Original Article

Outcomes of Percutaneous Coronary Intervention with Second Generation Drug-Eluting Stents in Patients with Unprotected Left Main Coronary Artery Disease

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Background: Patients with unprotected left main coronary artery disease (ULMCA) have a high mortality risk. Coronary artery bypass graft (CABG) had been the standard treatment for several decades. However, percutaneous coronary intervention (PCI) with drug-eluting stents (DES) is increasingly used as an alternative treatment.

Objective: To evaluate the safety and efficacy of second-generation drug-eluting stents in patients with ULMCA.

Materials and Methods: One hundred eighty-nine consecutive patients with ULMCA underwent PCI with second generation biolimus-eluting stents in three centers in the northeast region of Thailand. The primary end point was major adverse cardiac or cerebrovascular events (MACCE), which is a composite of all causes of mortality, myocardial infarction (MI), target vessel revascularization, and stroke.

Results: In a median follow-up of 43.0±3.6 months, MACCE occurred in 24.3% (46/189) of patients. In all causes of death, which occurred in 16.9% (32/189) of patients, there were 5.8% (11/189) of cardiac deaths and 11.1% (21/189) of non-cardiac deaths. There were 2.1% (4/189) MI and 7.4% (14/189) target vessel revascularization. No stroke occurred in the present study. Definite stent thrombosis occurred in three patients (1.6%).

Conclusion: PCI with second generation biolimus-eluting stents is considered acceptable as an alternative treatment in its safety and efficacy in patients with ULMCA.

Keywords: Unprotected left main coronary artery disease (ULMCA), Percutaneous coronary intervention (PCI), Drug eluting stent (DES)

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Unprotected left main coronary artery (ULMCA) disease is associated with a high mortality risk. The survival advantage of coronary artery bypass graft (CABG) over medical therapy in patients with left main coronary artery disease (LMCAD) has been demonstrated in many studies[1-3], which led to an establishment of CABG as the revascularization of choice for LMCAD[4,5].

Percutaneous coronary intervention (PCI) is an alternative treatment because of the advances in devices and an increase in operators' expertise. A randomized trial of PCI with first-generation DES in patients with unprotected LMCAD showed a significant reduction in repeat revascularization compared with bare-metal stents (BMS)[6,7]. The invention of second-generation DES further improved the outcomes of PCI in unprotected LMCAD compared with first generation DES[8,9].

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Several randomized trials showed comparable safety (all causes of death, myocardial infarction (MI), and stroke) between PCI with DES and CABG groups[10,11]. PCI with DES eventually became accepted as an alternative revascularization technique for selected patients with unprotected LMCAD, especially in the low and intermediate SYNTAX score (low scores are of 22 and lower, and intermediate scores are 23 to 32), in current practice[4,5].

As the use of second-generation DES in PCI for unprotected LMCAD is increasing worldwide, the data regarding its efficacy and safety is still limited. Here, the authors aimed to study the characteristics and results of such procedures in the present study region.

Materials and Methods

One hundred eighty-nine consecutive patients underwent implantation of biolimus-eluting stent (Biomatrix Flex or Biomatrix Neoflex, Biosensors, Switzerland) for significant ULMCA disease on de novo lesion (more than 50% diameter stenosis) between January 2009 and June 2015 at three hospitals in the north-east region of Thailand.

The decision to perform PCI instead of surgery (CABG) was considered when one of two conditions was presented, 1) suitable anatomy for stenting and high-risk for surgery or 2) suitable anatomy for stenting and preference by the patient.

Exclusion criteria was for any patient who had malignancy and an expected survival term of less than one year. The ethics committee of each participating center approved the study and written informed consents were obtained by all patients.

PCI with DES implantation was performed to fully cover disease segments[12]. Diagnostic angiograms were scored according to the SYNTAX score algorithm[13]. SYNTAX score reflects a comprehensive angiographic assessment of coronary vasculature, indicating anatomic complexity of coronary artery, which classified as 22 or below as a low score, 23 to 32 as an intermediate score, and 33 and over as a high score.

