Journal of Geriatric Cardiology (2015) 12: 634–640

Research Article · **Open Access** ·

Therapeutic effect of interventional therapy for unprotected left main coronary artery lesions in aged patients

Zhong-Hai WEI, Jie SONG, Lian WANG, Jing-Mei ZHANG, Wei HUANG, Biao XU

Department of Cardiology, Drum Tower Hospital, Medical School of Nanjing University, Nanjing, Jiangsu, China

Abstract

Objective To assesse the therapeutic effect of interventional therapy in aged patients with unprotected left main coronary artery (UPLM) lesions. **Methods** A total of 61 patients who were over 60 years and accepted interventional therapy of UPLM from January 2012 to November 2013 in our hospital were followed up for average 14.6 months by telephone call or outpatient visits. We analyzed the clinical features data of the interventional therapy and assessed the factors that likely influenced the clinical prognosis. **Results** The average age of the 61 patients was 73.9 years. The average left ventricular ejection fraction (LVEF) was 47.7%. The median of the estimated glomerular filtration rate (eGFR) was 52 mL/min per 1.73 mm^2. The average SYNTAX score was 27.4 and the median of stent length was 36 mm. The cumulative incidence of cardiac death at 30 days and major adverse cardiac events (MACE) after one year was 6.6% and 32.5% estimated by Kaplan-Meier plots respectively. No severe hemorrhagic complications were observed during follow-up period. On multivariate regression analysis with a COX proportional hazards model, LVEF was an independent predictor of cardiac death at 30 days [Hazard ratio (HR): 0.7, P = 0.01]. As for MACE after one year, LVEF and eGFR were both independent predictors (HR: 0.91, P = 0.06 for LVEF, HR: 0.03, P = 0.097 for eGFR). **Conclusions** The interventional therapy for UPLM was effective and safe in aged patients. LVEF was the only predictor of cardiac death at 30 days, while LVEF and eGFR were both independent predictors of MACE after one year.

J Geriatr Cardiol 2015; 12: 634–640. doi:10.11909/j.issn.1671-5411.2015.06.005

Keywords: Aged patients; Drug-eluting stent; Intervention; Left main coronary artery; Major adverse cardiac events

1 Introduction

The left main coronary artery (LM) is significant in that it provides 75% of the myocardial blood supply. The average diameter of the LM is 4.5 mm in men and 3.5 mm in women.[1] Due to its anatomical and physiological features, percutaneous coronary intervention (PCI) of unprotected LM (UPLM) lesions is usually highly risky and challenging. In recent decades, coronary artery bypass graft (CABG) has been regarded as gold standard therapy for UPLM. However, accompanied by the emergence of drug-eluting stent (DES) and intravascular ultrasound (IVUS), the therapeutic effect of intervention for UPLM is similar to that of CABG.[2,3] Age was no longer the contraindication of PCI for UPLM. In the real world, increasing number of patients with LM lesions prefer PCI to CABG because of aging, physical status, personal preference, and other factors. There were some studies that have been performed to evaluate the effectiveness of PCI for UPLM,[3–6] the results of which were different from each other significantly. It implied that the factors which would impact the outcomes of PCI for UPLM were complicated. Thus, the effectiveness and safety of PCI in aged patients with LM lesions deserves further assessment. We followed up 61 aged patients after PCI for UPLM in the current study. During the follow-up, 17 patients were suggested CABG preferably, but they preferred to PCI, while 20 patients were recommended PCI preferably due to the feature of LM lesions. The possible factors that could affect the clinical prognosis were analyzed.

2 Methods

2.1 Study population

The aged patients who underwent PCI of the UPLM from January 2012 to November 2013 were included in this study. The average age of the patients including 45 men and 16 women were 73.9 (61–89) years. Twenty patients were diagnosed with acute myocardial infarction, among which 6 with were ST-segment elevation myocardial infarction

Correspondence to: Biao XU, MD, PhD, Department of Cardiology, Drum Tower Hospital, Medical School of Nanjing University, Nanjing, Jiangsu, China. E-mail: xubiao@medmail.com.cn

Received: July 16, 2015 **Revised:** September 26, 2015
Accepted: October 27, 2015 **Published online:** November 3, 2015

