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Sirolimus-Eluting Stent Implantation for Treatment of Proximal Left Anterior Descending Coronary Artery Lesions: Long-Term Outcome and Predictors of Adverse Cardiac Events

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Objectives: Acute and long-term results after sirolimus-eluting stent (SES) implantation of proximal left anterior descending coronary artery (LAD) disease were evaluated. Background: Although SES has been used increasingly for the treatment of LAD disease, data regarding their safety and efficacy in a real-world population are limited. Methods: We investigate the short- and long-term results in 966 patients who underwent SES implantation for stenosis of proximal LAD. Results: The procedural success rate was 97.6%, and procedural non-Q-wave myocardial infarction (MI) rate was 14.5%. In-hospital major complications occurred in five patients (0.5%), including three deaths and two Q-wave MIs. During follow-up (20.4 ± 8.9 months), there were 16 deaths (1.7%; 10 cardiac, 6 noncardiac), 2 Q-wave MIs, and 22 target lesion revascularizations (2.3%). Late stent thrombosis occurred in two patients (0.2%), 14 and 23 months after the procedure. The event-free survival rates for cardiac death/Q-wave MI were 98.6% ± 0.4% at 1 year and 97.8% ± 0.6% at 2 years. The cumulative probabilities of survival without major adverse cardiac events (MACE) were 96.7% ± 0.6% at 1 year and 95.4% ± 0.8% at 2 years. In multivariate analysis, stented length (HR 1.04, 95%CI 1.01–1.07, $P = 0.009$) and infarct-related artery (HR 5.18, 95%CI 1.09–24.64, $P = 0.039$) were independently related to cardiac death/Q-wave MI. In addition, stented length (HR 1.04, 95%CI 1.02–1.06, $P < 0.001$) and left ventricular dysfunction (HR 2.66, 95%CI 1.07–6.63, $P = 0.036$) were significant independent predictors of MACE. Conclusions: SES implantation for proximal LAD disease appears safe and effective in a real-world population, and the independent predictors of MACE included stented length and left ventricular dysfunction.

Key words: left anterior descending coronary artery; long-term outcome; sirolimus-eluting stent

INTRODUCTION

The left anterior descending coronary artery (LAD) supplies blood to a large part of the myocardium, and proximal LAD disease is associated with a poor prognosis [1–3]. Percutaneous coronary intervention and coronary artery bypass surgery have been shown to result in similar rates of symptomatic benefit and long-term survival for these patients [4–10]. In the bare-metal stent era, however, patients with proximal LAD disease were frequently referred for bypass surgery because the former carries a high risk of restenosis. Sirolimus-eluting stents (SES) reduce the risk of restenosis compared with bare metal stents [11–14], as well as providing enhanced clinical benefits [15]. These trials, however, were usually performed on highly se-

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lected patients with relatively short narrowings. In routine clinical practice, however, multiple overlapping SES implantation is often required to treat diffuse disease [16], and the role of SES in more complex lesions has been questioned. To date, data regarding the long-term safety and efficacy of SES implantation in a real-world population have been limited. We therefore determined the long-term clinical outcome after SES implantation for treatment of proximal LAD disease and identified the predictors of major adverse cardiac events (MACE) in a large number of unselected patients.

METHODS

Study Patients

A consecutive series of 966 patients who had been treated with SES implantation for proximal LAD disease at our institution between February 2003 and December 2005 were enrolled. All patients had significant coronary artery disease involving the proximal segment of the LAD (diameter stenosis >50%) and clinical indications for percutaneous coronary intervention. Patients were excluded from this study if they had previous bypass surgery or significant disease (diameter stenosis >50%) in the left main coronary artery or the ostium of the left circumflex artery.

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, patients received a bolus of 8,000 U of heparin, with a repeat bolus of 2,000 U to maintain an activated clotting time ≥300 sec. Following the procedure, patients were treated with aspirin (100–200 mg/day) indefinitely and clopidogrel (75 mg/day) for at least 6 months.

Angiographic Analysis

All angiographic analyses were 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 (CASS 2.0, Pie Medical Imaging, Netherlands) were measured before predilation, after the stenting procedure and at follow-up. Angiographic measurements were made during diastole after intracoronary nitroglycerin administration using a guiding catheter to calibrate magnification. Single matched views with the worst diameter stenosis were compared.

