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Five-year outcomes after stenting of unprotected left main coronary artery stenosis in patients with normal left ventricular function

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Abstract

Background: We analyzed the long-term (5-year) outcome of patients treated with stenting for unprotected left main coronary artery (LMCA) stenosis.

Methods: Between January 1995 and September 2001, 187 consecutive patients with unprotected LMCA stenosis and normal left ventricular function underwent elective stenting. Patients were examined or interviewed after 1, 3 and 6 months, and every 4 months thereafter for the occurrence of major adverse cardiac events (MACE), including death, myocardial infarction (MI) and target lesion revascularization (TLR).

Results: The procedural success rate was 99.5%. During hospitalization, there were no deaths and only one stent thrombosis. Six-month angiography in 162 patients (follow-up rate, 86.6%) showed a restenosis rate of 33.3%. During 5-year follow-up, there were 13 deaths (6 cardiac, 7 noncardiac) and 2 nonfatal MI. TLRs were required in 36 (20.9%) patients and new lesion revascularizations were required in 13 (5.0%) patients. At 1, 3 and 5 years, the cumulative probabilities for freedom from MACE were 79.9±1.8%, 77.5±2.5% and 77.5±2.5%, respectively.

Conclusion: The initial favorable outcomes of patients with normal left ventricular function after stenting of unprotected LMCA stenosis were sustained for up to 5 years.

Keywords: Coronary disease; Left main coronary artery; Stents

1. Introduction

The advent of drug-eluting stent (DES) has changed the paradigm of treatment strategies for coronary artery disease, with percutaneous coronary interventions (PCI) now available for several coronary lesion subsets considered not suitable for interventional treatment during the pre-DES era. One of the most challenging lesions in coronary intervention is unprotected left main coronary artery (LMCA) disease, in which DES has recently shown promising results [1–3]. To date, coronary artery bypass graft surgery (CABG) has been considered optimal in the treatment of LMCA disease, with a 3–5-year survival rate of 88% to 93% [4–6].

The use of PCI in the treatment of LMCA disease resulted in discouraging outcomes prior to stenting, but more recent advances in procedural techniques, devices, medications, patient selection and experience of the operators have improved outcomes, suggesting that PCI may become an attractive alternative to CABG. However, long-term outcomes (over 5 years) after PCI of unprotected LMCA using

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bare-metal stents (BMS), or DES, have not been determined. We therefore analyzed long-term outcomes in patients who underwent PCI of unprotected LMCA prior to the use of DES in our hospital.

2. Methods

2.1. Study population

Between January 1995 and September 2001, 187 consecutive patients with unprotected LMCA stenosis and normal left ventricular function underwent elective BMS implantation. Eligible patients had angina pectoris with LMCA disease or documented myocardial ischemia and angiographic evidence of <50% diameter stenosis of the LMCA suitable for stent implantation. Exclusion criteria included contraindications to antiplatelet or anticoagulation therapy and left ventricular dysfunction (ejection fraction <40%). Those patients with left ventricular dysfunction were mostly referred for CABG except few cases of PCI performed in emergency situation or for life-saving. We routinely used aspirin indefinitely and ticlopidine for 1 month for patients undergone PCI. Informed written consent was obtained from all patients in accordance with the Declaration of Helsinki.

2.2. Data collection and follow-up

A database of baseline clinical characteristics and procedural data for all patients was maintained. Quantitative angiographic data were obtained before predilation, after the stenting procedure and at 6-month follow-up. Clinical follow-up was performed after 1, 3 and 6 months, and every 4 months thereafter, by clinic visits or by telephone interviews, for the occurrence of major adverse cardiac events (MACE), including death, myocardial infarction (MI) and target lesion revascularization (TLR). All patients were followed up for at least 45 months (range, 45–117 months).

