Twelve-year outcomes after revascularization for ostial/shaft lesions in unprotected left main coronary artery

Xian-Peng YU1, Yu LI1, Ji-Qiang HE1, Ze-Ning JIN1,2,#
1Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China
2Department of Cardiology and Macrovascular Disease, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

Abstract
Objective To evaluate a very long-term clinical outcomes of patients treated with coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) with drug-eluting stents (DES) for ostial/shaft lesions in unprotected left main coronary artery (ULMCA).
Methods & Results A total of 472 patients with isolated ostial/shaft lesions in ULMCA were enrolled, who received DES implantation or underwent CABG between January 2003 and July 2009 in Beijing Anzhen Hospital. The major endpoints of this study were death, repeat revascularization, non-procedural myocardial infarction (MI) and stroke. The median follow-up was twelve years (interquartile range: 9.4–14.0 years) in the overall patients. There were no significant differences of incidence of death (23.3% vs. 25.6%, P = 0.227), repeat revascularization (27.3% vs. 28.4%, P = 0.423), non-procedural MI (20.0% vs. 14.5%, P = 0.561), and stroke (6.1% vs. 9.3%, P = 0.255) between PCI and CABG groups before multivariate adjusting. After adjusting covariates with multivariate Cox hazard regression model, there were still no significant differences between PCI and CABG groups.
Conclusions During the median follow-up of twelve years, we found that PCI with DES was as effective and safe as CABG in patients with left main ostial/shaft lesion in this observational study.

Keywords: Coronary artery bypass grafting; Left main ostial/shaft lesions; Percutaneous coronary intervention; Prognosis

1 Introduction
According to current guidelines, coronary artery bypass grafting (CABG) was considered the standard treatment for unprotected left main coronary artery (ULMCA) disease.[1] Percutaneous coronary intervention (PCI) with drug-eluting stents (DES) has emerged as an acceptable treatment for selected patients with ULMCA disease.[2–6] However, long-term (> ten years) data was very limited.[3] Ostial/midshaft left main coronary artery (LMCA) has several advantages for PCI, including large lumen diameter, less concerns for plaque shift and subsequent stenosis, compared with bifurcation lesions. Thus, in ULMCA disease, nonbifurcation lesions showed favorable outcomes after PCI compared with distal bifurcation lesions.[7,8] However, there were rare studies to directly compare PCI and CABG for the treatment of ostial and midshaft lesions in LMCA.[9,10] In this observational study, we aimed to compare long-term (> ten years) real-world outcomes of patients with ostial/midshaft lesions of ULMCA underwent PCI with DES and CABG.

2 Methods
2.1 Patients and procedure
ULMCA disease was defined as left main coronary artery stenosis ≥50% and no bypass grafts to the left anterior descending or left circumflex coronary artery. Patients with isolated ostial/midshaft lesions in de novo ULMCA were enrolled consecutively, who received DES implantation or underwent CABG between January 2003 and July 2009 in Beijing Anzhen Hospital. Patients with prior stents implanted at the LMCA were excluded. Patients with age > 80 years old when the procedures were operated, prior CABG, concomitant valvular or aortic surgery or cardiogenic shock were excluded. Those ST-segment elevation myocardial infarction/non-ST-segment elevation myocardial infarction patients who underwent primary PCI or urgent CABG were excluded. A total of 472 patients were finally enrolled and analyzed (DES, n = 271; CABG, n = 201).

The decision to perform CABG or PCI was dependent on complications of the patient, physician’s choice, and/or patient preference. Coronary angioplasty and stent implanta-
tion were performed according to the operator’s criteria following the center’s usual practice. The choice of sirolimus-, paclitaxel- or zotarolimus-eluting stents was at the discretion of the physician (zotarolimus-eluting stents became available for clinical use in our center in September 2006). CABG was performed with standard bypass techniques. The internal thoracic artery was preferentially used for revascularization of the left anterior descending artery.