Definitions and Clinical Follow-Up

All demographic, clinical, angiographic, and procedural characteristics were prospectively entered into the Asan Medical Center database. Follow-up information was obtained by chart review and telephone interviews, and all follow-ups were at least 6 months. The primary endpoint of this study was MACE, defined as cardiac death, Q-wave myocardial infarction (MI) or target lesion revascularization. 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 > three times normal in the absence of new pathologic Q waves on postintervention electrocardiograms. Deaths were classified as either cardiac or noncardiac. Deaths that could not be classified were considered cardiac. MI during follow-up was diagnosed when CK-MB was elevated > threefold with chest pain ≥30 min or with the appearance of new electrocardiographic changes.

Statistical Analysis

Data were expressed as mean ± SD for continuous variables and as frequencies for categorical variables. Continuous variables were compared using unpaired student's t test and categorical variables by the χ^2 test. A Cox proportional hazard analysis was used to assess the association between variables and clinical events. The Kaplan–Meier method was used to analyze the occurrence of clinical events during follow-up. Statistical significance was defined as a two-sided P value <0.05.

RESULTS

Baseline Characteristics

The baseline clinical and angiographic characteristics are listed in Tables I and II. The mean age of the patients was 60.0 ± 10.5 years (range, 23–88 years); 26.7% had diabetes mellitus, 11.0% had left ventricular dysfunction (ejection fraction ≤45%) and 14.0% had ostial LAD disease (>50% diameter stenosis rising within 3 mm of the LAD orifice), and 30.4% received multivessel stent placement. The mean number of stents implanted per lesion was 1.57 ± 0.72 (range,

TABLE I. Clinical Characteristics

Characteristic	$N = 966$
Age (years)	60.0 ± 10.5
Men	704 (72.9%)
Current smoker	272 (28.2%)
Diabetes mellitus	258 (26.7%)
Total serum cholesterol (≥200 mg/dl)	203 (21.0%)
Hypertension	478 (49.5%)
Clinical presentation	
Stable angina pectoris	492 (50.9%)
Unstable angina pectoris	347 (35.9%)
Acute myocardial infarction	127 (13.1%)
Previous myocardial infarction	78 (8.1%)
Previous percutaneous coronary intervention	171 (17.7%)
Multivessel coronary disease	553 (57.2%)
Left ventricular ejection fraction (%)	58.1 ± 8.8

TABLE II. Angiographic and Procedural Characteristics

Characteristic	$N = 966$
Lesion characteristics	
ACC/AHA B_2C lesion	793 (82.1%)
Bifurcation	223 (23.1%)
Chronic total occlusion	67 (6.9%)
Infarct related artery	102 (10.6%)
In-stent restenosis	91 (9.4%)
Ostial lesion	135 (14.0%)
Procedural characteristics	
Balloon to artery ratio	1.25 ± 0.13
Maximal inflation pressure (atm)	16.0 ± 12.5
Stents per lesion	1.57 ± 0.72
Stented length per lesion (mm)	39.1 ± 19.1
Quantitative coronary angiography	
Lesion length (mm)	30.9 ± 16.4
Reference vessel diameter (mm)	2.96 ± 0.41
Preintervention	
Minimal lumen diameter (mm)	0.82 ± 0.49
Diameter stenosis (%)	70.3 ± 14.6
Postintervention	
Minimal lumen diameter (mm)	2.81 ± 0.45
Diameter stenosis (%)	3.4 ± 12.8
Acute gain	1.99 ± 0.56
Use of glycoprotein IIb/IIIa inhibitor	25 (2.6%)
Intravascular ultrasound guidance	716 (74.1%)

1–5) and the mean stented length was 39.1 ± 19.1 mm (range, 8–112 mm).

Procedural Results and In-Hospital Complications

The procedural success rate was 97.6%, and the rate of procedural non-Q-wave MI was 14.5%. In-hospital major complications (cardiac death, Q-wave MI, repeat revascularization or emergency bypass surgery) developed in five patients (Table III). Three patients presented with acute MI and died of cardiogenic shock soon after the procedure. Two other patients developed acute stent thrombosis with Q-wave MI immediately and 1 day, respectively, after the procedure.