The choices of devices, techniques and medical therapy depended on the local interventional cardiologist. All patients were recommended for dual antiplatelet therapy at least 6 to 12 months and then 75 to 150 mg of aspirin lifelong.

Outcomes

The primary end point was a composite of major adverse cardiac and cerebrovascular (MACCE) events, defined as 1) all causes of death, 2) MI, 3) target vessel revascularization (TVR), and 4) cerebrovascular event (stroke).

Death was considered either cardiac or non-cardiac. A death that could not be classified was considered cardiac. Periprocedural MI was defined as the elevation of creatine kinase MB (CKMB) to a level 10 times more than the upper reference limit, or more than five times if additional angiographic, electrocardiographic, or imaging evidence of infarction was present[14].

Spontaneous MI was defined as the elevation of CKMB or troponin more than the upper normal limit. Target vessel revascularization was defined as a repeated intervention (CABG or PCI) to treat a luminal stenosis within the stent or in the 5 mm distal or proximal segments adjacent to the stent, including the ostium of the left anterior descending artery (LAD) and/or circumflex artery (LCX) (in the case of stenting at a bifurcation). Procedure success was defined as revascularization with less than 30% residual stenosis by angiography after procedure or intravascular ultrasound (IVUS) showed cross sectional area of left main (LM) of more than 9 mm^2.

The incidence of stent thrombosis was evaluated in accordance with the Academic Research Consortium Definition of stent thrombosis[15].

Statistical analysis

The continuous variables were presented as mean and standard variation. The categorical variables were presented as frequency and percentage. Survival analysis was performed by Kaplan-Meier estimate survival. All the statistical analysis was done by Stata version 10.0.

Results

Patient enrolment

Between January 2009 and June 2015, one hundred eighty-nine patients with ULMCA disease were treated with PCI and biolimus A9 eluting stent (DES) in three hospitals in the north-east of Thailand. Follow-up for primary end points was continued until December 2016.

Baseline and procedure characteristics

Baseline clinical characteristics of the study's population are shown in Table 1, lesion characteristics are shown in Table 2, and procedural characteristics are shown in Table 3.

The mean age of patients was 63.7±11.2 years and 68.8% were male. Seventy-one patients (37.6%) had diabetes mellitus. Ninety-eight patients

Table 1. Baseline characteristics of patients (n=189)

	n (%)
Age (years), Mean±SD	63.7±11.2
Sex: male	130 (68.8)
Cardiovascular risk factors	
Diabetes mellitus	71 (37.6)
Hypertension	117 (61.9)
Hypercholesterolemia	123 (65.1)
Smoking	71 (37.6)
CKD (Cr > 1.5 mg/dl)	43 (22.8)
PVD	5 (2.7)
Previous CHF	33 (17.5)
LVEF (%), Mean±SD	51.2±16.1
Cardiogenic shock	14 (7.4)
Presentation of CAD	
Acute coronary syndrome	
• STEMI	40 (21.1)
• NSTE ACS	50 (26.5)
• Unstable angina	8 (4.2)
Stable CAD	88 (46.6)
Silent	3 (1.6)

CKD=chronic kidney disease; PVD=peripheral vascular disease; CHF=congestive heart failure; LVEF=left ventricular ejection fraction; STEMI=ST elevation myocardial infarction; NSTE ACS=non-ST elevation acute coronary syndrome; CAD=coronary artery disease

(51.9%) presented with acute coronary syndrome, 40 patients (21.2%) had ST elevation MI. The mean left ventricular ejection fraction was 51.2±16.1% and 14 patients (7.4%) had cardiogenic shock (Table 1).

Most lesions were located at distal LM (164 patients or 86.8%). Eighty-two patients (43.4%) had LM plus 3-vessel disease and 71 patients (37.6%) had LM plus 2-vessel disease. One hundred thirty-six patients (72%) had right coronary artery disease and 107 patients (56.6%) had concomitant treatment (Table 2).

The SYNTAX score, which indicates anatomic complexity, was low (22 or below) in 23.8% of the patients, intermediate (23 to 32) in 45.5% of the patients, and high (33 or higher) in 30.7% of the patients.