Before stent implantation, all patients received aspirin according to their physicians’ normal procedures and either clopidogrel 75 mg/day for three days before the procedure or a preprocedural loading dose of clopidogrel ≥ 300 mg. Patients were continued on clopidogrel for at least one year (75 mg/day) and aspirin indefinitely (100 mg/day) after the procedure.

All patients provided informed consent for both the procedure and subsequent data collection and analysis for research purposes. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University, Beijing, China (No.2009002X). There was no industry involvement in the design, conduct, financial support, or analysis of the study.

2.2 Outcomes and follow-up

All the follow-up data were collected by outpatient or telephone interview and angiographic follow-up. After the revascularization procedure, angiographic follow-up was recommended if there were ischemic symptoms or signs during the follow-up. Angiographic follow-up was not mandatory.

The endpoints of this study were death, repeat revascularization, non-procedural myocardial infarction (MI), stroke, cardiac death, and MACCE (major adverse cardiac and cerebrovascular events; the composite of cardiac death, non-procedural MI, stroke or repeat revascularization). Any death due to proximate cardiac cause (e.g., MI, low-output failure, and fatal arrhythmia), unwitnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment, will be classified as cardiac death. MI after the periprocedural period was defined as any typical increase and decrease of biochemical markers of myocardial necrosis with one of the following: cardiac symptoms, development of Q waves on electrocardiography, or electrocardiographic changes indicative of ischemia. Stroke, as indicated by neurologic deficits, was confirmed by a neurologist based on imaging studies. Repeat revascularization included PCI and CABG.

All events were based on clinical diagnoses assigned by the patients’ physicians. In the cumulative analysis of endpoints, events were counted only once, whichever occurred first.

2.3 Statistical analysis

Continuous variables were presented as mean ± SD or medians [interquartile range (IQR)] compared between the study group with independent sample Student’s t-test or Mann-Whitney U-test, dependent on if the data followed a normal distribution. Categorical variables were reported as counts and percentages, and differences between the two groups were assessed by means of the Chi-square test. Cumulative event curves were generated with the Kaplan-Meier method and the log-rank test will be applied to compare the incidence of the endpoint between patients treated with PCI and CABG. Cox proportional hazards models were used to compare risks of adverse events between patients underwent PCI with DES as well as CABG and for multivariate adjusting. Cox proportional hazard models were tested with PCI as the reference category. All statistical analyses were performed with the Statistical Package for Social Sciences version 22.0 system for Windows (SPSS Inc., Chicago, IL, USA). A P-value < 0.05 was considered statistically significant.

3 Results

A total of 472 patients were finally analyzed (DES, n = 271; CABG, n = 201). Baseline clinical and procedure characteristics were shown in Table 1. The mean age of the patients was 61.2 ± 9.7 years, 75.0% of patients were male, and 28.8% had diabetes. CABG group has significantly higher proportions of prior MI, left main plus triple-vessel disease and chronic total occlusion compared with PCI group. The left ventricular ejection fraction in the CABG group is lower than PCI group.

The median follow-up was twelve years (IQR: 9.4–14.0 years) overall and 12.5 years (IQR: 10.1–14.5 years) in survivors. Complete follow-up was obtained in 90.9% of the overall cohort. During the overall follow-up, 93 patients (19.7%) died (PCI, n = 46; CABG, n = 47), of whom 50 (10.6%) died of the cardiovascular cause. A total of 63 patients (13.3%) suffered the non-procedural MI, and 31 patients (6.6%) suffered the stroke. Repeat revascularization was performed in 105 patients (22.2%).