TABLE III. Major Clinical Events During Hospitalization

Characteristic	$N = 966$
Death	3 (0.3%)
Q-wave myocardial infarction	2 (0.2%)
Death/Q-wave myocardial infarction	5 (0.5%)
Stent thrombosis	2 (0.2%)
Procedural non-Q-wave myocardial infarction	141 (14.6%)
Repeat intervention	2 (0.2%)
Emergent bypass surgery	0 (0%)

TABLE IV. Predictors of Long-Term Clinical Outcomes

	Univariate analysis			Multivariate analysis		
Variables	HR	95%CI	*P*	HR	95%CI	*P*
Cardiac death/Q-wave MI						
Stented length	1.03	1.01–1.06	0.007	1.04	1.01–1.07	0.009
IRA	5.24	1.75–15.67	0.003	5.18	1.09–24.64	0.039
Procedural non-Q-MI	3.98	1.39–11.51	0.011			
Acute MI	4.04	1.35–12.06	0.012			
Lesion length	1.04	1.01–1.07	0.020			
LVEF ≤ 45%	3.84	1.16–12.75	0.028			
MACE						
Stented length	1.03	1.02–1.05	<0.01	1.04	1.02–1.06	<0.01
LVEF ≤ 45%	2.92	1.36–6.29	0.01	2.66	1.07–6.63	0.036
Lesion length	1.04	1.02–1.06	<0.01			

IRA, infarct-related artery; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events (cardiac death, Q-wave MI, or target lesion revascularization); MI, myocardial infarction.

Long-Term Outcomes and Predictors of Cardiac Events

During follow-up (20.4 ± 8.9 months), there were 16 deaths (1.7%; 10 cardiac, 6 noncardiac), 2 Q-wave-MIs (0.2%), and 22 target lesion revascularizations (2.3%; 20 repeat interventions, 2 bypass surgeries). Late stent thrombosis occurred in two patients (0.2%), 14 and 23 months, respectively, after the procedure. All of these patients developed Q-wave-MI without death. The event-free survival rates for cardiac death/Q-wave-MI were 98.6% ± 0.4% at 1 year and 97.8% ± 0.6% at 2 years. The cumulative probabilities of survival without MACE were 96.7% ± 0.6% at 1 year and 95.4% ± 0.8% at 2 years.

Univariate and multivariate predictors of clinical events are shown in Table IV. Multivariate analysis showed that stented length (HR 1.04, 95%CI 1.01–1.07, $P = 0.009$) and infarct-related artery (HR 5.18, 95%CI 1.09–24.64, $P = 0.039$) were independently related to cardiac death/Q-wave-MI. In addition, stented length (HR 1.04, 95%CI 1.02–1.06, $P < 0.001$) and left ventricular dysfunction (HR 2.66, 95%CI 1.07–6.63, $P = 0.036$) were significant independent predictors of MACE. As shown in Figure 1, the cumulative incidence of MACE was significantly increased according to the stented length or left

