Two-Year Outcomes of the Sirolimus-Eluting Stent According to Unprotected Left Main Lesion

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ABSTRACT

Background: The data of long-term outcomes of sirolimus-eluting stent (SES) according to lesion location of unprotected left main coronary artery (LMCA) is scarce.

Hypothesis: The purpose of this study was to evaluate the long-term outcomes after implantation of the SES in LMCA.

Methods: A total of 84 patients (51 males) who had undergone SES implantation for the treatment of native LMCA stenosis were enrolled. The patients were divided into 2 groups based on angiographic lesion location: those with significant stenosis in the ostium and/or body (group 1; n = 39) and those involving bifurcation (group 2; n = 45).

Results: All of the group 1 patients were treated with simple lesion coverage while different stenting techniques were used in group 2 (cross-over: 44.8%, T: 6.7%, kissing: 37.8%, and crush techniques: 11.1%). The 8-month quantitative angiographic findings and in-hospital and 2 year rates of major adverse cardiac events (MACE) were compared between the 2 groups. Although angiographic success and in-hospital MACE rates were similar in both groups with 1 cardiac death due to acute stent thrombosis in group 2, at 2-year follow-up, the MACE rate was significantly higher in group 2 than in group 1 at 2 years (22.2% vs 2.6%, respectively, $P = 0.008$). Coronary angiography revealed a significantly higher binary restenosis rate in group 2 compared with group 1 (20% vs 0%, respectively, $P = 0.003$).

Conclusions: Interventional treatment using SES in left main lesions showed favorable short-term and long-term outcomes in selected patients with lesion location being an important determinant of clinical and angiographic outcomes.

Introduction

Percutaneous coronary intervention (PCI) with drug-eluting stent (DES) has been associated with marked reductions in restenosis rates[1] and neointimal hyperplasia formation;[2] this also appears to be the case for the treatment of unprotected left main coronary artery (LMCA) lesions,[3–5] an observation that stands in contrast with the fact that in the bare-metal stent era an LMCA lesion was a definite indication for coronary artery bypass graft (CABG) surgery. However, there is little data on the long-term outcomes according to LMCA lesion complexity and location and therefore this registry study was aimed at evaluating long-term clinical and angiographic outcomes according to LMCA lesion location post sirolimus-eluting stent (SES) implantation.

Methods

Study Population

From July 2003 to August 2005, 84 consecutive patients (male, n = 51) who underwent PCI for unprotected left main stenosis at Yeungnam University Medical Center, Keimyung University Dong-san Hospital, and In-je University Baik Hospital in Busan were enrolled in this study. Patients were divided into 2 groups according to the lesion location: group 1 (n = 39) was defined as patients with significant stenosis in the LMCA ostium and/or body, and group 2 (n = 45) as those who had a LMCA lesion involving bifurcation. The respective institutional committees approved the study protocol and written informed consent was obtained from all patients. The LMCA was considered to be unprotected if there were no patent CABGs in the left anterior descending artery (LAD) or in the left circumflex artery (LCX). The indication of PCI instead of surgery was considered in case of suitable anatomy for stenting and preference by patient and by referent physician for a percutaneous approach or suitable anatomy for stenting and unfavorable for surgery defined as a European system for cardiac operative risk stratification (EuroSCORE) ≥ 6 and/or Parsonnet score ≥ 13.[6]

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Medications and Procedures

All patients received aspirin 325 mg orally and a loading dose of 300 mg of clopidogrel before coronary angiography (CAG), or after PCI in emergency cases. After PCI, patients were routinely treated with aspirin 100 mg/day, clopidogrel 75 mg/day, and/or cilostazol 200 mg/day for 6 months. The glycoprotein IIb/IIIa inhibitors were not used in both groups.

Coronary angiography was performed after administration of 0.2 mg of intracoronary nitroglycerin. Using the guiding catheter for magnification and calibration, quantitative coronary angiography (QCA) was performed before and immediately after the procedure, and at 8-month follow-up.

Left main coronary artery lesion treatment was performed by the simple "cross-over," "T," "crush," or "kissing" stenting techniques at the discretion of the operator according to the characteristics of the lesion and the anatomy of the left coronary artery. In all patients, the sirolimus-eluting stent (Cypher, Cordis, Johnson and Johnson Corp., Miami, FL) was used. A "kissing" balloon inflation was the final step of the procedure at the discretion of the operator.