(STEMI) and 14 with non-ST-segment elevation myocardial infarction (NSTEMI). The others had unstable angina. In the study cohort, 17 patients (27.9%) were recommended CABG preferably due to the complex lesions; 24 patients (39.3%) were suitable for both PCI and CABG; 20 patients (32.8%) were suggested PCI preferably due to the feature of LM lesions. The patient demographic characteristics, medical history, laboratory test results, and PCI information were recorded and assessed. All the patients underwent routine thoracic echocardiography by experienced physician using a Phillips iE33 within 24 h after hospitalization. Left ventricular ejection fraction (LVEF) was assessed using Simpson's method.[7] Estimated glomerular filtration rate (eGFR) was calculated using MDRD equation within 48 h after hospitalization.[8]

2.2 Procedural details

All of the patients were administered a loading dose of aspirin 300 mg and clopidogrel 300–600 mg and followed by a maintenance dose of aspirin 100 mg and clopidogrel 75 mg once daily. After a radial or femoral artery puncture, a 6F sheath was inserted. Heparin was administered at a dose of 70–100 IU/kg, while tirofiban was added if necessary. As a guidance of PCI, intravascular ultrasound (IVUS) was performed using a commercially available imaging system (Volcano Therapeutics, Inc. Rancho Cordova, CA, USA). The Eagle Eye image catheter (2.9F, 20MHz) was inserted in the coronary artery and was performed pullback manually (0.5 mm/s). Nitroglycerin (0.2 mg) was administrated before IVUS run. Different stent techniques, such as the crossover, culottes, and mini-crush, were adopted according to the LM lesion characteristics. All of the procedures were carried out by experienced and qualified doctors.

2.3 Follow-up and endpoints

All the patients were followed up for 12–20 months by telephone or outpatient visits. The endpoints included cardiac death at 30 days and major adverse cardiac events (MACE) after one year.

MACE was defined as cardiac death, nonfatal myocardial infarction, nonfatal cerebral infarction, recurrence of angina, exacerbation of heart failure, target vessel revascularization (TVR), or target lesion revascularization (TLR).

Cardiac death was defined as death due to cardiac diseases such as myocardial infarction, arrhythmia, heart failure, and any death that was not clearly non-cardiac. The diagnostic criteria of myocardial infarction were in accordance with the 3rd universal definition of the ESC/AHA/ACCF.[9] Cerebral infarction was defined as a cerebral ischemic lesion accompanied by a new-onset focal neurological deficit that was not reversible within 24 h. TVR was defined as a repeated PCI or CABG. TLR was defined as reintervention of the implanted stents as well as the area 5 mm proximal or distal to them.

As a safety assessment, bleeding complications were classified as severe, moderate and minor bleeding according to GUSTO study.[10] Severe bleeding was intracerebral hemorrhage or resulting in substantial hemodynamic compromise requiring treatment. Moderate bleeding was defined by the need for transfusion. Minor bleeding referred to other bleeding, not requiring transfusion or causing hemodynamic compromise.

2.4 Statistical analysis

The statistical analysis was performed with Stata version 11.0 (StataCorp., College Station, Texus, USA). Continuous normally distributed variables are shown as mean ± SD, while those that were not normally distributed are presented as median and interquartile range (IQR). Categorical variables are shown as frequencies and percentages. The cumulative incidence of cardiac death at 30 days and MACE after one year was estimated using Kaplan-Meier plots. Univariate and multivariate regression analyses were performed using a COX proportional hazards model. Values of $P < 0.05$ were considered statistically significant. On multivariate regression analysis, variables with values of $P < 0.1$ were considered significant covariates.

3 Results

3.1 Patient demographic and clinical characteristics

The average age of the 61 aged patients was 73.9 ± 7.6 years, and the patient cohort included 73.8% men and 26.2% women. The risk factors were in different proportions: hypertension (60.7%), diabetes (31.2%), hyperlipidemia (16.4%), cerebral infarction (19.7%), smoking (37.7%), and family history of coronary heart disease (8.2%). The median eGFR was 52 mL/min per 1.73 mm^2. The average LVEF was 47.7% ± 8.9% (Table 1).