Treatment for LM coronary artery disease involved a bifurcation in 164 patients (86.8%). Majority of distal LM stenting used one stent technique (133 patients or 81.1%). Thirty-one patients (18.9%)

Table 2. Lesion characteristics of study population (n=189)

	n (%)
Non-distal LM (ostial or body) disease	25 (13.2)
Distal LM disease	164 (86.8)
Number of diseased vessels	
Isolated LM disease	9 (4.8)
LM + 1 vessel disease	27 (14.3)
LM + 2 vessel disease	71 (37.6)
LM + 3 vessel disease	82 (43.4)
RCA disease	136 (72.0)
RCA concomitant treatment	107 (56.6)
SYNTTAX score, Mean±SD	27.4±7.6
0 to 22	45 (23.8)
23 to 32	86 (45.5)
≥33	58 (30.7)
EuroSCORE	2.2

LM=left main; RCA=right coronary artery

Table 3. Procedural characteristics of study population (n=189)

	n (%)
Non-distal LM stenting (ostial + body)	25 (13.2)
Bifurcation stenting (distal LM)	164 (86.8)
Bifurcation technique	
1 stent (cross-over)	133 (81.1)
• Kissing balloon	14 (10.5)
2 stent technique	31 (18.9)
• Kissing balloon (2 stent)	28 (90.3)
- Crush (classical crush + mini crush)	9 (5.5)
- Culotte	9 (5.5)
- T-stent	10 (6.1)
- TAP	3 (1.8)
Stent diameter (mm), Mean±SD	3.6±0.3
Rotational stherectomy	9 (4.8)
IVUS	98 (51.9)
GP IIb/IIIa inhibiter	6 (3.2)
IABP	17 (9.0)
Radial artery approach	52 (27.5)
Femoral artery approach	137 (72.5)

LM=left main; TAP=T-stenting and small protrusion; IVUS=intravascular ultrasound; GP=glycoprotein; IABP=intra-aortic balloon pump

Table 4. Clinical events patient numbers (n=189)

	n (%)
MACCE	46 (24.3)
Total deaths	32 (16.9)
Cardiac death	11 (5.8)
Non cardiac death	21 (11.1)
MI	4 (2.1)
Stroke	0 (0.0)
TVR	14 (7.4)

MACCE=major adverse cardiac or cerebrovascular events; MI=myocardial infarction; TVR=target vessel revascularization

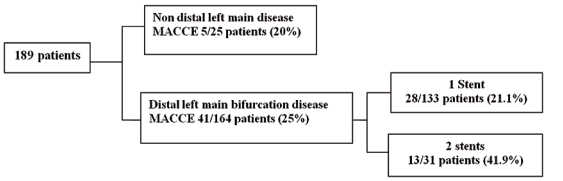

Figure 1. MACCE, non-distal LM and distal LM disease (non-comparative description).

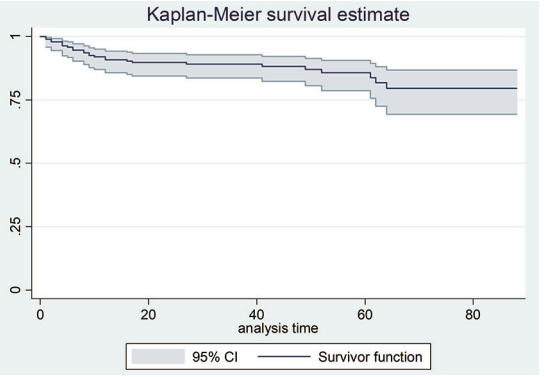

Figure 2. Primary end points. Kaplan-Meier estimate of major adverse cardiac and cerebrovascular events (MACCE)-free survival, the analysis time was presented in months.

of distal LM stenting used two stent techniques and kissing balloon was performed in 28 patients (90.3%) of two stent techniques. The mean diameter of stent was 3.6±0.3 mm. Rotational atherectomy was used for lesion preparation in nine patients (4.8%) and intra aortic balloon pump was used in 9% of patients. Fifty-two patients (27.5%) underwent a radial artery approach and IVUS was used in 98 patients (51.9%) (Table 3).