Definitions, Follow-up, and Clinical Endpoint

Procedural success was defined as residual diameter stenosis $\leq$ 30% and the absence of any in-hospital major adverse cardiac event (MACE), including cardiac death, acute myocardial infarction (AMI), target-lesion revascularization (TLR), or target-vessel revascularization (TVR). Myocardial infarction was diagnosed when cardiac enzymes (CK-MB) were elevated more than 3-fold the normal levels, with chest pain lasting $\geq$ 30 minutes, or with the appearance of new electrocardiographic changes. Target-lesion revascularization was defined as either surgical or percutaneous reintervention driven by significant (>50%) luminal diameter narrowing within the stent or the 5 mm borders proximal and distal to the stent and was undertaken in the presence of either anginal symptoms or objective evidence of ischemia. Target-vessel revascularization was defined as revascularization within the target vessel encompassing the target lesion. At 8 months postprocedure, all living patients were invited back for angiographic follow-up. Angiographic restenosis was defined as a $\geq$ 50% diameter stenosis within the target lesion. Cumulative rates of event-free survival and MACE (cardiac death, AMI, TLR, TVR) were analyzed over a 2-year follow-up period. The Parsonnet score and EuroSCORE were used to stratify the risk of death at 30 days.[7,8] The patients were stratified as high risk in the presence of a EuroSCORE $\geq$ 6 and/or Parsonnet score $\geq$ 13.

Clinical follow-up was performed for all patients at 1, 3, 6, 12 months, and thereafter every 3 months regularly in the outpatient department or by direct telephone call to the patients.

Statistical Analysis

Data are expressed as mean $\pm$ SD for continuous variables, and as frequencies for categorical variables. A 2-tailed Student t test was used to assess differences among continuous variables. The χ^2 test was used for comparison of categorical variables. Major adverse cardiac event-free survival distributions were estimated according to the Kaplan-Meier method. The log-rank test was used to compare MACE-free survival between the 2 groups. Probability values of $< .05$ were considered significant. Data were analyzed with the SPSS 12.0 software for Windows (SPSS, Chicago, IL).

Results

Baseline characteristics including age, sex, diabetes mellitus (DM), hypertension, left ventricular function, and old myocardial infarction, among others, did not differ between the 2 groups (Table 1). High mortality risk scores (EuroSCORE $\geq$ 6 and/or Parsonnet $\geq$ 15)[13] were present

Table 1. Baseline Clinical Characteristics in the 2 Groups

	Group 1	Group 2	*P* Value
Number of patients	39	45	
Age (y)	59 ± 12	61 ± 9	0.458
Male gender (%)	64.1	57.8	0.554
Diabetes mellitus (%)	23.1	17.8	0.448
Hypertension (%)	38.5	48.9	0.386
Smoking (%)	35.9	28.9	0.415
LDL cholesterol (mg/dL)	116 ± 34	117 ± 49	0.945
LVEF (%)	55 ± 13	59 ± 10	0.123
EuroSCORE	3 ± 2	3 ± 2	0.512
Parsonnet score	10 ± 6	9 ± 5	0.662
EuroSCORE $\geq$ 6 and/or	35.9	22.2	0.227
Parsonnet $\geq$ 13 (%)			
GP IIb/IIIa inhibitor use	0	0	
Previous history (%)			0.506
MI	5.1	2.2	
PCI	17.9	8.9	
CABG	2.6	2.2	

Data are presented as mean ± SD or percentages
Abbreviations: CABG, coronary artery bypass graft; GP IIb/IIIa, glycoprotein IIb/IIIa; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

in 24 patients (28.5%) and the proportions of patients with higher risk profiles were not statistically different (35.9% in group 1 vs 22.2% in group 2, $P = 0.227$; Table 1).

Table 2 summarizes quantitative coronary angiographic data. Although a greater number of diseased vessels were present in group 2 as compared to group 1, the numbers of vessels subjected to intervention were not significantly different between the 2 groups (Table 3). More complex stenting techniques, such as kissing, T, and crush were performed in group 2 and final kissing balloon techniques were used more often in group 2 than in group 1 (Table 3). Final post dilatation with a noncompliant balloon was done in 97% of group 1 and 22% of group 2. The balloon was 3.1 ± 0.5 mm in diameter and 15.8 ± 5.1 mm in length and high pressure with 15 ± 4 atm was applied.

