Clinical Results of Unprotected Left Main Coronary Stenting

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ABSTRACT: **Background:** Although unprotected left main coronary artery disease is considered by contemporary guidelines to be an indication for surgery, percutaneous coronary intervention may be necessary in patients at high surgical risk.

Objectives: To assess the outcome of angioplasty in the treatment of unprotected LMCA disease.

Methods: Angiographic and clinical data were collected prospectively for all patients who underwent emergent or non-emergent (planned) therapeutic PCI for unprotected LMCA disease at our center from 2003 to 2007. Baseline values were compared with findings at 1, 6 and 12 months after the procedure.

Results: The study group comprised 71 consecutive patients with a mean age of 74 ± 12 years; 63% were men, and 31% had diabetes. Forty-three patients had a planned procedure and 28 an emergent procedure. Mean EuroScore was 7.3 ± 3.6 (range 5–12). Forty-nine percent of the procedures were performed with bare metal stents and 51% with drug-eluting stents. Procedural success was achieved in 100% of cases. The overall mortality rate was 11.3% at 1 month, 18.3% at 6 months and 19.7% at 12 months. Elective PCI was associated with significantly lower mortality (2.3% vs. 25% at 1 month, 4.6% vs. 39% at 6 months and 6.9% vs. 39% at 12 months), and the use of drug-eluting stents was associated with lower rates of target vessel revascularization and major adverse cardiac events than use of bare metal stents (2.8% vs. 14% at 1 month, 8.3% vs. 43% at 6 and 12 months). Variables that correlated with increased mortality or MACE at 6 and 12 months were cardiogenic shock, emergent PCI, ejection fraction < 35%, renal failure, distal left main stenosis location, and reference diameter < 3 mm.

Conclusions: PCI is a feasible and relatively safe therapeutic option for unprotected LMCA. The less favorable outcome of emergent compared to planned PCI is probably attributable to the overwhelming acute myocardial ischemic injury in emergent cases. The use of drug-eluting stents may improve the intermediate-term restenosis rate. *IMAJ* 2009;11:154–159

KEY WORDS: left main coronary artery, angioplasty

LMCA = left main coronary artery
PCI = percutaneous coronary intervention
MACE = major adverse cardiac events

Significant left main coronary artery disease (> 50% stenosis) is detected during cardiac catheterization in 3%–5% of patients. The recommended optional treatment is coronary artery bypass grafting, which has been shown to improve survival in affected patients [1]. In most centers, percutaneous coronary intervention has traditionally been restricted to patients who are at high surgical risk for or who had previous bypass surgery (protected LMCA disease); PCI may also be used as a salvage procedure in cases of angioplasty complications [2]. The results depend on the clinical background and the baseline left ventricular function. The introduction of coronary stents renewed interest in the use of PCI for the treatment of LMCA disease. Several case series of patients who were treated electively even though they were at low risk for coronary artery bypass grafting reported a near-zero procedural mortality rate and a 3.1% to 4.2% one year mortality rate [3-6]. With the use of bare metal stents, restenosis remained a significant concern. However, more recent registry reports of trials with the newer drug-eluting stents noted a dramatic decrease in restenosis rates. The 6–12 month mortality rate of PCI with drug-eluting stents ranged from 0 to 11%; the angiographic restenosis rates ranged from 7 to 44%; and the target lesion revascularization rates ranged from 2% to 38% [7-12].

The aim of the present study was to analyze our experience with catheter-based treatment of unprotected LMCA stenosis in a heterogenous group of patients.

PATIENTS AND METHODS

The study sample included all patients with *de novo* unprotected LMCA stenosis who were treated with the catheter-based approach at Rabin Medical Center from January 2003 to October 2007. The data were prospectively collected into a special database at the center. Unprotected LMCA disease was defined as ≥ 50% left main stenosis in the absence of a patent coronary graft to one of the major branches of the left coronary arteries. Procedures were performed on either an emergent or non-emergent (planned) basis, according to the clinical indications. The decision to perform coronary artery bypass grafting or PCI was left to the discretion of

the physician, based on the clinical findings, patient's age, co-morbidities, and surgical risk score. The surgical risk score (risk of death within 1 month) was calculated according to EuroSCORE (the European System for Cardiac Operative Risk Evaluation) [13]. All patients received a detailed explanation of the options and provided informed consent.