The crude relative risk are presented in Figure 1 and Table 2. There were no significant differences of incidence of death (23.3% vs. 25.6%, P = 0.227), repeat revascularization (27.3% vs. 28.4%, P = 0.423), non-procedural MI (20.0% vs. 14.5%, P = 0.561), stroke (6.1% vs. 9.3%, P = 0.255), and MACCE (43.6% vs. 49.6%, P = 0.198) between
Table 1. Baseline clinical and procedural characteristics.

| Variables                        | PCI (n = 271) | CABG (n = 201) | P-value |
|----------------------------------|---------------|----------------|---------|
| Age, yrs                         | 61.7 ± 10.3   | 60.6 ± 8.8     | 0.217   |
| Male                             | 201 (74.2%)   | 153 (76.1%)    | 0.629   |
| Diabetes mellitus                | 78 (28.8%)    | 58 (28.9%)     | 0.986   |
| Smoking history                  | 131 (48.3%)   | 93 (46.2%)     | 0.656   |
| Hypertension                     | 152 (56.1%)   | 101 (50.2%)    | 0.208   |
| Family history                   | 22 (8.1%)     | 16 (8.0%)      | 0.950   |
| Dyslipidemia                     | 135 (49.8%)   | 78 (38.8%)     | 0.017   |
| Prior stroke                     | 6 (2.2%)      | 25 (12.4%)     | < 0.001 |
| Prior myocardial infarction      | 47 (17.3%)    | 54 (26.9%)     | 0.013   |
| Prior PVD                        | 12 (4.4%)     | 14 (7.0%)      | 0.232   |
| Prior PCI                        | 38 (14.0%)    | 24 (11.9%)     | 0.508   |
| EuroSCORE                        | 5 (3–6)*      | 5 (3–6)*       | 0.660   |
| LVEF, %                          | 64 (59–70)*   | 62 (55–68)*    | 0.002   |
| Serum creatinine, μmol/L         | 78.0 (68.0–93.0)* | 79.6 (68.9–91.1)* | 0.372   |
| Indications for revascularization| < 0.001       |                |         |
| NSTEMI                           | 6 (2.0%)      | 2 (1.8%)       |         |
| STEMI                            | 22 (9.4%)     | 12 (6.4%)      |         |
| Stable angina                    | 26 (10.1%)    | 42 (22.7%)     |         |
| Unstable angina                  | 200 (72.5%)   | 145 (69.1%)    |         |
| Silent ischemia                  | 17 (6.0%)     | 0              |         |
| Extent of diseased vessel        | < 0.001       |                |         |
| LM only                          | 54 (19.9%)    | 14 (7.0%)      |         |
| LM plus single-vessel disease    | 74 (27.3%)    | 32 (15.9%)     |         |
| LM plus double-vessel disease    | 82 (30.3%)    | 52 (25.9%)     |         |
| LM plus triple-vessel disease    | 61 (22.5%)    | 103 (51.2%)    |         |
| Chronic total occlusion          | 40 (14.8%)    | 76 (37.8%)     | < 0.001 |
| Complete revascularization**     | 198 (73.1%)   | 124 (61.7%)    | 0.009   |
| Number of stents                 | 2 (1–3)*      | 187 (93.0%)    |         |
| Off-pump CABG                    |                | 3 (2–3)*       |         |
| Vessel bypassed                  |                | 177 (88.1%)    |         |

Data are presented as means ± SD or n (%). *Presented as median (interquartile range). **Refer to all lesions occupying > 50% diameter of a segment with a reference diameter of ≥ 1.50 mm were treated. CABG: coronary artery bypass grafting; EuroSCORE: European System for Cardiac Operative Risk Evaluation; LM: left main; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; PVD: peripheral vascular disease; STEMI: ST-segment elevation myocardial infarction.

P CI and CABG groups. The occurrence of cardiac death (13.5% vs. 16.2%, P = 0.022) was significantly higher with the CABG group. After multivariate adjusting, there were no significant difference in all the endpoints between PCI and CABG groups (Table 2). The subgroup analysis showed there were similar occurrence of all-cause mortality (Table 3).

4 Discussion

During the median follow-up of twelve years, PCI for ostial/midshaft lesions with DES were associated with comparable clinical outcomes seen with CABG. Event rates of all-cause mortality, cardiac death, non-procedural MI, stroke, repeat revascularization, MACCE and the composite end-point of death, non-procedural MI, and stroke were found to be similar between PCI and CABG groups.