3.2 Interventional therapy for the study patients

The mean LM diameter stenosis was 74.7% ± 17.6%. The mean modified Gensini score was 14.2 ± 2.9,[11] while the mean SYNTAX score was 27.4 ± 7.0. The SYNTAX score was divided to tertiles according to the values (SYNTAX score ≤ 22: low; 23–32: intermediate; ≥ 33: high). The number of patients with low, intermediate and high SYNTAX score was 13 (21.3%), 35(57.4%) and 13 (21.3%), respectively. Fifty-five patients (90.2%) were analyzed with

Table 1. Patient demographics and clinical characteristics (*n* = 61).

Age, yrs	73.9 ± 7.6
Male sex	45 (73.8)
Hypertension	37 (60.7)
Diabetes	19 (31.2)
Hyperlipidemia	10 (16.4)
Cerebral infarction	12 (19.7)
Smoke	23 (37.7)
Family history of coronary heart disease	5 (8.2)
Acute myocardial infarction	20 (32.8)
STEMI	6 (9.8)
NSTEMI	14 (23.0)
eGFR, mL/min per 1.73mm^2, median (IQR)	52 (45–65)
LVEF(%), mean ± SD	47.7 ± 8.9

Data are presented as mean ± SD or *n* (%) unless other indicated. eGFR: estimated glomerular filtration rate; IQR：interquartile range; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction.

IVUS technique during the procedure; six patients (9.8%) did not take IVUS assessment due to emergency procedure (four cases of STEMI and two cases of NSTEMI). Stents deployment in both the left anterior descending branch (LAD) and the left circumflex branch (LCX) at the bifurcation lesion of the distal LM was adopted in 19.7% of the patients (6.6% for T stent, 11.5% for mini-crush, and 1.6% for culotte), whereas the crossover technique at the bifurcation lesion was adopted in 57.4% of the patients. A total of 3.3% of the patients underwent rotational atherectomy of the LM. The median implanted stent size was 36 mm (Table 2).

3.3 Patient medications

All patients were given double anti-platelet therapy for at least one year after PCI. Angiotensin converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), β-receptor blocker, spironolactone, furosemide, and nitrate ester were used in different percentages of patients (Table 3).

3.4 Follow-up results

3.4.1 Endpoints

All of the patients were followed up for 14.6 ± 3.9 months. The cumulative incidence of cardiac death at 30 days and MACE after one year was 6.6% and 32.5% estimated by Kaplan-Meier plots respectively (Figure 1A and Figure 1B). During the follow-up, 11 cases (18.0%) of MACE occurred. Six cases of cardiac death (9.84%) occurred at 1, 7, and 8, and 12 days as well as 6 and 12 months after PCI. One case of nonfatal cerebral infarction (1.6%) occurred at 19 months after PCI. One case of heart failure exacerbation (1.6%) occurred at 18 months after PCI. Three

Table 2. Patient interventional therapies (*n* = 61).

Stenosis of LM	74.7% ± 17.6%
Modified Gensini score	14.2 ± 2.9
SYNTAX score	27.4 ± 7.0
Low SYNTAX score (≤ 22)	13 (21.3)
Intermediate SYNTAX score (23–32)	35 (57.4)
High SYNTAX score (≥ 33)	13 (21.3)
IVUS assessment	55 (90.2)
Position of LM lesions	
Ostial lesion	11 (18.0)
Bifurcation lesion	23 (37.7)
Body lesion	14 (23.0)
Diffused lesion	13 (21.3)
Lesions of other coronary main vessles	
Single-vessles disease	17 (19.7)
Double-vessles disease	21 (34.4)
Triple-vessles disease	10 (16.4)
Rotational artherectomy of LM	2 (3.3)
Strategy of stenting in bifurcation lesion	
T stent	4 (6.6)
Mini-crush	7 (11.5)
Culottes	1(1.6)
Crossover	35 (57.4)
Length of the stents, mm, median (IQR)	36 (25-51)

Data are presented as mean ± SD or *n* (%) unless other indicated. IQR: interquartile range. LM: left main coronary artery.

Table 3. Patient medications (*n* = 61).