Data on baseline characteristics, clinical events, angiographic details, and quantitative coronary angiographic parameters were collected for all patients.

PROCEDURE

All patients received aspirin and a loading dose of 300–600 mg clopidogrel before coronary angiography or immediately after in emergent cases. Anticoagulation treatment with unfractionated heparin (70 U/kg loading) was administered prior to PCI, with additional boluses during the procedure, to achieve an activated clotting time of 200–300 seconds. Platelet glycoprotein IIb/IIIa receptor inhibitors were used at the discretion of the operator. PCI was performed by the conventional technique (dilatation before stenting) or with rotational atherectomy before stenting (in cases of heavy calcification), or by direct stenting, at the discretion of the operator with consideration of the lesion's location and morphology. The technique for bifurcation or trifurcation lesions included stenting of the left main artery into a major branch of the left coronary artery with or without stenting of the other branch, depending on the degree of residual stenosis of the other branch (e.g., left anterior descending or left circumflex). All stents were implanted with moderate to high deployment pressure (10–16 atm) followed by systematic high pressure (16–20 atm) after dilatation with a non-compliant balloon. Kissing balloon inflation was used as the final step of the procedure in cases of bifurcation or trifurcation lesions. The selection of a drug-eluting stent or bare metal stent was left to the operator's discretion, as was the use of intracoronary ultrasonic imaging during the procedure.

All patients were prescribed life-long aspirin and clopidogrel for 6–12 months after DES implantation. Coronary angiography was recommended for all eligible patients at 3 to 6 months after the procedure to verify stent patency.

QUANTITATIVE CORONARY ANGIOGRAPHY

Coronary angiograms were recorded at baseline and after PCI. All angiograms were performed by an experienced cardiologist at the center's Angiograph Core Laboratory using the MDViewTM QA System (Medcon Telemedicine Technology – McKesson, Israel) with an automated edge-detection technique. The analysis was performed independently of the clinical outcome. A contrast-filled guiding catheter (6–8 French) served as the calibration standard. The reference and minimal lumen diameters were determined before and after PCI. Standard morphological criteria were used to identify lesion location, lumen diameter, and stent length and thrombus, and on the basis of these measurements the percent diameter stenosis was determined. TIMI flow grade (0 to 3) was measured prior to and at completion of the procedure. Success of the stent procedure was defined as angiographic residual stenosis of < 30% with TIMI 3.

DES = drug-eluting stent

FOLLOW-UP AND CLINICAL ENDPOINTS

Immediate and in-hospital events were recorded, and each patient completed a standardized questionnaire either by telephone or in the outpatient clinic at 1, 6 and 12 months after the procedure. The primary endpoint of the study was the occurrence of major adverse cardiac events, defined as cardiac death, acute myocardial infarction (Q and non-Q), and repeated target lesion revascularization or target vessel revascularization at 1, 6 and 12 months. Patients with more than one event were assigned the highest ranked one according to our pre-study list. Repeated MI was defined as a clinical episode of prolonged chest pain suggestive of acute MI and an increase in serum cardiac enzyme levels to at least twice the upper limit of normal, or the appearance of new pathological Q waves. TVR was defined as any revascularization that involved the target vessel (parent or side branch) or the need for coronary artery bypass grafting in the treated vessel during follow-up. TLR was defined as a successful revascularization procedure (PCI or surgical bypass) performed because of the reappearance of stenosis at the treated site (including 5 mm proximal and distal to the lesion borders). Stent thrombosis was defined according to the Academic Research Consortium [14] as "definite" in the context of acute coronary syndrome and/or re-infarction in the culprit coronary territory with angiographically proven thrombosis of the previously implanted stent. All events were further assessed by a research coordinator and reviewed by an experienced cardiologist from our research team.

