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Factors Predictive of Cardiac Events and Restenosis After Sirolimus-Eluting Stent Implantation in Small Coronary Arteries

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Objectives: Predictors of cardiac events and restenosis after sirolimus-eluting stent (SES) implantation in small coronary arteries were evaluated. Background: Although SES implantation has markedly reduced the risk of restenosis, small vessel disease remains a major cause of SES failure. Methods: We prospectively investigated the factors predictive of cardiac events and restenosis in 1,092 consecutive patients who received SES implantation for 1,269 lesions in small coronary arteries (≤2.8 mm). Follow-up angiography at 6 months was performed in 751 patients with 889 lesions (follow-up rate 70.3%). Results: Restenosis (diameter stenosis ≥ 50%) was angiographically documented in 65 patients with 77 lesions (8.7%): 55 focal (71.4%), 8 diffuse (10.4%), 2 diffuse proliferative (2.6%), and 12 total (15.6%). Lesion length, stent length, reference artery size, and in-stent restenotic lesions were univariate predictors of restenosis. By multivariate analysis, lesion length (OR 1.04; 95% CI 1.02–1.05; $P < 0.001$) and in-stent restenotic lesions (OR 3.38; 95% CI 1.80–6.35; $P < 0.001$) were significant independent predictors of restenosis. During follow-up (23.2 ± 7.9 months), there were 17 deaths (5 cardiac and 12 noncardiac), 5 nonfatal Q-wave myocardial infarctions, and 42 target lesion revascularizations. The cumulative probability of survival without major adverse cardiac events (MACE) was (96.6 ± 0.6)% at 1 year and (95.1 ± 0.7)% at 2 years. In multivariate analysis, lesion length (HR 1.04; 95% CI 1.01–1.07; $P = 0.004$) and in-stent restenotic lesions (HR 3.29; 95% CI 1.58–6.86; $P = 0.001$) were independently related to MACE. Conclusions: SES implantation in small coronary arteries is safe and effective, with lesion length having a major impact on restenosis and MACE.

Key words: sirolimus-eluting stents; predictors; restenosis

INTRODUCTION

Revascularization of small coronary arteries is problematic because of a high risk of restenosis. Before the development of drug-eluting stents, the restenosis rate in these lesions was very high, ranging from 30 to 50%, and there was little benefit from stent implantation [1–5]. Drug-eluting stents, however, have markedly reduced the risk of restenosis, [6,7] and their benefits should be evident in small vessels. In patients with small-vessel coronary disease, the use of sirolimus-eluting stents (SESs) was associated with significantly lower restenosis rates than those observed in patients treated with bare metal [8] or paclitaxel-eluting [9] stents. Small vessel disease, however, remains a major cause of SES failure, requiring a further refinement of predictive factors in this high-risk subgroup [7,10]. We therefore investigated the clinical, lesion-related, and procedural variables that could predict the risk of cardiac events and angiographic restenosis after SES implantation in small coronary arteries.

METHODS

Study Patients

Between February 2003 and September 2005, a total of 1,092 consecutive patients with reference vessel size

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≤2.8 mm were treated with SESs for 1,269 lesions at our institution. All patients had clinical indications for percutaneous coronary intervention. Patients were followed-up by angiography at 6 months, or earlier, if there were symptoms, unless they were >80 years old ($n = 12$), experienced any major adverse cardiac event during the first 30 days after the procedure ($n = 2$), or there were medical conditions contraindicating angiographic follow-up ($n = 10$).

Stenting Procedure

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

Angiographic Analysis

All angiographic results were analyzed 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, after the stenting procedure, and at follow-up. Angiographic measurements were made during diastole after intracoronary nitroglycerin administration using the guiding catheter to calibrate magnification. Single matched views with the worst diameter stenosis were compared.