Primary end points

The results of primary end points are provided in Table 4. The median duration of follow-up was 43.0±3.6 months. During the follow-up period, MACCE occurred in 46 patients (24.3%), 32 patients (16.9%) died, of whom 11 patients (5.8%) died of cardiac causes. Four patients (2.1%) had MI and 14 patients (7.4%) had target vessel revascularization. No patients had a stroke.

Stent thrombosis occurred in three patients, 1.6% (9, 10, and 17 months, respectively) (Table 5). MACCE occurring in non-distal LM and distal LM disease (generally, distal LM stenting has more complexity resulting in more MACCE than non-distal LM) is shown in Figure 1). MACCE occurred in five patients out of 25 (20%) in non-distal LM stenting. MACCE occurred in 41 patients out of 164 (25%) in distal LM stenting. One hundred thirty-three patients used 1-stent technique and MACCE occurred in 28 patients (21.1%). Thirty-one patients used 2-stent technique and MACCE occurred in 13 patients (41.9%).

Survival analysis of primary end points (all-cause of death, MI, targeted vessel revascularization, and stroke) (Figure 2) showed the estimated MACCE-free survival (95% confidence interval (CI) at 1, 2, 3, 4, and 5 years of 0.91 (0.86 to 0.94), 0.90 (0.84 to 0.93), 0.89 (0.84 to 0.93), 0.88 (0.82 to 0.92), and 0.86 (0.79

Table 5. Characteristics of stent thrombosis 3 patients

LM	Clinical	LVEF	Lesion location	SYNTAX score	Technique	IVUS	MACCE	Time of MACCE
LM1	CAD	58%	Distal LM	34	1 stent (rotablator)	-	MI, death	9 months
LM2	ASTEMI	70%	Distal LM	31	2 stent (T-stent)	Used	MI, TVR	10 months
LM3	CAD	35%	Distal LM	38	1 stent	Used	MI, TVR	17 months

LM=left main; LVEF=left ventricular ejection fraction; IVUS=intravascular ultrasound; MACCE=major adverse cardiac or cerebrovascular events; CAD=coronary artery disease; ASTEMI=acute ST elevation myocardial infarction; MI=myocardial infarction; TVR=target vessel revascularization

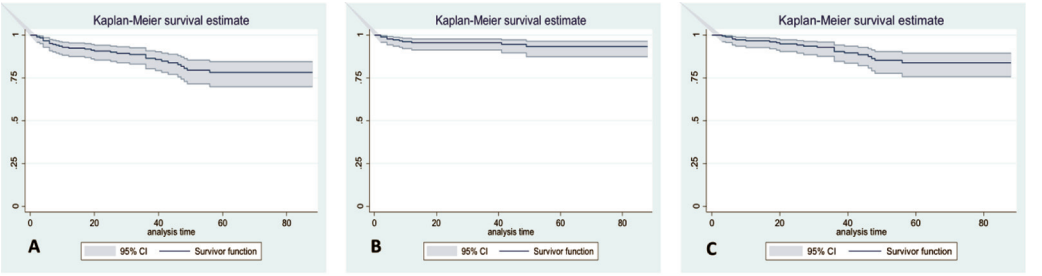

Figure 3. Survival. Kaplan-Meier estimate of overall survival (A), survival from cardiac death (B), and survival from non-cardiac death (C), the analysis time was presented in months.

to 0.91) and overall survival at 1, 2, 3, 4, and 5 years (Figure 3A) were 0.91 (0.86 to 0.95), 0.90 (0.84 to 0.93), 0.086 (0.79 to 0.90), 0.80 (0.72 to 0.86), and 0.77 (0.69 to 0.84).

The survival from cardiac death and survival from non-cardiac death are also presented in Figure 3B and 3C, respectively.