DAPT	61 (100)
ACEI/ARB	29 (47.5)
β receptor blocker	50 (82.0)
Furosemide	24 (39.3)
Spironolactone	23 (37.7)
Nitrate ester	28 (45.9)

Data are presented as *n* (%). ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; DAPT: double anti-platelet therapy.

cases of angina (4.91%) occurred at 4, 7, and 8 months after PCI.

3.4.2 Bleeding complications after PCI

There were no cases of severe bleeding complications but 12 cases (19.7%) of minor bleeding complications: two cases of epistaxis (3.3%), five cases of petechiae or ecchymosis (8.2%), and five cases of gingival bleeding (8.2%).

3.4.3 Regression analysis with the COX proportional hazards model

Univariate regression analysis with the COX proportional hazards model demonstrated that reduced LVEF increased the cardiac death rate at 30 days (P = 0.03). Furth-

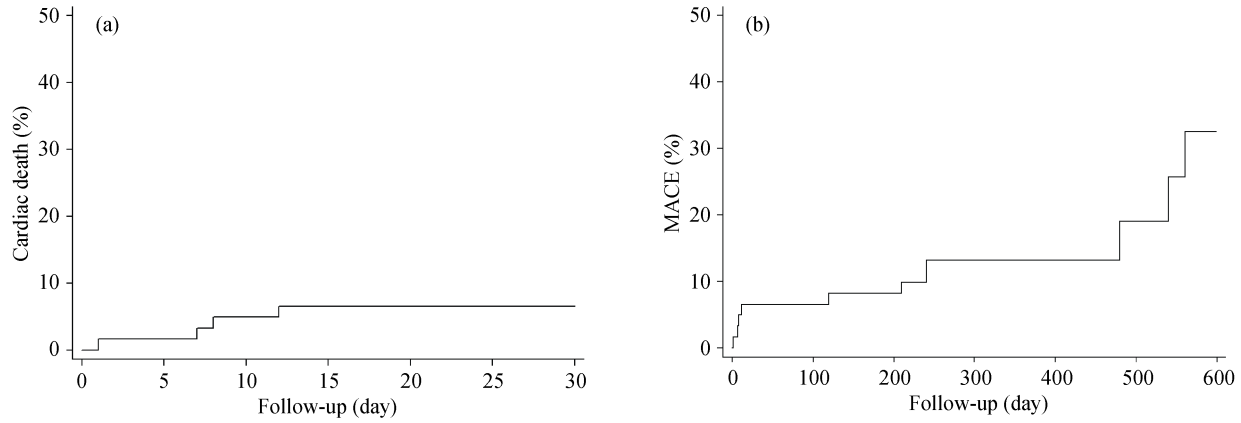

Figure 1. Cardiac death rate at 30 days (A) and cumulative incidence of MACE after one year (B) estimated by Kaplan-Meier Plot.
MACE: major adverse cardiac events.

more, an decreased LVEF and eGFR would increased the cumulative incidence of MACE (P = 0.01 and P = 0.047, respectively). An elevated SYNTAX score and tertiles of SYNTAX score also increased the cumulative incidence of MACE (P = 0.02 and P = 0.03). While increased age showed a trend toward an increased risk of MACE (P = 0.06), (Table 4).

Multivariate regression predetermined the significant covariates with values of $P < 0.1$. As a result, LVEF was the only predictor of cardiac death at 30 days (P = 0.01). As for MACE after one year, LVEF and eGFR were retained as significant predictors (P = 0.06 and P = 0.10, respectively). Notably, in contrast, SYNTAX score as well as its tertiles were excluded on multivariate regression analysis. Meanwhile, the disadvantage of increasing age in increasing MACE risks shown on univariate analysis also vanished on multivariate regression analysis (Table 5).

4 Discussion

The short- and long-term effects of interventional therapy for UPLM are reportedly similar to those of CABG.[2,12–17] The safety and effectiveness of PCI for UPLM has also been documented in critically ill patients with contraindications for CABG.[4] The appropriate technical progresses are mainly attributed to the availability of DES as well as IVUS, which could help tremendously with the implantation of suitable stents within the LM.