Definitions and Follow-Up

All clinical, angiographic, and procedural variables were prospectively entered into the Asan Medical Center angiographic database. Follow-up information was obtained by chart review and telephone interview, and all follow-ups were extended to at least 9 months. Restenosis and major adverse cardiac events (MACE) (cardiac death, Q-wave myocardial infarction (MI), and target lesion revascularization) were evaluated. Procedural success was defined as successful stenting at the desired position with <30% residual stenosis and the absence of death, Q-wave MI or need for either emergency bypass surgery or repeat revascularization during hospitalization. The diagnosis of procedural non-Q-wave MI was based on CK-MB elevation more than three times normal in the absence of new pathologic Q waves on postintervention electrocardiograms. Restenosis was defined by diameter stenosis ≥50% in the segment inside the stent or 5 mm proximal or distal to it at angiographic follow-up. Deaths were classified as cardiac or noncardiac. MI during follow-up was diagnosed when CK-MB was elevated >3-fold with chest pain ≥30 min or with the appearance of new electrocardiographic changes.

TABLE I. Clinical Characteristics

Characteristics	$N = 1,092$
Age (years)	60.8 ± 9.9
Men/women	752/340
Current smoker	367 (33.6%)
Diabetes mellitus	361 (33.1%)
Total serum cholesterol ≥200 mg/dl	232 (21.2%)
Hypertension	569 (52.1%)
Clinical presentation	
Stable angina pectoris	491 (45.0%)
Unstable angina pectoris	307 (28.1%)
Acute myocardial infarction	115 (10.5%)
Previous myocardial infarction	88 (8.1%)
Previous percutaneous coronary intervention	229 (21.0%)
Previous coronary bypass surgery	21 (1.9%)
Multivessel coronary disease	538 (49.3%)

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 test and categorical variables by the χ^2 test. Regression analysis was performed on all variables to identify determinants of restenosis, and the Kaplan-Meier method was used to analyze the occurrence of clinical events during follow-up. Statistical significance was defined as a two-sided value of $P < 0.05$.

RESULTS

Patient baseline clinical and angiographic characteristics are summarized in Tables I and II. Patient mean age was 60.8 ± 9.9 years (range, 23–88 years); 33.1% had diabetes mellitus and 5.3% had left ventricular dysfunction (ejection fraction < 45%). The procedural success rate was 99.5%. The incidence of procedural non-Q-wave MI was 15.0%, which was independently related to stented length (OR 1.018, 95% CI 1.010–1.021, $P < 0.001$). During hospitalization, one patient developed acute stent thrombosis and died 1 day after the procedure. The other patients experienced MACE after discharge.

Angiographic Restenosis

Angiographic follow-up was performed in 751 of the 1,068 eligible patients (follow-up rate, 70.3%), with 889 of the 1,269 lesions. Patients who returned for fol-

low-up angiography had similar baseline clinical and angiographic characteristics as those who did not return (data not shown). Restenosis was documented in 65 patients with 77 lesions (8.7%) (in-stent 6.5%; in-segment 8.7%). There were 55 incidents of focal restenosis (71.4%), 8 of diffuse (10.4%), 2 of diffuse proliferative (2.6%), and 12 of total (15.6%) restenosis. In-stent restenotic lesion was the only predictor of nonfocal type of restenosis (OR 3.115, 95% CI 1.046–9.282, $P = 0.041$).

Predictors of Restenosis

Clinical characteristics did not differ between the restenosis and nonrestenosis groups. Diabetes was not a significant predictor of restenosis (OR 0.79, 95% CI 0.47–1.33, $P = 0.378$). The restenosis group, however, had longer lesion and stented lengths, smaller reference artery size, and more in-stent restenotic lesions than did the nonrestenosis group (Table III). There was a significant correlation between restenosis rate and lesion length (Fig. 1), and restenosis rate was highest (29.4%) in patients with very long lesions (≥60 mm). Multivariate analysis showed that lesion length (OR 1.04; 95% CI 1.02–1.05; $P < 0.001$) and in-stent restenotic lesion (OR 3.38; 95% CI 1.80–6.35; $P < 0.001$) were significant independent predictors of restenosis (Table III).