Ostial/midshaft LMCA has several advantages, including large lumen diameter, less concerns for plaque shift and subsequent stenosis. Thus, ostial/midshaft lesions showed favorable outcomes after PCI compared with distal bifurcation.
lesions. However, CABG is still considered the gold standard. Despite the fact that other studies have examined the role of PCI compared with CABG in the treatment of ULMCA disease, the impact of lesion location has not been fully evaluated. Data of comparison between PCI and CABG for ostial/midshaft LMCA lesions was very limited. Lee, et al. reported PCI for ostial ULMCA lesions was associated with similar MACCE and target vessel revascularization rates compared with CABG. This study included 263 patients within the five-year follow-up. Naganuma, et al. reported among 856 patients with ostial/midshaft lesions, PCI had similar rates of all-cause death, MI, and stroke; but significantly higher rate of target vessel revascularization during a median follow-up of 3.5 years.

CABG offers the advantage of overcoming the overall burden of complex and diffuse atherosclerotic disease by constructing the anastomosis distal to diseased segments, whereas PCI only treats significant flow-limiting lesions without protecting the distally diseased vessels. Due to the high patency of LIMA graft, limited duration of follow-up (usually less than five years) incompletely depicts the advantages of CABG; as initially accrue with time, but it may also eventually be eroded by progressive vein graft failure. Results of several large randomized controlled trials about LMCA disease was mixed. Five-year follow-up of the EXCEL trial showed PCI had significantly higher rates of all-cause death and repeat revascularization for the 1905 LMCA patients with SYNTAX score of 32 or less. The NOBLE trial demonstrated the PCI was associated with significantly higher rates of non-procedural MI and revascularization during the five-year follow-up. Ten-year follow-up of SYNTAX trial showed PCI of LMCA disease had similar all-cause death rate compared with CABG (26% vs. 28%) in the subgroup.

Our study provides unique long-term insights into the prognosis after PCI versus CABG for ostial/midshaft LMCA lesions the by extending follow-up to the median follow-up of twelve years. Most previous studies compared PCI and CABG suffered the limited follow-up, whereas evidence had shown CABG had survival benefit over pure medical
Table 2. Clinical outcomes of PCI versus CABG for the ostial/shaft lesions in unprotected left main coronary artery.

| Outcomes                  | Incidence of adverse events | P-value | HR (95% CI) |
|---------------------------|-----------------------------|---------|-------------|
| **Unadjusted**            |                             |         |             |
| Death                     | 23.3%                       | 0.227   | 1.287 (0.855–1.938) |
| Cardiac death             | 13.5%                       | 0.022   | 1.941 (1.098–3.430) |
| Non-procedural MI         | 20.0%                       | 0.561   | 0.860 (0.518–1.429) |
| Stroke                    | 6.1%                        | 0.255   | 1.506 (0.744–3.052) |
| Repeat revascularization  | 27.3%                       | 0.423   | 0.852 (0.575–1.261) |
| MACCE                     | 43.6%                       | 0.198   | 1.206 (0.907–1.604) |
| Death/MI/stroke           | 36.5%                       | 0.447   | 1.135 (0.818–1.575) |
| **Multivariate adjusted** |                             |         |             |
| Death                     | 20.1%                       | 0.775a  | 1.069 (0.676–1.690) |
| Cardiac death             | 9.4%                        | 0.358b  | 1.346 (0.714–2.535) |
| Non-procedural MI         | 17.8%                       | 0.235c  | 0.725 (0.427–1.233) |
| Stroke                    | 3.2%                        | 0.184d  | 1.732 (0.771–3.889) |
| Repeat revascularization  | 26.0%                       | 0.509e  | 0.871 (0.578–1.312) |
| MACCE                     | 45.2%                       | 0.671f  | 1.068 (0.787–1.451) |
| Death/MI/stroke           | 34.4%                       | 0.492g  | 0.879 (0.609–1.269) |