STATISTICAL ANALYSIS

Continuous variables are presented as means ± standard deviations, and categorical variables as frequencies (%). Differences in continuous variables were analyzed with Student's *t*-test, and in categorical variables with chi-square or Fisher's exact test. Multivariate logistic regression analysis was performed to identify variables with a significant effect on 6 month outcome. All analyses were performed with STATISCA software (StatSoft, Inc, USA). *P* values < 0.05 were considered statistically significant for all analyses.

MI = myocardial infarction
TVR = target vessel revascularization
TLR = target lesion revascularization

Table 1. Baseline clinical characteristics of the study population

	Unprotected LMCA (N=71)
Age (yrs, mean ± SD)	74.8 ± 11.3
Female gender	26 (37%)
Systemic hypertension	48 (68%)
Diabetes mellitus	22 (31%)
Current or former smoker	25 (35.5%)
Hyperlipidemia	50 (70.4%)
Chronic renal failure	19 (26.8%)
History of stroke	14 (19.7%)
Peripheral vascular disease	11 (15.5%)
Left ventricular ejection fraction < 35	36 (50.7%)
EuroSCORE (mean ± SD)	7.3 ± 3.6
Parsonet score (mean ± SD)	16.1 ± 8.5
Clinical presentation	
Cardiogenic shock	12 (16.9%)
Acute myocardial infarction	18 (25.4%)
Unstable angina	35 (49.2%)
Stable angina	18 (25.4%)

RESULTS

BASELINE AND PROCEDURAL CHARACTERISTICS

The analysis included 71 consecutive patients who underwent PCI in an unprotected LMCA scenario. Their baseline demographic and clinical characteristics are summarized in Table 1. The mean age was 74 ± 12 years; 57% of the patients were over 75. Sixty-three percent were male. Half the group had significantly impaired left ventricular systolic ejection. Mean EuroScore was 7.3 ± 3.6 (range 5–12). Twenty-eight patients (39%) underwent an emergent procedure because of findings of acute ST elevation or non-ST elevation MI or cardiogenic shock; in the remaining 43 patients (61%) the procedure was planned.

The angiographic procedural characteristics are summarized in Table 2. The stenotic lesion was located in the distal left main bifurcation in 32 (45%) of the treated patients. More than two-thirds of the group was found to have concomitant multivessel coronary disease. As shown in Table 2, only 28% of patients underwent unprotected left main stenting alone while 72% of patients had additional intervention into the LAD artery (44%), left coronary artery (6%) or both (22%). Procedural success was achieved in 100% of patients. Glycoprotein IIb/IIIa inhibitors and intra-aortic balloon pump were administered to half the patients. Rotational atherectomy was used in 5 patients (7%). Ultrasonic imaging was used in 32 patients (45%) during the procedure in order to define lesion characteristics and/or optimized stent expansion.

LAD = left anterior descending

Table 2. Angiographic and procedural characteristics in patients with unprotected left main coronary stenosis

	Value (N=71)
Triple-vessel coronary disease	44 (62%)
Left main location	
Ostium	22 (31%)
Shaft	17 (24%)
Distal bifurcation	32 (45%)
Pre-reference vessel diameter (mm, mean ± SD)	3.4 ± 0.6
Lesion length (mm, mean ± SD)	9.5 ± 5.1
Pre-diameter stenosis	71 ± 22
Pre- MLD (mm, mean ± SD)	0.9 ± 0.6
Post-diameter stenosis	7 ± 6%
Post- MLD (mm, mean ± SD)	3.4 ± 0.8
Stent diameter (mm, mean ± SD)	3.6 ± 0.4
Direct stenting	28 (39.4%)
DES used	36 (50.7%)
Left main stenting alone	20 (28.2%)
Left main-LAD stenting	31 (43.7%)
Left main-CX stenting	4 (5.6%)
Left main-LAD-CX stenting	16 (22.5%)
Kissing technique	37 (52%)
Maximum inflation pressure (atm, mean ± SD)	18 ± 3.8
Cutting balloons	8 (11.3%)
Rotational atherectomy	5 (7.1%)
Angiographic success*	100%
ACT (sec, mean ± SD)	277 ± 56
Glyoprotein IIb/IIIa	29 (41%)
IABP	29 (41%)

* TIMI (thrombolysis in myocardial infarction) grade 3 and diameter stenosis < 30% at the end of the procedure

MLD = minimal luminal diameter, LAD = left anterior descending artery, CV = circumflex artery, ACT = activated clotting time, IABP = intra-aortic balloon pump.