TABLE II. Angiographic and Procedural Characteristics

Characteristics	$N = 1,269$
Lesion characteristics	
Target coronary vessel	
Left anterior descending	763 (60.1%)
Left circumflex artery	276 (21.7%)
Right coronary artery	230 (18.1%)
Type B2/C lesions	957 (75.4%)
Chronic total occlusion	86 (6.8%)
Ostial lesion	60 (4.7%)
Bifurcation	173 (13.6%)
In-stent restenosis	141 (11.1%)
Infarct-related artery	94 (7.4%)
Procedural characteristics	
Balloon to artery ratio	1.31 ± 0.16
Maximal inflation pressure (atm)	15.5 ± 3.6
Stents per lesion	1.4 ± 0.7
Stented length per lesion (mm)	34.8 ± 19.2
Quantitative coronary angiography	
Lesion length (mm)	27.7 ± 15.2
Reference vessel diameter (mm)	2.47 ± 0.24
Preintervention	
Minimal lumen diameter (mm)	0.75 ± 0.46
Diameter stenosis (%)	70.0 ± 16.8
Postintervention	
Minimal lumen diameter (mm)	2.52 ± 0.36
Diameter stenosis (%)	−1.0 ± 13.2
Acute gain (mm)	1.74 ± 0.52

Late Clinical Outcomes

During follow-up (23.2 ± 7.9 months), there were 17 deaths (5 cardiac and 12 noncardiac), 5 nonfatal Q-wave MIs, and 42 target lesion revascularizations. Late stent thrombosis occurred in four patients (0.4%), 2–20 months after the procedure, all of whom developed Q-wave MIs, and two of whom died. The event-free survival rate for cardiac death/Q-wave MI was (99.2 ± 0.3)% at 1 year and (98.9 ± 0.3)% at 2 years (Fig. 2). No factors were predictive of cardiac death/Q-wave MI. The cumulative probability of survival without MACE was (96.6 ± 0.6)% at 1 year and (95.1 ± 0.7)% at 2 years (Fig. 2). Lesion length (HR 1.04; 95% CI 1.01–1.07; $P = 0.004$) and in-stent restenotic lesions (HR 3.29; 95% CI 1.58–6.86; $P = 0.001$) were independently related to MACE.

DISCUSSION

We have shown here that SES implantation was safe and effective in unselected patients with small vessel disease, providing a rationale for its routine use in these lesions. We also found that lesion length was a powerful predictor of restenosis and MACE; multiple overlapping stents in very long small vessel disease (lesion length ≥ 60 mm) was associated with a high risk of SES failure, requiring further procedures to overcome this problem. In addition, there appears to be a high rate of procedural CK-MB elevation, which may be related to a heavy plaque burden. Although it was not associated

TABLE III. Predictors of Angiographic Restenosis by Logistic Regression Analysis

	Univariate Analysis			Multivariate Analysis		
Variables	OR	95% CI	*P* value	OR	95% CI	*P* Value
Lesion length	1.04	1.02–1.05	<0.001	1.04	1.02–1.05	<0.001
In-stent restenosis	2.99	1.70–5.28	<0.001	3.38	1.80–6.35	<0.001
Total stented length	1.02	1.01–1.03	0.001			
Lesion length > 40 (mm)	2.72	1.64–4.53	<0.001			
Stented length > 40 (mm)	2.14	1.33–3.44	0.002			
Reference artery diameter	0.40	0.18–0.89	0.025			

CI, confidence interval; OR, odds ratio.

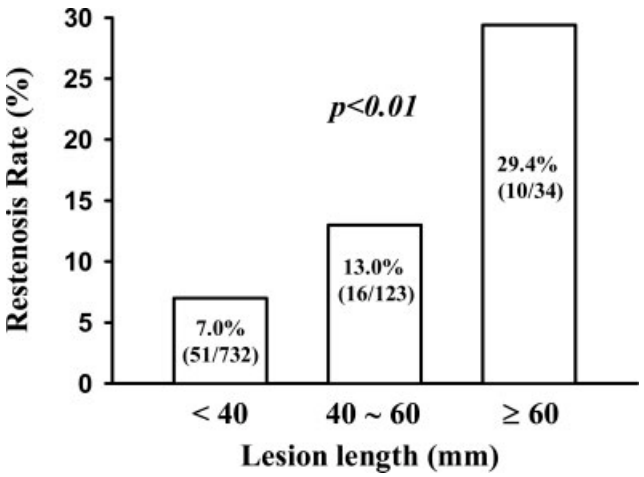

Fig. 1. Effects of lesion length on restenosis rate.