A number of Chinese aged patients prefer PCI to CABG due to surgical intolerance or subjective preference. It is noteworthy which factors affect the therapeutic prognosis of PCI in these aged patients. In the current study, 61 aged patients after PCI for UPLM were followed up. Most of the patients were considered suitable for PCI according to their angiography and clinical characteristics. Nonetheless, LM lesions accompanied by triple vessel diseases affected 10% of patients in the current study. These patients with complex lesions were recommended CABG preferably after angiography. However, they refused open heart surgery, mainly in fear of the large incision, surgical intolerance, stroke risk, or other reasons. A few of them were considered intolerant to anesthesia due to poor pulmonary function.

Table 4. Univariate regression of the endpoints.

	HR	SE	*P* value	95% CI
Predictors of cardiac death at 30 day				
LVEF	0.76	0.07	0.003	0.63–0.91
Predictors of MACE after 1 year				
Age	1.09	0.05	0.06	1.00–1.19
Ln (eGFR)*	0.02	0.04	0.047	0.00–0.95
LVEF	0.90	0.03	0.01	0.84–0.97
SYNTAX score	1.10	0.05	0.02	1.02–1.22
Tertiles of SYNTAX score	2.92	1.41	0.03	1.13–7.52

* Transfer skewed distribution to normal distribution by natural logarithm. eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction. MACE: major adverse cardiac events.

Table 5. Multivariate regression of the endpoints.

	HR	SE	*P* value	95% CI
Predictors of cardiac death at 30 day				
LVEF	0.70	0.10	0.01	0.53–0.92
Predictors of MACE after one year				
Ln (eGFR)*	0.03	0.07	0.097	0.00–0.84
LVEF	0.91	0.05	0.06	0.82–1.00

* Transfer skewed distribution to normal distribution by natural logarithm. eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction. MACE: major adverse cardiac events.

Consequently, only six of them suffered cardiac death within 18 months after PCI, among whom four patients died within 30 days. The cumulative incidence of cardiac death at 30 days was 6.6%, which implied a good result.

Of note, four cases of cardiac death occurred in hospital due to cardiac shock caused by STEMI with LM as the infarct artery. Different studies demonstrated a relatively high in-hospital mortality in this setting despite successful primary PCI, which ranged from 16%–38%.[18–21] UPLM as infarct artery usually causes large area of ischemia and deteriorates the left ventricular function. As soon as the coronary flow recovers, the cardiac function is usually subject to reperfusion injury. Ischemia and reperfusion injury mainly account for the hemodynamic instability in this setting, which are also the major causes of high in-hospital mortality. In current study, there were another two patients of cardiac shock also with LM as infarct artery, but they survived fortunately. Therefore, the in-hospital mortality of aged patients was 66.7% in the current study, remarkably higher than aforementioned data. We confirmed that LVEF was a strong predictor of cardiac death at 30 days either on univariate or multivariate regression analysis, which was similar to previous studies.[19,22,23] Yet STEMI was not identified as a predictor of cardiac death at 30 days. There were two possible explanations: firstly, in-hospital mortality depended on the hemodynamic status and LVEF rather than STEMI itself; secondly, we included a relative small population in the study, which further led to a low test power.

Tzifos, *et al*.[4] found that DES implantation into LM lesions was effective and safe in high-risk patients or those who were not candidates for CABG. During the 2.5-year follow-up period, the incidence of MACE was 30.6%, which was similar to the result of the current study. Our study also included a subset of high-risk patients, especially those for open heart surgery, the percentage of whom was smaller to the Tzifos study. We included recurrence of angina, heart failure, and ischemic stroke in the definition of MACE, unlike the definitions used in the Tzifos study. The incidence of MACE would be lower if the MACE criteria were the same between the two studies.