OUTCOME

The overall mortality rate was 11.3% at 1 month, 18.3% at 6 months and 19.7% at 12 months. Compared to the patients who underwent an emergent procedure, the planned-procedure subgroup was characterized by significantly lower mortality at 1 month (2.3% vs. 25%), 6 months (4.6 vs. 39%) and 12 months (6.9 vs. 39%) ($P < 0.01$ for both), and a significantly lower composite incidence of MACE (4.7% vs. 25% at

1 month, 14 vs. 43% at 6 months, 16.3 vs. 43% at 12 months; $P < 0.01$) [Table 3]. Among the treated cohort with restenosis, 6 patients (8.5%) underwent repeat angioplasty procedure and 4 patients (5.6%) were referred for CABG surgery. PCI with DES was associated with significantly lower rates of TVR and MACE than BMS at 1 month (2.8% vs. 14%), 6 and 12 months (8.3 vs. 43% and 11.1 vs. 43%, respectively) ($P < 0.01$ and $P = 0.05$) [Figure 1].

Variables found to be significantly correlated with increased mortality at 6 and 12 months were cardiogenic shock ($r = 0.5$, $P < 0.001$), emergent unprotected LMCA procedure due to acute MI or hemodynamic instability ($r = 0.4$, $P = <0.001$), ejection fraction < 35% ($r = 0.3$, $P = 0.01$), and renal failure ($r = 0.5$, $P = 0.001$). MACE at 6 and 12 months correlated with cardiogenic shock ($r = 0.4$, $P < 0.001$), emergent procedure ($r = 0.3$, $P = 0.01$), renal failure ($r = 0.4$, $P = 0.001$), distal LMCA lesion location ($r = 0.3$, $P = 0.05$), LMCA reference diameter < 3 mm ($r = 0.3$, $P = 0.03$), and diabetes mellitus ($r = 0.3$, $P = 0.05$). Multivariate analysis identified emergent procedure (odds ratio 2.8, $P = 0.02$) as the most powerful independent determinant of mortality or MACE at 6 and 12 months.

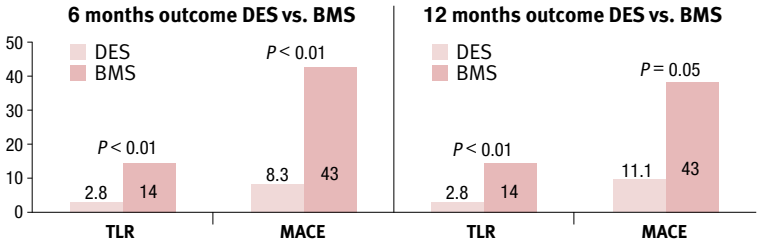
By 6 months, angiographic follow-up was performed in 25 patients (35.2%). This rate accounts for 40% of patients who were alive at 1 month follow-up. Fourteen patients (56.2%) were reevaluated because of symptoms and signs (chest pain, positive thalium scan, or acute coronary syndrome) and 11 (44%) as part of their routine surveillance. Angiography revealed stent restenosis in 10 patients (40%) and a patent left main stent in 15 patients (60%). The median time to follow-up angiography was 105 days with 25th and 75th interquartiles of 77–196 days. Between 6 and 12 months, five additional patients underwent repeat angiographic evaluation, thus the overall angiographic follow-up rate was 42% among initially treated patients and 48% of patients alive during 1 month. No additional angiographic restenosis was discovered among those five patients undergoing extensive evaluation.