In-hospital MACE rates were compared between the 2 groups. There were no MACE in group 1 while in group 2 there was 1 death due to acute thrombosis and myocardial infarction due to left circumflex coronary dissection during the procedure; the difference in MACE rates was not statistically different.

The duration of mean clinical follow-up was 839 ± 339 days. During subsequent follow-up to post PCI, 4 patients (11%) underwent repeat intervention, 3 (4.4%) had a surgical operation, and 1 (2.2%) died in group 2 while there was only 1 (2.5%) death in group 1. Total MACE rates were therefore 22% (10 patients) in group 2 and 2.5% (1 patient) in group 1 ($P = 0.008$; Table 4), with 1 death in each group during clinical follow-up to 2 years. MACE-free survival during the 2-year follow-up period was significantly different between the 2 groups (nonbifurcation and bifurcation lesions) and it is shown in the Figure.

The only fatality case in group 1 was a 70-year-old woman who experienced sudden death during sleep at 34 days after discharge. She was compliant on dual antiplatelet therapy with aspirin 100 mg and clopidogrel 75 mg daily, and we presumed late stent thrombosis as the cause of death. One of the fatalities in group 2 was a 55-year-old man who developed acute stent thrombosis and cardiogenic shock after PCI and did not respond to aggressive treatment including intra-aortic balloon pumping. The other was a 66-year-old man in group 2 with ischemic dilated cardiomyopathy and late stent thrombosis leading to pump failure and death.

An 8-month angiographic follow-up was performed in 62 patients (73.8%). A total of 28 (71.7%) patients in group 1 and 34 (75.6%) in group 2 were angiographically followed up and this was not statistically significant ($P = 0.252$). All restenosis events occurred in group 2 at a rate of 10.7%, 2 events in the left main trunk and 7 in the left circumflex

Table 2. Quantitative Coronary Angiographic Analysis

	Group 1	Group 2	*P* Value
Proximal reference (mm)	3.6 ± 0.3	3.6 ± 0.4	0.257
Distal reference (mm)			
LAD	3.4 ± 0.3	3.3 ± 0.3	0.946
LCX	2.9 ± 0.1	2.9 ± 0.3	0.156
Average reference (mm)			
LAD	3.5 ± 0.3	3.4 ± 0.3	0.833
LCX	3.3 ± 0.2	3.3 ± 0.4	0.914
Lesion length (mm)	11.8 ± 4.3	15.4 ± 3.2	0.043
Minimal lumen diameter (mm)			
Before	0.7 ± 0.3	0.7 ± 0.5	0.981
After	3.0 ± 0.3	2.9 ± 0.3	0.689
Diameter stenosis (%)			
Before	77 ± 10	79 ± 9	0.156
After	11 ± 8	12 ± 8	0.938

Data are presented as mean ± SD or percentages
Abbreviations: LAD, left anterior descending artery; LCX, left circumflex artery.

Table 3. Procedural Characteristics of the 2 Groups

	Group 1	Group 2	*P* Value
Number of patients	39	45	
Other site lesion (>50% stenosis except left main lesion)			
≥2 vessels (%)	20.5	51.2	0.019
Other site intervention (%)			0.441
LAD	10.3	13.3	
LCX	7.7	2.2	
RCA	2.5	0	
Methods of stenting (%)			0.001
Cross-over	100	44.8	
Kissing	0	37.8	
T-stenting	0	6.7	
Crush	0	11.1	
Final kissing balloon (%)	2.5	77.7	0.001
Intra-aortic balloon pump (%)	0	2.2	1.000

Abbreviations: LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

Table 4. Major Cardiac Events During Hospital Stay and at 2-Year Clinical Follow-up

	Group 1	Group 2	*P* Value
Number of patients	39	45	
In-hospital			0.537
Reintervention (%)	0	2.2	
Bypass surgery (%)	0	0	
Myocardial infarction (%)	0	2.2	
Cardiac death (%)	0	2.2	
2-year			0.075
Reintervention (%)	0	8.8	
Bypass surgery (%)	0	6.6	
Myocardial infarction (%)	0	0	
Cardiac death (%)	2.6	2.2	
Total (%)	2.6	24.2	0.008