Outcomes according to SYNTAX score (non-comparative description)

MACCE occurred in12 patients (6.4%) with low SYNTAX scores (0 to 22), 17 patients (9%) with intermediate SYNTAX scores (23 to 32), and 17 patients (9%) with high SYNTAX scores (33 and above).

Discussion

The main findings of the present study, in patients with significant ULMCA disease, were that MACCE occurred in 24.3% of PCI with biolimus drug-eluting stents. Out of 189 patients, there were 32 patients (16.9%) for all causes of death. Twenty-one patients (11.1%) had non-cardiac death, 11 patients (5.8%) had cardiac death, and four patients (2.1%) had MI. No stroke occurred in our patients. In the group of non-cardiac death, the mean age of 75.7±9.1 years, (mean LVEF 48.3±19.0% and mean SYNTAX score 24.2±7.1), was greater than the mean age of our wider study (63.7±11.2 years).

In SYNTAX trial, major adverse cardiac and cerebrovascular events at 5-years in 705 patients were similar between both arms of the study in patients with low (0 to 22), or intermediate, SYNTAX scores (22 to 32). In patients with high SYNTAX scores (of 33 and above), MACCE was higher in the PCI arm than in the CABG arm[10].

In the present study (non-comparative description), 29 from 131 patients (22.1%) had MACCE with low or intermediate SYNTAX scores and 17 from 58 patients (29.3%) had MACCE in high SYNTAX scores (of 33 and above). This represented higher MACCE in high SYNTAX score patients than in low, or intermediate SYNTAX score patients due to greater anatomic complexity in the high SYNTAX scores. Procedure related stroke is a serious complication after revascularization. Stroke was significantly increased in LM CABG randomized patients at 5-years of SYNTAX trial (1.5% in PCI group and 4.3% in CABG group). No stroke occurred in the present study.

Most patients (164 out of 189 patients) (86.8%) had LM bifurcation involvement, consistent with the previous study[10]. Single stent cross-over provisional approach was used whenever possible for treatment. The strategies for 2-stent technique depended on local interventional cardiologists. A primary 2-stent technique rather than a 1-stent technique was used when the lesions had a true bifurcation, significant long lesion disease (more than 5 mm), and large side branches.

The events were higher in the 2-stent technique than the 1-stent technique. The optimum stent implantation technique for LM coronary artery disease is still uncertain, but adequate expansion and good apposition of stents is important.

IVUS is one of the important imaging tools to evaluate the exact diameter of a vessel for the good apposition of stents. IVUS guided PCI in ULMCA disease had a lower three-year mortality rate when compared with angiographic guided PCI in MAIN-COMPARE registry[16]. In the present study, IVUS guided PCI was used in 51.8% of patients. Twenty-six patients (26.5%) had MACCE in IVUS guided PCI group and 20 patients (22%) had MACCE in angiographic guided PCI.

Definite stent thrombosis occurred in three patients (1.6%), which was less than the first-generation stent in SYNTAX trial, 3.3% in one year and 5.1% in five years, suggesting an improvement

with the second-generation stents.

In the future, if a higher percentage of IVUS guided PCI is used in ULMCA disease, especially in complex bifurcation LM cases, there would probably be a reduction in MACCE and stents thrombosis.

Limitation

There were many limitations to the present study. First, it was a non-randomized, observational study in a limited geographical region. Second, the sample size was small, and the period of follow-up was short, compared with traditional studies. Third, the authors could not compare MACCE between 1-stent and 2-stent techniques in distal bifurcation LM because of the difference in the number of patients in both groups and the 2-stent technique procedures usually had true bifurcation and more anatomic complexity than the 1-stent technique group.

Conclusion

PCI with second-generation biolimus-eluting stents is considered acceptable for alternative treatment in its safety and efficacy in patients with ULMCA disease.

What is already known on this topic?

PCI with first-generation DES in ULMCA disease, with high-risk patients, has been performed increasingly as an alternative to CABG.

What this study adds?

This study, using the second-generation DES in PCI, confirms both their effectiveness and safety in ULMCA disease.

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Conflicts of interest

The authors declare no conflict of interest.

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