Table 3. Clinical outcome at 1 and 6 months after PCI

	1 month	6 months	12 months
Death (overall)	8 (11.3%)	13 (18.3%)	14 (19.7%)
Death (planned procedure)	1 (2.3%)	2 (4.6%)	3 (6.9%)
Death (emergent procedure)	7 (25%)	11 (39%)	11 (39%)
Re-myocardial infarction	0%	5 (7%)	5 (7%)
TVR	1 (1.4%)	6 (8.5%)	6 (8.5%)
CABG	1 (1.4%)	4 (5.6%)	4 (5.6%)
Stent thrombosis	0	0	0
MACE (overall)	9 (12.7%)	18 (25.3%)	19 (26.8%)
MACE (planned procedure)	2 (4.6%)	6 (14%)	7 (16.3%)
MACE (emergent procedure)	7 (25%)	12 (43%)	12 (43%)

TVR = target vessel revascularization, CABG = coronary artery bypass grafting, MACE = major adverse cardiac events.

Figure 1. Outcomes at 1, 6 and 12 months for PCI with DES vs. BMS



DISCUSSION

The main finding of the present study in a heterogenous, consecutive group of patients with unprotected LMCA stenosis was that treatment with catheter-based angioplasty is feasible and has an acceptable procedural success rate. Although our study group was characterized by relatively advanced age, high prevalence of multivessel disease and impaired cardiac function and/or diabetes mellitus, and high average EuroScore, PCI was associated with a favorable intermediate-term outcome that varied by clinical presentation and the evolving nature of the procedure itself (i.e., planned versus emergent).

SAFETY OF UNPROTECTED LEFT MAIN STENTING

Over the past decade, advances in interventional techniques for the treatment of unprotected LMCA disease have led to improved procedural outcomes. Studies of PCI with the bare metal stent or the drug-eluting stent [3,5-11] in acute cases reported excellent procedural success rates and near-zero hospital mortality. We found that these results held true also in a mixed population of patients at low and high surgical risk. We assume that when PCI is performed by experienced hands, its technical feasibility and safety is no longer of major concern. The procedure can relieve most LMCA obstructions with very good immediate results. Nevertheless, the durability of the results and the survival benefit of PCI compared to surgery remain important concerns.

INTERMEDIATE-TERM OUTCOME

In our study, the overall 1, 6 and 12 month mortality rates were 11.3%, 18.3% and 19.7%, respectively. Although these figures seem high compared to other reports, we need to take risk stratification and patient characteristics into account.

CABG = coronary artery bypass graft
BMS = bare metal stent

Most cases of death (e.g., 11/14 patients at one year) occurred in the emergent PCI group. Those "emergent" patients were afflicted by acute coronary syndromes. In the ULTIMA registry, 1 year mortality for the low surgical risk patients was 3.4% [4]. Similarly, Takagi and colleagues [5] reported a 3 year cardiac mortality rate of 4.2% in low risk patients, and Park et al. [6] reported a 3.1% total mortality rate over an average of 19.9 months and no cardiac deaths in patients with normal left ventricular function. In studies using drug-eluting stents for LMCA in selected patients, the 6 to 12 month mortality rates ranged from 2% to 4% [7,8,10,11]. However, very few patients with acute MI were included in these registries. Alternatively, in other reports of patients who presented acutely with ST-elevation MI or cardiogenic shock and significant LMCA disease, the 6 month mortality rate was 59% and the event-free survival rate 27% [15,16]. Patients at high surgical risk had a 21% cardiac mortality at 3 years follow-up [5]. Our patient sample was representative of the "real world" of patients with LMCA disease who were admitted at our institution or were referred from surgical departments because they were considered unsuitable for aortocoronary surgery. Therefore, the group had a relatively high percentage of high risk features (e.g., advanced age, impaired left ventricular ejection fraction, concomitant multivessel disease, acute coronary syndrome at presentation, diabetes); almost 75% presented with acute ischemic syndrome, and 39.4% required emergent procedures. Thus, our results are in accordance with the 11% one year mortality rate reported by Valgimigli et al. [9] in a cohort in which 33.6% of patients presented with acute MI or cardiogenic shock, and with the 7.3% 6 month mortality reported by Khattab and team [17] in a cohort where 11.1% of patients presented with ST-elevation acute MI or cardiogenic shock. Sanmartin et al. [12] reported a 7% mortality rate at 9 months in a cohort in which 17% of patients presented with ST-elevation acute MI or cardiogenic shock, and Dubois and colleagues [18] reported a one year mortality of 22% in a cohort where 17% of patients had ST-elevation acute MI and 11% had cardiogenic shock. Our experience indicates that mortality is strongly dependent on patient selection, rising as high as 78% in patients with poor left ventricular function and acute ischemic syndrome, and dropping to as low as 3.4% in patients with lower risk profiles [19].