*a*Refer to adjust for age, LVEF, serum creatinine, diabetes mellitus, extent of diseased vessel, CTO, and complete revascularization. 
*b*Refer to adjust for age, sex, LVEF, serum creatinine, diabetes mellitus, and smoking history. 
*c*Refer to adjust for age, sex, LVEF, serum creatinine, prior peripheral vascular disease, prior stroke, and smoking history. 
*d*Refer to adjust for age, LVEF, prior peripheral vascular disease, prior stroke, complete revascularization, and dyslipidemia. 
*e*Refer to adjust for serum creatinine, prior peripheral vascular disease, diabetes mellitus, extent of diseased vessel, CTO, and complete revascularization. 
*f*Refer to adjust for age, LVEF, serum creatinine, diabetes mellitus, extent of diseased vessel, CTO, prior peripheral vascular disease, and smoking history. 

CABG: coronary artery bypass grafting; CI: confidence interval; CTO: chronic total occlusion; HR: hazard ratio; LVEF: left ventricular ejection fraction; MACCE: major adverse cardiac and cerebrovascular events; MI: myocardial infarction; PCI: percutaneous coronary intervention.

Table 3. Hazard ratio of all-cause mortality in subgroups of patients.

| Subgroup     | P-value | HR (95% CI) |
|--------------|---------|-------------|
| Prior MI     | 0.959   | 1.246 (0.553–2.809) |
| No prior MI  | 0.355   | 1.252 (0.777–2.018) |
| Diabetes     | 0.181   | 1.506 (0.827–2.744) |
| No-diabetes  | 0.630   | 1.148 (0.655–2.014) |
| Age ≥ 65 yrs | 0.065   | 1.648 (0.969–2.804) |
| Age < 65 yrs | 0.343   | 1.369 (0.715–2.620) |

CI: confidence interval; HR: hazard ratio; MI: myocardial infarction.

therapy during the twelve-year follow-up for the LMCA lesions.[11] This might be attributed to the high patency of LIMA graft, which was usually conducted to left anterior artery. Our data showed all-cause death, the most robust endpoint, was similar between PCI and CABG groups, which was the same as the ten-year result of the SYNTAX LM subgroup.[3] Possible reasons for this include the fact that ostial/midshaft lesions are in general simpler to treat for PCI as they do not involve the bifurcation and that vessel diameter at this location tends to be larger compared with that in distal bifurcation ULMCA sites, thus allowing the use of larger diameter stents. The ten-year result of the SYNTAX three-vessel disease subgroup had shown CABG group had less all-cause death than PCI group,[3] indicating diffusion of disease is the limiting factor for PCI.

Most previous studies showed PCI was associated with significantly higher rate of repeat revascularisation by comparing PCI and CABG for the LMCA lesions.[4–6] In contrast, we found no difference in the occurrence of repeat revascularisation between the DES and CABG groups in patients with ostial/midshaft LMCA lesions. In ULMCA disease, ostial/midshaft lesions showed favorable outcomes after PCI compared with distal bifurcation lesions.[7,8] Ostial/midshaft LMCA lesions had large vessel diameter and they are usually treated with single/simple stenting, which probably decreased the rate of restenosis resultant in repeat revascularisation. On the other hand, the occlusion rate of the vein graft was 40%–50% during the ten-year follow-up.[12] The progressive vein graft failure accrued with
time, which might be accounted for the late catch-up in the occurrence of repeat revascularisation ten years after the procedure as we observed in the CABG group (Figure 1).

Apart from the lesion location, the other important pathophysiological features may mitigate against the success of PCI: up to 80% of left main patients also have multivessel coronary artery disease, of which CABG may already offer a survival advantage.[13] In our study, PCI group had significantly lower portion of left main plus triple-vessel disease compared with that in the CABG group (22.5% vs. 51.2%). Although the multivariate Cox proportional hazards regression analyses were carried out to adjust the imbalance, it still might be an important factor for PCI group had comparable endpoints with CABG group. Our study suffers the most important limitations of non-randomized and observational studies. The second limitation was lack of subgroup analysis according to SYNTAX score.

In conclusion, this observational study demonstrates that PCI for ostial/midshaft lesions in ULMCA is associated with comparable clinical outcomes compared with CABG during the median follow-up of twelve years.

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