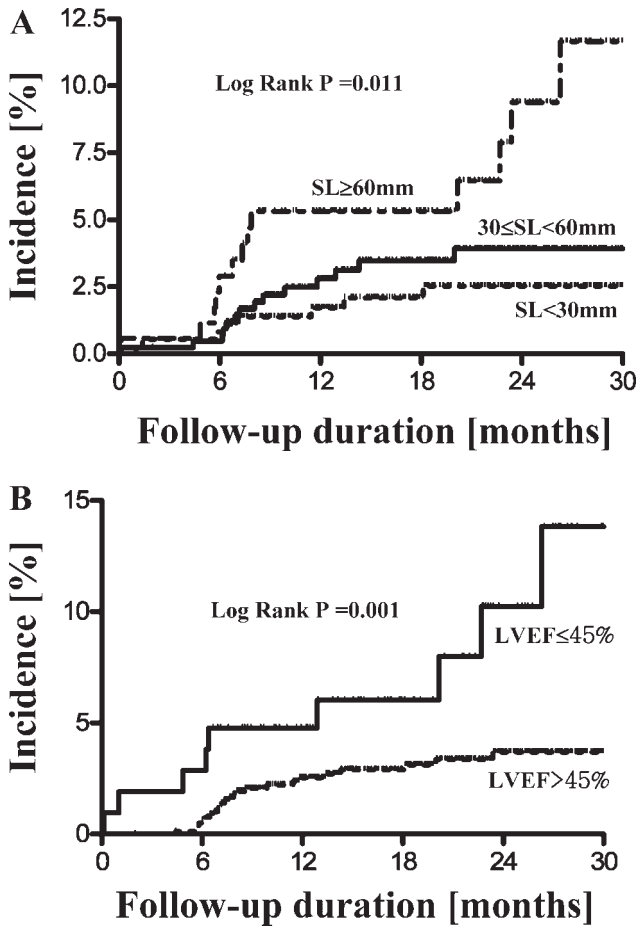

Fig. 1. Cumulative incidence of MACE relative to stented length (A) and left ventricular dysfunction (B). Abbreviations: LVEF, left ventricular ejection fraction; SL, stented length.

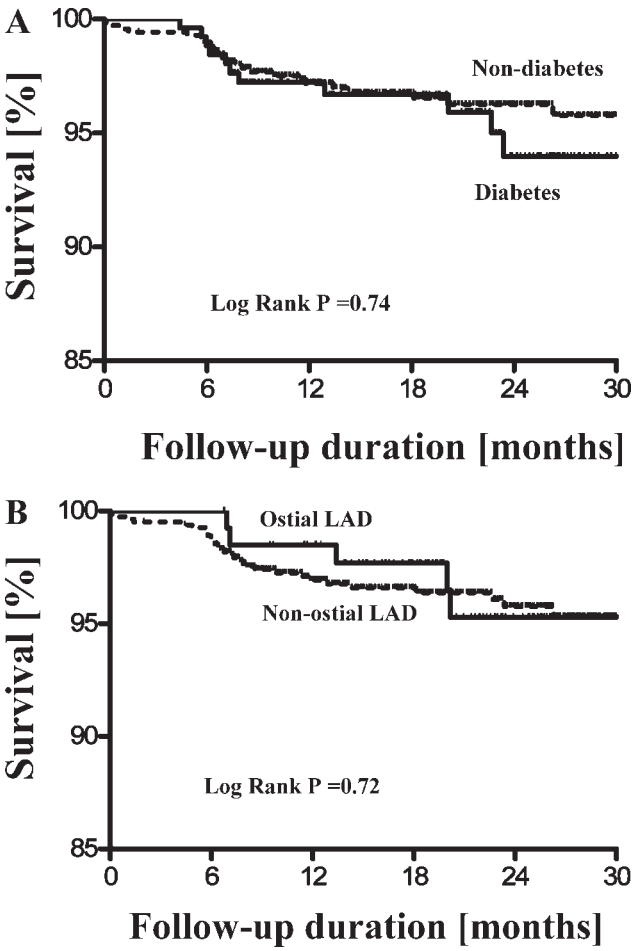

Fig. 2. Event-free survival curves for MACE according to the presence or absence of diabetes (A) or ostial LAD disease (B). Abbreviations: LAD, left anterior descending coronary artery.

ventricular dysfunction. In contrast, the presence of diabetes or ostial LAD disease was not related to MACE (Fig. 2).

DISCUSSION

We have shown here that SES implantation for treatment of proximal LAD disease was both safe and efficacious in a real-world population. We also found that the independent predictors of MACE included stented length and left ventricular dysfunction. In addition, the presence or absence of ostial LAD stenosis was not a significant determinant of clinical outcomes after SES implantation. These findings suggest that SES implantation for proximal LAD lesions in appropriately selected patients may be an effective therapeutic strategy, with clinical outcome dependent on the extent of atherosclerosis and left ventricular function, but not on the target lesion per se.