Table 1
Baseline patient characteristics ($n=187$)

Characteristic	
Age (years)	56.2±11.2
Men (%)	128 (68.4%)
Hypertension	51 (27.3%)
Diabetes mellitus	37 (19.8%)
Total cholesterol >200 mg/dl	57 (30.5%)
Current smoker	69 (36.9%)
Prior myocardial infarction	12 (6.4%)
Unstable angina pectoris	92 (49.2.8%)
Left ventricular ejection fraction (%)	62.4±8.3
Extent of coronary artery disease	
Left main only	130 (69.5%)
Left main and other coronary artery	57 (30.5%)
Lesion locations	
Ostium	91 (48.7%)
Body	27 (14.4%)
Distal	69 (36.9%)
Debulking atherectomy before stenting	52 (27.8%)

Table 2
Quantitative angiographic data ($n=187$)

Characteristics	
Reference artery (mm)	4.0±0.7
Lesion length (mm)	11.6±4.9
Minimal luminal diameter (mm)	
Pre-procedural	1.2±0.5
Post-procedural	4.1±0.6
Follow-up	2.8±1.1
Diameter stenosis (%)	
Pre-procedural	70.3±13.0
Post-procedural	−4.1±12.7
Follow-up	31.4±25.3
Acute gain (mm)	2.93±0.72
Late loss (mm)	1.37±0.94
Loss index	0.49±0.39
Balloon/artery ratio	1.10±0.21
Maximum inflation pressure (atm)	14.8±3.1
Angiographic restenosis rate	33.3%
Ostium	25.0%
Shaft	4.5%
Bifurcation	46.9%

2.3. Definitions

Procedural success was defined as ≤30% residual diameter stenosis by quantitative coronary angiography, with no major procedural or in-hospital complications (i.e. death, Q-wave MI or emergency bypass surgery). Angiographic binary restenosis was defined as ≥50% diameter stenosis of a target lesion in follow-up coronary angiography. A major adverse cardiac event (MACE) was defined as the occurrence of cardiac death, nonfatal MI or TLR during follow-up. Deaths were classified as either cardiac or noncardiac. Deaths that could not be classified were considered cardiac. MI was diagnosed when cardiac enzymes (creatine kinase-MB) were elevated more than three times normal, with chest pain lasting ≥30 min or with the appearance of new electrocardiographic changes.

2.4. Statistical analysis

Data are expressed as mean±S.D. for continuous variables and as frequencies for categorical variables. Survival and MACE-free survival distribution were estimated according to the Kaplan–Meier method. Multivariate logistic regression analysis was performed on all variables to identify factors predicting MACE over 5 years. Statistical significance was defined as $p<0.05$. All statistical analyses were performed using SPSS statistical software (ver. 12.0, SPSS Inc., Chicago, Illinois).

3. Results

3.1. Baseline characteristics

Clinical characteristics and angiographic data are shown in Tables 1 and 2. Of the 187 lesions, 91 (48.7%) were located

Table 3
Medication profiles (n=187)

Medication	
Aspirin	183 (97.9%)
Beta-blocker	69 (36.9%)
Calcium channel blocker	134 (71.7%)
Nitrate	103 (55.1%)
ACE inhibitor	22 (11.8%)
Lipid-lowering agent	43 (23.0%)

ACE=angiotension converting enzyme.

Table 4
Major adverse cardiac events (MACE) during 5-year follow-up (n=172)

Cardiac events	
Death	13 (7.6%)
Cardiac	6
Noncardiac	7
Nonfatal myocardial infarction	2 (1.1%)
Repeat revascularization	
Target lesion revascularization	36 (20.9%)
New lesion revascularization	13 (7.6%)
MACE[a]	42 (24.4%)

[a] Cardiac death, myocardial infarction and target lesion revascularization.

in the ostial LMCA, 27 (14.4%) in the body and 69 (36.9%) in the distal portion. Eighty patients (42.8%) had combined coronary artery disease other than LMCA disease and 63 patients (33.7%) underwent PCI for other coronary lesions. The bifurcation lesions were treated by simple stenting across the origin of circumflex artery (n=50, 72.5%) or T (Y) stenting (n=19, 27.5%). The procedural success rate was 99.5%. There were no in-hospital deaths and only one case of stent thrombosis (0.5%) with Q-wave MI, which was treated by repeated balloon angioplasty. None of the other patients experienced any clinical events during hospitalization. Six-month angiographic follow-up was performed in 162 patients (86.6%), and the binary restenosis rate was 33.3%.