Our cohort included patients who were considered ineligible or poor candidates for surgery; this subgroup had a much higher post-procedural intermediate-term mortality rate [3]. The high rate of MACE was attributable in large part to our high proportion of high risk and emergent cases (39.4%) relative to other recent registries. For example, in the studies of Price et al. [11] (44% MACE at 9 months) and Lee et al. [10] (17% MACE at 12 months), it was the increased need for repeated revascularization that drove the MACE rate up. Our findings are consistent with previous studies demonstrating a poor prognosis for patients who present with acute MI or cardiogenic shock, for which the 6 month mortality rate approached 80% [20]. Left ventricular ejection fraction is an important determinant of outcome, particularly in patients with LMCA disease [5]. In our study, 6 and 12 month mortality correlated with lower left ventricular ejection fraction.

DES VS. BMS

Our study demonstrated a significantly greater reduction in MACE and TLR at 6 and 12 months in the patients treated with DES compared to BMS. These findings are in agreement with several recent registry reports indicating excellent procedural results and decreased restenosis rates for DES [7-9,21]. Chieffo and co-authors [8] also reported a lower cardiac death rate in their DES group (3.5% vs. 9.3%, $P = 0.17$).

Unrecognized and therefore untreated restenosis of LMCA may present as sudden cardiac death. In a later study Chieffo et al. [22] reported a restenosis rate of 0.9% with a late loss of 0.01 mm for ostial and mid-shaft lesions, but a significantly higher rate for distal left main lesions. In one registry in which all the patients were ineligible for coronary artery bypass grafting and 94% had distal lesions, the TVR rate was 38% [11]. Both the RESEARCH and T-SEARCH registries reported higher TVR and death/MI rates in patients with distal disease compared to patients without distal disease [23]. In our study, on univariate analysis, a distal left main lesion, found in about half the patients, was associated with an adverse 6 and 12 month clinical outcome. A low reference vessel diameter was another angiographic prognosticator of MACE, in accordance with previous studies where a low final stent lumen diameter was the only significant predictor of cardiac mortality [19] and a minimal post-procedural lumen diameter was a significant predictor of MACE [24].

LIMITATIONS OF THE STUDY

Our single-center registry design precluded a large sample size. In addition, the follow-up period was only 12 months. We did not detect any cases of stent thrombosis, perhaps by chance or perhaps because we limited our analysis to "definite," angiographically proven, thrombosis. Furthermore, some of the deaths in the patients who did not present for repeated angiography may have been due to stent thrombosis. Finally, no systematic angiographic follow-up was available in our series; consecutive intracoronary ultrasonic evaluation was performed during the index procedure which is of potential benefit in a percutaneous LMCA scenario and might have improved our clinical results.

DES = drug-eluting stent
BMS = bare metal stent

CONCLUSIONS

PCI seems to be a safe and feasible approach to the emergent or elective treatment of unprotected LMCA stenosis in patients at high or low surgical risk. Emergent PCI is associated with a less favorable outcome than planned PCI probably because of the presence of overwhelming myocardial ischemia and/or damage in this patient subgroup. Use of the drug-eluting stent seems to be associated with less restenosis than use of the bare metal stent.

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