Proximal LAD disease has been regarded as a high-risk lesion because this artery supplies about 50% of the left ventricular myocardium. An occlusion of this site would jeopardize a large portion of the myocardium, placing the patient at risk for severe left ventricular dysfunction or death [1–3]. Revascularization with bypass surgery or angioplasty offers better symptomatic improvement and quality of life benefits as compared with medical management [9]. Despite numerous studies comparing surgical and percutaneous revascularization, however, the optimal choice of treatment for proximal LAD disease remains unclear [4–10]. Trials comparing percutaneous coronary intervention with coronary artery bypass surgery for isolated proximal LAD disease have demonstrated that both treatments result in similar rates of long-term survival and MI but that the former is associated with a much greater need for repeat revascularization [4,5]. For example, in one trial in 120 patients with isolated proximal LAD disease, stent implantation and balloon angioplasty had similar rates of immediate procedural success, but the former had a significantly higher event-free survival

rate (87% vs. 70%, $P = 0.04$) and a significantly lower rate of restenosis (19% vs. 40%, $P = 0.02$) at 12 months [10]. A second trial comparing minimally invasive bypass surgery with stent implantation for patients with isolated proximal LAD lesions showed that stenting yielded excellent short-term results with fewer procedural adverse events, whereas surgery was superior with regard to the need for repeated intervention in the target vessel (8% vs. 29%, $P = 0.003$) [6]. Overall, bare-metal stent implantation reduced the reintervention gap between percutaneous and surgical revascularization, but the rate of repeat revascularization remained higher in the stent group.

The use of SES has opened a new era in the prevention of restenosis and improved the long-term durability of percutaneous coronary intervention [11–14]. SES can be considered as a valid alternative to coronary artery bypass surgery, given the excellent results of clinical trials of this therapy. Of the 1,101 patients in the SIRIUS trial, 459 with LAD stenosis were randomized to percutaneous intervention with either sirolimus-eluting or bare-metal stents [15]. At a mean follow-up period of 1 year, treatment with SES was associated with significantly lower rates of reintervention (6% vs. 23%, $P < 0.001$) and MACE (10% vs. 25%, $P < 0.001$), suggesting that SES may eliminate the reintervention gap between surgical and percutaneous interventions for isolated proximal LAD disease. In the SERIUS trial, however, the majority of lesions were tubular type B lesions (69.7%) with a mean lesion length of 14.0 mm, and ostial, multiple, and bifurcation lesions were excluded. Our study was performed in a consecutive series of unselected patients with proximal LAD disease who underwent SES implantation, representing a real-practice situation. Despite these differences, the rate of 1-year MACE in our study was similar to the historical rate with bypass surgery [17] and to that of the SERIUS trial, extending the role of SES for the treatment of proximal LAD disease. Surgical revascularization of the LAD using the left internal mammary carries a low incidence of target vessel failure with 2–8% at 1 year of follow-up [4–8]. In our study, the rate of target vessel revascularization was 2% at 1 year of follow-up, suggesting that the difference between surgical and percutaneous therapy in terms of target vessel failure disappears. Since no randomized study to date has, however, compared outcomes in patients treated with bypass surgery and SES implantation, additional studies are required to compare the relative benefits of these two forms of revascularization.

Ostial LAD disease remains a challenging lesion for the interventional cardiologist due to the difficulty of the intervention itself and the high restenosis rates thereafter [18,19]. Coronary stents have improved outcomes, but higher restenosis rates are observed in ostial compared with nonostial stenosis. We have shown that SES decreases the risk of restenosis compared with bare-metal stents [20]. In the present study, outcomes of SES implantation for ostial LAD stenosis were comparable with those of nonostial proximal LAD stenosis, suggesting that SES is an effective therapeutic option for these lesions. Interestingly, diabetes was not a significant predictor of MACE, supporting the concept that diabetes may be less important in predicting risk of restenosis in patients undergoing SES implantation [21]. Finally, multiple overlapping SES in our study seemed to be safe and effective, but stented length $\geq$60 mm was related to increased risks of procedural non-Q-wave-MI (OR 1.82, 95%CI 1.20–2.77, $P = 0.005$) and late MACE (HR 2.76, 95%CI 1.39–5.48, $P = 0.004$), suggesting that different approaches should be considered in this situation, especially in patients with left ventricular dysfunction.

Among the potential limitations of our study was its observational, nonrandomized design, with no control group treated with bypass surgery, thus precluding a determination of the role of treatment differences on clinical outcomes. Second, our patient cohort included only patients treated with SES, thus precluding generalization to other drug-eluting stent systems.

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