3.2. Long-term outcomes

Medication was maintained as shown in Table 3. During the follow-up period of 71.2±26.3 months (range, 45–117 months), 13 patients (7.6%) died, 6 (46.2%) of cardiac causes (Table 4), including 4 from sudden death (Table 5) and 1 each from congestive heart failure and coronary vasospasm after CABG. Of the seven noncardiac deaths, two each were due to malignant disease and stroke, and one each to sepsis, pneumonia and a traffic accident. Most deaths occurred within 24 months, and there were no further events during the 5-year follow-up period. The 5-year survival rate was 95.9±1.5% (Fig. 1).

There were two nonfatal MIs (1.1%), and 36 target lesion revascularizations of the LMCA restenosis (20.9%), 20 for repeat PCI and 16 for CABG. Thirteen patients (7.6%) underwent PCI for a nontarget lesion during the follow-up period. Most target lesion revascularization events occurred within 9 months and reached a plateau thereafter, whereas the incidence of nontarget lesion revascularizations increased beyond 6 months after index procedure (Fig. 2). At 1, 2, 3 and 5 years, the cumulative probability of MACE-free survival was 79.9±1.8%, 77.5±2.5%, 77.5±2.5% and 77.5±2.5%, respectively. For bifurcation lesions, there were no significant differences in TLR rate (16.0% vs. 36.8%, p=0.099) and the incidence of sudden cardiac death (6.0% vs. 0%, p=0.556) between different bifurcation stenting techniques [simple stenting across the origin of circumflex artery vs. T (Y) stenting]. In the patients who required TLR, the most frequent site of restenosis was bifurcation in both groups of each stenting techniques [simple stenting across

Table 5
Clinical characteristic of patient of sudden death

	Patient 1	Patient 2	Patient 3	Patient 4
Sex	Male	Male	Male	Female
Age at index procedure	68	56	72	51
Cause of death	Unknown	Unknown	Unknown	Unknown
Duration to death	5	18	106	116
Preprocedural characteristics				
Clinical presentation	Stable angina	Acute MI	Unstable angina	Acute MI
Left ventricular ejection fraction	54%	47%	57%	52%
Associated disease	Diabetes	None	Diabetes hypertension	None
Lesion location	Ostium	Bifurcation	Bifurcation	Bifurcation
Multivessel disease	None	Yes	Yes	Yes
Known arrythmia	None	None	None	None
Noncardiac operation beafore death	None	None	None	None
Stenting technique	Single stent placement	Stenting across the circumflex artery	Stenting across the circumflex artery	Stenting across the circumflex artery
Antiplatelet therapy	As protocol[a]	As protocol[a]	As protocol[a]	As protocol[a]

MI=myocardial infarction.
[a] Aspirin indefinitely+triclopidine for 1 month.

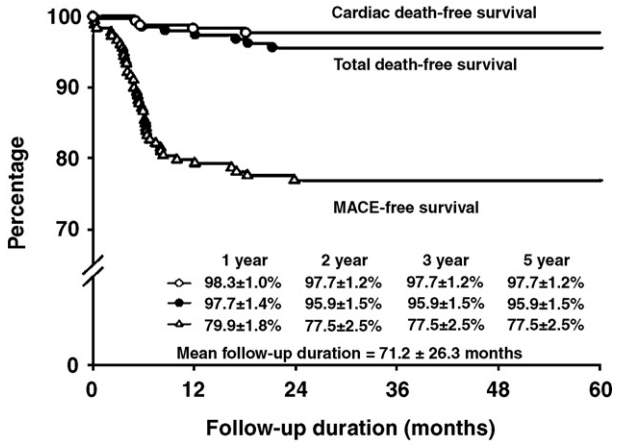

Fig. 1. Cumulative probability of survival free from cardiac death, total death and major adverse cardiac events (MACEs).

the origin of circumflex artery 70.0% vs. T (Y) stenting 100%, $p=0.279$].

