2.98 ± 0.48
Preintervention		
Minimal lumen diameter (mm)	0.82 ± 0.46	0.87 ± 0.46
Diameter stenosis (%)	71.5 ± 15.2	70.0 ± 14.1
Postintervention		
Minimal lumen diameter (mm)	2.78 ± 0.48	2.91 ± 0.58
Diameter stenosis (%)	2.7 ± 12.7	1.8 ± 13.6
Acute gain (mm)	1.96 ± 0.59	2.04 ± 0.65

Values in parentheses indicate the percentages.
*$P < 0.01$.

TABLE III. Summary of Major Adverse Cardiac Events According to Time Interval

	0–30 days		30 days–1 year		>1 year	
	BMS	DES	BMS	DES	BMS	DES
Death	1	1	3	1	3	0
Cardiac death	1	1	0	1	1	0
Q-wave MI	0	1	1	0	1	1
Stent thrombosis	0	1	1	0	0	1
TLR	0	0	8	6	9	2

BMS, Post-BMS group; DES, Post-DES group; MI, myocardial infarction; TLR, target lesion revascularization.

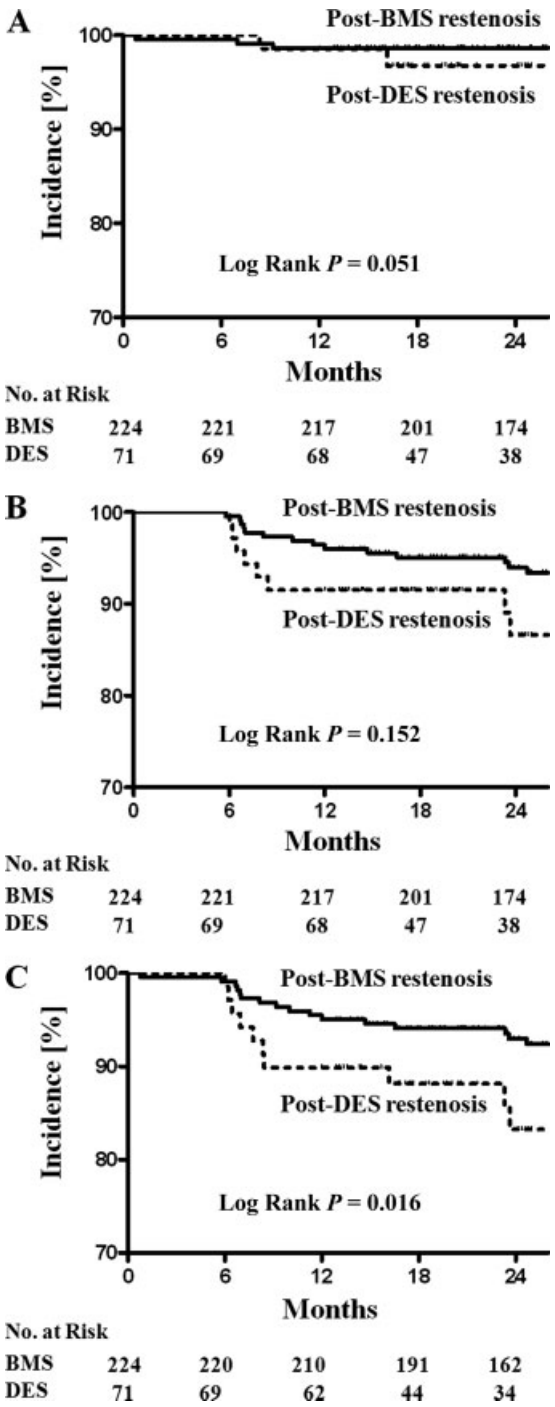

Fig. 1. Kaplan-Meier curves of cumulative event-free survival: (A) cardiac death or myocardial infarction; (B) target lesion revascularization; (C) major adverse cardiac events. BMS, bare-metal stent; DES, drug-eluting stent.