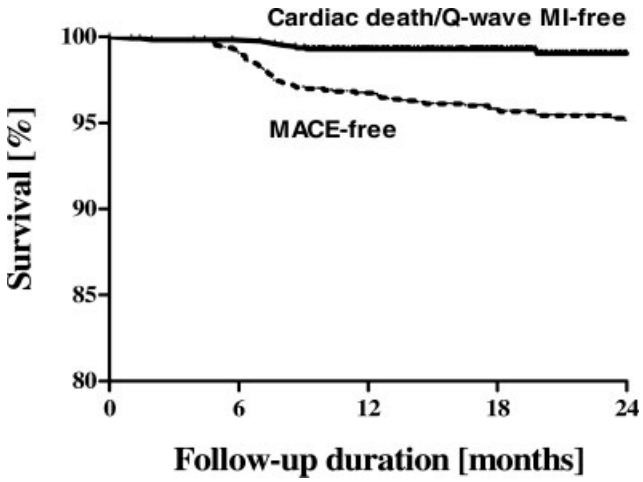

Fig. 2. Event-free survival curves for cardiac death/Q-wave myocardial infarction (MI) and major adverse cardiac events (MACE).

with MACE during the follow-up, procedural CK-MB elevation may be a limitation of this approach.

Sirolimus-Eluting Stents

Small vessel disease has become more common, and the proportion of patients requiring coronary intervention is likely to further increase. These patients, however, have higher clinical and angiographic restenosis rates following small vessel angioplasty [1–5]. The risk of complications and restenosis in many of these patients is increased by other factors, particularly diffuse disease and diabetes mellitus. Although bare-metal stenting has an advantage in acute gain compared with balloon angioplasty, the former results in more late loss due to neointimal overgrowth. This tissue encroachment presents a greater problem in small than in large vessels because it leaves little room for lumen in the former [11]. Using bare-metal stents, the long-term results of small vessel stenting were disappointing, and provisional stenting was considered a better option. The use of drug-eluting stents in small coronary arteries, however, has reduced the rate of restenosis in comparison to bare-metal stents. Two types of drug-eluting stents, paclitaxel-eluting Taxus stents and sirolimus-eluting Cypher stents, are widely used in clinical practice. In head-to-head comparison studies, however, SES was associated with a lower rate of late lumen loss, [12–14] suggesting that SES may be more effective in preventing restenosis in high risk patients. In the present study, the safety and efficacy of SES were similar to those observed in clinical trials, suggesting that SES can benefit a broader range of patients. In routine clinical practice, patients not having standard indications are often treated with SES, and our results represent realistic outcomes in this challenging population.

Predictors of Restenosis

It is difficult to predict the occurrence of restenosis after SES implantation. Among the patient- and lesion-related factors related to the risk of restenosis are diabetes, small vessel size, and long lesions [7,9,10,15]. Since patients in these randomized trials were from a highly selected group with favorable lesion characteristics, including a relatively short narrowing, it is not clear if results from these trials can be extrapolated to patients seen in routine clinical practice, in which multiple overlapping stents are often required for full lesion coverage. Little data are available about the safety and efficacy of multiple overlapping SESs in very long small vessel disease. We observed that lesion length was a major predictor of restenosis, and SES implantation in very long small vessel disease (lesion length $\geq$ 60 mm) was related to a high risk of SES failure, suggesting that different treatment strategies should be considered in this situation.

Coronary revascularization procedures in diabetic patients have been associated with poorer clinical outcomes, with a higher risk of restenosis, when compared with nondiabetic patients [16]. Randomized trials have shown that SES markedly reduced restenosis in subsets of diabetic patients and demonstrated durable clinical and angiographic benefits. However, published data regarding the impact of diabetes mellitus on restenosis after SES implantation are still limited and controversial [17]. In the present study, diabetes mellitus was not a significant predictor of restenosis, indicating that SES can benefit this patient population [10].

In-stent restenosis remains a therapeutic challenge with a high risk of recurrence. Various catheter-based strategies, including balloon angioplasty, debulking ath-

erectomy, and stent implantation, are usually unsatisfactory. Although coronary brachytherapy has been the standard therapy for in-stent restenosis, a recent study showed that SES had significant advantages over brachytherapy, making SES the treatment of choice for in-stent restenosis in clinical practice [18]. We found, however, that the risk of SES failure in these lesions was higher than that in native coronary lesions.

Study limitations

This study had several limitations. It was not randomized and did not include comparisons with a control group treated with other therapies. In addition, our study was limited by the incomplete angiographic follow-up, which could possibly lead to an error in the restenosis rate.

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