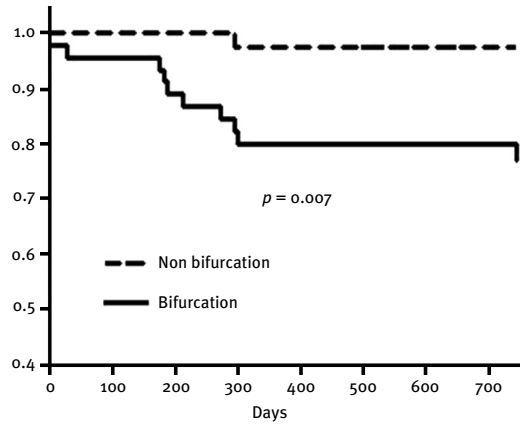

Figure 1. Kaplan-Meier survival curves for the freedom from the combined endpoint of cardiac death, myocardial infarction, or any revascularization during the 2-year follow-up period.

artery. Stent thrombosis, 1 acute in group 1 and 2 late in group 2, lead to death in all cases.

Discussion

The major finding of this study was that PCI of left main coronary artery lesions using the SES is feasible and yields good results in short-term and long-term follow-up. In addition, lesion location in LMCA disease has a great impact on MACE.

Current American Heart Association/American College of Cardiology guidelines give a class IIa indication for PCI of LMCA lesions. When the patient is eligible for CABG, PCI has a class III indication irrespective of the lesion location.[9] However, advances in intervention techniques and the use of DES are providing encouraging results in the treatment of LMCA stenosis.[10] In fact, DES have emerged as the favored percutaneous treatment modality for LMCA stenosis because of significant reductions in restenosis and TLR rates[11] as shown by a number of registries and nonrandomized studies that have demonstrated the effectiveness of DES for LMCA stenosis;[3–5,12,13] however, there has been scant data available on long-term clinical follow-up in LMCA lesions treated with DES.

Left main coronary artery stenosis can be categorized into 2 major anatomic subsets depending on whether the lesion involves LMCA distal bifurcation or not. Recently, 1 study showed that long-term outcomes were favorable after DES implantation in nonbifurcation LMCA lesions.[14] In that study, DES implantation in nonbifurcation lesions was safe with a long-term over 2 year MACE rate of 7.4% and a restenosis rate of 0.9%. However, the story has been different for bifurcation lesions with several studies showing LMCA distal bifurcation lesions as unfavorable settings for percutaneous intervention due to lower procedural success and higher restenosis rates.[15–17] To site 1 example, Price et al[18] published data on 50 patients with 94% of distal bifurcation lesions and 9 months follow-up; MACE rate was 10% in-hospital and 44% at 9 months with an overall angiographic restenosis rate of 42%.

In our study, mortality, MACE, and restenosis rate were 3.5%, 13.1%, and 10.7%, respectively, over the 2 years. All death events were likely caused by stent thrombosis. More favorable long-term MACE and restenosis rates of 2.6% and 0%, respectively, were obtained for nonbifurcation lesions in contrast to the 22% and 20%, respectively, obtained for bifurcation lesions. This result is consistent to that of other studies that have shown that bifurcation lesions yield higher restenosis and MACE rates than ostial and/or body lesions. In this study, most adverse events happened mainly during in-hospital and mid-term follow-up periods after left main stenting with MACE rarely developing later on. Therefore, left main stenting using DES appears relatively safe in long-term follow-up; however, it is still limited by relatively frequent restenosis, which more frequently involves the left circumflex ostium (7 out of 9 cases in this study), an observation that may be explained by the acute bend of the left circumflex ostium predisposing to nonapposition of the stent strut.[19]

A limitation of this study is that the study population was not large enough, that is, the study was not statistically powered to compare outcomes between the bifurcation and nonbifurcation lesions. Also, because a complete postprocedural intravascular ultrasound study was not performed, (just only 10 cases in group 2 and 2 cases in group 1) it is not possible to assess whether optimal stent expansion was achieved, and stent under expansion has been considered a significant cause of drug-eluting stent

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restenosis. Another limitation involves technical aspects of LMCA stenting, such as the use of a final kissing balloon. In our study, a final kissing balloon was performed in 77% of patients with bifurcated lesion, and the fact that it was not universally performed may affect outcome rates.

Conclusion

We showed that PCI using the siroliums-eluting stent in left main lesion yielded favorable short-term and long-term outcomes in selected patients with lesion location being an important determinant of clinical and angiographic outcomes.

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