TLRs (Table III). Late stent thrombosis was angiographically documented in 2 patients (1 in each group). There were no between-group differences in cardiac or total deaths. The post-BMS group, however, tended to have lower frequencies of cardiac death/MI (98.7% ± 0.8% vs. 95.6% ± 2.4% at 1 year; 98.7% ± 0.8% vs. 94.0% ± 2.9% at 2 years; Log Rank P = 0.051) and TLR (96.4% ± 1.2% vs. 91.6% ± 3.3% at 1 year; 94.0% ± 1.6% vs. 86.6% ± 1.6% at 2 years; Log Rank P = 0.152) than the post-DES group. The cumulative probability of MACE-free survival was significantly better for the post-BMS than for the post-DES group (95.0% ± 1.5% vs. 87.3% ± 4.0% at 1 year; 93.0% ± 1.7% vs. 81.0% ± 5.2% at 2 years; Log Rank P = 0.016) (Fig. 1). There was no difference in

incidence of MACE between post-Taxus and post-Cypher stent restenosis patients (9.1% vs. 26.7%, respectively, $P = 0.123$). In multivariate analysis, post-DES restenosis was the only significant predictor of MACE (OR 3.29, 95%CI: 1.13–9.61, $P = 0.029$).

DISCUSSION

We have shown here that the use of sirolimus-eluting stents for treatment of in-stent restenosis was effective, with a low incidence of rerestenosis and a favorable long-term outcome. Post-DES restenosis, however, was associated with poorer outcomes than post-BMS restenosis, suggesting that these two types of lesion have different biological responses after sirolimus-eluting stent implantation.

In-stent restenosis remains a major problem in percutaneous coronary intervention, requiring patients to undergo repeat revascularization. Post-DES restenosis, although less frequent than post-BMS restenosis, is becoming increasingly prevalent because of the increased use of DES [1–4]. DESs were recently shown to be superior to conventional brachytherapy, the only FDA-approved treatment for in-stent restenosis, for the treatment of post-BMS restenosis. In the TAXUS V ISR trial [7], 396 patients with post-BMS restenosis were randomized to receive brachytherapy or paclitaxel-eluting stent placement. At 9 months follow-up, the rates of restenosis (15% vs. 31%; $P < 0.001$) and target vessel revascularization (17.5% vs. 10.5%; $P < 0.05$) were significantly lower in the DES group. In the SISR trial [8], 384 patients with post-BMS ISR were randomized in a 1:2 ratio to brachytherapy or sirolimus-eluting stent placement. At 6 months, stenting tended toward a lower rate of restenosis than brachytherapy (20 vs. 30%; $P = 0.07$) and, at 9 months, stenting showed a significantly lower rate of clinical target-vessel failure (12 vs. 22%; $P = 0.02$).

Although DESs are commonly used for treatment of in-stent restenosis, there is no consensus on how to treat post-DES restenosis. Several small trials [8–12] found that various treatment strategies, including balloon angioplasty, radiation therapy and DESs, resulted in acceptable outcomes. In an analysis of 174 patients with 201 lesions treated for DES restenosis with the same DES (107 lesions) or a different DES (94 lesions), the rates of TLR were 15.9% and 16%, respectively (P = NS) [9]. In patients with nonfocal DES restenosis, however, the TLR rate after repeated DES implantation was relatively high. MACE rates were found to be high in a cohort of 116 patients with post-DES restenosis who were treated with repeat DES, 32.6% for a different DES and 35.0% for the same DES ($P = 0.814$) [13]. In our study, despite the shorter lesion length, the MACE rate was also significantly higher in the post-DES than in the post-BMS restenosis group. These findings show that the DES ''sandwich'' technique for the treatment of DES restenosis is associated with a high risk of treatment failure, indicating that different approaches should be considered when restenosis occurs within a DES [14]. Several potential mechanisms may be responsible for rerestenosis, including stent underexpansion, geographic miss, drug resistance, and inflammation. Additional studies, however, are needed to assess the effects of stent overlap, polymers, and drugs on stent thrombosis and rerestenosis.

One of the limitations of this study is its retrospective nature. In addition, since all patients with in-stent restenosis were treated with sirolimus-eluting stents, our findings may not be applicable to patients undergoing implantation with other types of DES. Furthermore, the number of patients in the DES group was too small to compare treatment effects on restenosis within different types of DES. Finally, the number of total patients assessed was also relatively small with a potential bias on the selection of device or patients for restudy, thus limiting our ability to draw definitive conclusions about optimal therapy for DES restenosis.

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