Univariate analysis showed that age, diabetes mellitus, reference diameter, postprocedural minimal lumen diameter and the presence of other combined coronary arterial disease were predictors of MACE during the 5-year follow-up period. Multivariate analysis showed that the presence of other combined coronary arterial disease (OR 2.316, 95% CI 1.148 to 4.672, $p=0.019$) and postprocedural minimal lumen diameter (OR 0.363, 95% CI 0.195 to 0.676, $p=0.001$) were significant predictors of MACE (Table 6).

4. Discussion

The results presented here, on patients with normal left ventricular function who underwent stenting of unprotected LMCA stenosis, show that the initial favorable outcomes were sustained for up to 5 years, that target lesion revascularization was a significant problem, that combined coronary arterial disease and postprocedural minimal lumen diameter were important predictors of MACE over 5-year follow-up, and that later coronary events were mainly

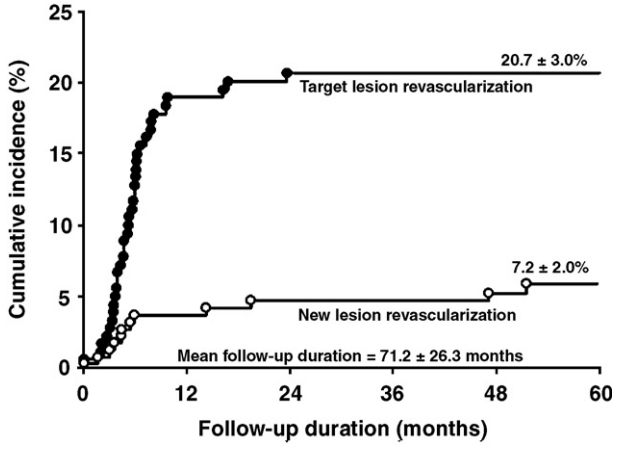

Fig. 2. Kaplan–Meier analysis of the incidence of repeat revascularizations.

Table 6
Correlates of major adverse cardiac events

Variables	Odds ratio	95% CI	*P* value
Univariate predictor			
Age	0.984	0.956–1.013	0.265
Diabetes mellitus	1.324	0.591–2.967	0.526
Reference size	0.439	0.259–0.743	0.003
Combined CAD	2.218	1.135–4.334	0.020
Post-MLD	0.537	0.305–0.945	0.001
Multivariate predictor			
Combined CAD	2.316	1.148–4.672	0.019
Post-MLD	0.036	0.195–0.676	0.001

CAD=coronary artery disease, post-MLD=postprocedural minimal lumen diameter.

associated with the development of new lesions. These results are consistent with those of our previous 3-year follow-up multicenter study [7]. Neither death nor MACE occurred more than 24 months after the initial procedure, but four noncardiac deaths occurred, at 62, 80, 88 and 98 months after PCI, respectively. Although significant mortality was observed after about 5 years, all four patients died of noncardiac causes not related to their earlier coronary problems, specifically, advanced cancer, stroke, sepsis and a traffic accident.

Our finding, that postprocedural minimal lumen diameter and other combined coronary arterial disease were significant predictors of MACE, is consistent with the results of our 3-year follow-up study [7]. It is also consistent with the findings of other studies showing that clinical and angiographic restenosis is related to the final stent cross sectional area and that postintervention lumen area, as determined by intravascular ultrasound, is a predictor of target lesion revascularization after stenting of protected LMCA [8,9]. Our results, showing that "the bigger, the better", are also valid for unprotected LMCA stenting. As shown in non-LMCA disease, elderly patients who have multivessel disease may be at particular risk of higher mortality rates after the index procedure. This may be due to more extensive coronary artery disease, with possibly less complete revascularization, in this group of patients. Compared with PCI, CABG was shown to be associated with better survival in patients with multivessel coronary artery disease and many high-risk characteristics, and the presence of LMCA disease favored CABG over PCI (OR 0.06, 95% CI 0.03 to 0.09, $p<0.0001$) [10]. It is therefore not clear if bypass surgery should be recommended for these patients, especially after the initial use of DES. Comparing with other studies [11,12] of unprotected LMCA stenting in bare-metal stent era, our data showed superior clinical outcomes. This may be due to several factors. We performed PCI for patients with normal left ventricular function only, and isolated LMCA disease limited in ostium or shaft were more frequent in our patient group (48%, 48% vs. 63%). Our strategy of careful selection of enrolled patients may partly contributed excellent long-term outcome of this study. Most of study patients had preserved left ventricular function and less