Univariate regression showed LVEF, eGFR, SYNTAX score and tertiles of SYNTAX score were all significant predictors, which was similar to the findings of previous studies.[24,25] Age tended to increase the risk of MACE, but the difference was not significant. It was noteworthy that LVEF and eGFR were still significant factors on multivariate regression, whereas SYNTAX score, its tertile levels and age were not significant to the risk of MACE at all. The predictive value of SYNTAX score in PCI of LM lesions has been investigated in previous studies. Kim, *et al*.[25] found that in comparison of SYNTAX score tertile level, the incidence of MACE was the lowest in patients with SYNTAX $\leq$ 23，while patients with SYNTAX $\geq$ 36 had similar MACE incidence to patients with SYNTAX between 23–26. However, SYNTAX score was identified as a relative weak predictors for MACE (death, Q-wave MI, Stroke and TVR) after discrimination and calibration procedure. In another study, Capodanno *et al*.[26] also demonstrated the MACE incidence was lower in patients with SYNTAX score $\leq$ 18 than that in patients with SYNTAX score between 18–27 as well as SYNTAX score $\geq$ 27. SYNTAX score was deemed as a suitable predictor of MACE, which was mainly driven by its ability to predict cardiac mortality. In our study, SYNTAX score and its tertile levels were not demonstrated as independent predictors on multivariate regression. It was speculated that LVEF or eGFR maybe more powerful predictors and masked the SYNTAX score predictive effect. Therefore, SYNTAX score is a useful tool for risk stratification as well as a predictor in patients of LM disease. Its role is also influenced by many other factors, which leads to inconsistent results in different studies. Previous studies reported the apparent prognostic value of LVEF for long-term outcomes after PCI of LM and decreased LVEF was related to a high long-term mortality.[27,28] Likewise, our study identified LVEF as an independent predictor in aged patients after PCI of LM. Despite the disadvantage of decreased LVEF in PCI, coronary revascularization in patients with LM lesions and concomitant impaired LVEF would still improve cardiac function.[29] On the contrary, another study found that LVEF was an univariate predictor of MACE, but not a significant predictor on multivariate regression,[24] which implied that the prognostic impact of LVEF was due to combination with other adverse features, such as renal dysfunction. Renal dysfunction may independently predict a high one-year mortality in acute coronary syndrome patients.[30] Patients with renal dysfunction usually have more comorbidities and are less likely to undergo revascularization. Meanwhile, these patients probably have more contraindications to drugs, such as angiotensin converting enzyme inhibitor, angiotensin receptor blocker, spironolactone. Even so, coronary revascularization could improve the one-year prognosis in acute coronary syndrome patients, including aged patients, despite of renal dysfunction.[30,31] Thus, cardiac and renal dysfunction should not be considered as contraindications to PCI, although decrease of both indices independently predicted a high risk of MACE.

The bleeding complication rate was approximately 20%. It was minor, however, no major bleeding events were observed during the follow-up period despite the high risk of

bleeding in aged patients.

In addition, the stenting strategy in both LAD and LCX at the bifurcation of the distal LM did not influence the incidence of MACE in the current study, which was similar to the results of the NORDIC study.[32] It was also reported that different strategies of stenting at the bifurcation of the distal LM would produce different prognoses.[33, 34] Nevertheless, the crossover technique was adopted in most of the bifurcation lesions of the distal LM, which precluded us from analyzing the impact of the different stenting strategies at bifurcation lesions on the risk of MACE.

In general, interventional therapy for UPLM could provide the opportunity for revascularization in aged patients, particularly those who did not intend to undergo or were intolerant to open heart surgery. The incidence of cardiac death at 30 days was quite low, and the risk of MACE after one year as well as bleeding complications was considered acceptable. LVEF, eGFR, SYNTAX score, tertiles of SYNTAX score and age were predictive of MACE; of them, LVEF and eGFR were the more powerful predictors.

4.1 Study limitations

The outcomes of the aged patients after revascularization of LM lesions were always a hotspot. It was believed that there were probably different characteristic among different age groups. This study included a relatively small sample size in a single center, thus, there was not enough test power to compare the outcomes among the tertiles of age in the cohort (60–70 years, 70–80 years and ≥ 80 years). Nonetheless, we identified insignificance of age for cardiac death and MACE in multivariate regression. Besides, the robustness of our results is also limited due to sample size. During the follow-up, most of the patients refused to undergo a second angiography mainly for economic reasons, which would probably result in an underestimation of the stent restenosis rate and further bias the assessed MACE rate. Regarding the stenting strategy, most of the patients underwent a single stent implantation at the bifurcation lesion of the distal LM, which made it impossible to analyze the influence of the different stenting strategies at the bifurcation of the LM on MACE incidence.

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