involvement of bifurcation lesion, which has been considered as predictors of favorable long-term outcomes.

Unlike the continuous need for new lesion revascularizations, we found that incidents of target lesion revascularization showed plateau 9 months after PCI and reached a steady state thereafter. This finding suggests that, following intervention, stabilized lesions maintain long-term stability, thus alleviating concern about the long-term stability of stented coronary lesions [13]. Early detection of restenosis is very important, because LMCA in-stent restenosis may result in fatal outcomes in patients with a large area of myocardium in jeopardy. Therefore, some operators advocate routine surveillance stress testing or cardiac catheterization at 3 and 6 months, even in asymptomatic patients, a strategy adopted in this study [11,14]. Although we did not routinely perform further diagnostic tests for restenosis following early surveillance, our 5-year clinical outcome was excellent, indicating that the clinical course after stenting of unprotected LMCA stenosis is similar to that of non-LMCA intervention. Moreover, our findings are consistent with those showing that the restenotic process after stenting is time-limited, with little progression occurring after 6 months [15,16].

To date, PCI of the unprotected LMCA has been not recommended by American College of Cardiology (ACC)/American Heart Association (AHA) guidelines [17]. Initial experience using PCI in the 1980s for LMCA stenosis was quite discouraging, with high in-hospital mortality rates (9.1–36%) [18–21]. These rates, however, gradually decreased to 0–3% [11,22]. Despite initial findings showing favorable outcomes after LMCA intervention using BMS in low-risk patients, in-stent restenosis after BMS implantation remains the most important reason for using CABG as the first choice for treating LMCA stenosis. We recently reported, however, that sirolimus-eluting stent implantation, performed on 102 patients with unprotected LMCA lesions and normal ventricular function, was safe and associated with a low procedure-related complication rate, and was followed by periods without deaths or stent thromboses [3]. Although patients with more complex lesions, including multivessel disease, bifurcation lesions and longer lesion lengths, were enrolled in this study, our initial outcomes were also favorable, with a procedural success rate of 100%; no in-hospital deaths, stent thromboses or Q-wave MIs; and markedly reduced angiographic restenosis (7.0%) and target vessel revascularization (2.0%) at 1-year follow-up. In addition, several studies have reported that DES showed no evidence of "late catch-up" in 2- to 3-year follow-up studies [23,24]. In the present study, patients who had been MACE-free during the first year after BMS implantation had an excellent long-term clinical outcome thereafter. These results, showing the long-standing safety of LMCA intervention using BMS and markedly improved early and mid-term outcome following application of DES for LMCA lesions, indicate that PCI may become an attractive alternative for using CABG to treat LMCA stenosis.

4.1. Study limitations

We cannot generalize our results to the entire range of patients with unprotected LMCA stenosis, because selected patients were excluded from this study. Another limitation of our results was that there were no mandated angiograms after the first follow-up angiogram, and all subsequent events were clinically driven; thus, we could not determine whether there had been any incidents of subclinical coronary pathology in patients with treated LMCA or other combined coronary lesions.

4.2. Conclusion

Clinical follow-up after BMS implantation of unprotected LMCA stenosis in patients with normal left ventricular function showed that the initial favorable outcome was sustained for up to 5 years. There was no evidence of late clinical deterioration of the stent at 2 to 5 years, which should alleviate some concerns about late adverse consequences of left main coronary stenting.

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