Impact of main vessel calcification on procedural and clinical outcomes of bifurcation lesion undergoing provisional single-stenting intervention: a multicenter, prospective, observational study

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Abstract

Background Few data on the combined effects of bifurcation and calcification on coronary artery disease (CAD) patients undergoing percutaneous coronary intervention (PCI) are available. This study evaluated the impact of main vessel (MV) calcification on the procedural and long-term outcomes in patients with CAD who underwent provisional single stent PCI.

Methods This is a multicenter, prospective, observational study. Patients with bifurcation lesions were enrolled at 10 PCI centers in China from January 2015 to December 2017. Intravascular ultrasound or optical coherence tomography was performed in all patients to evaluate the MV calcification. Patients were treated with provisional single stent strategy using drug eluting stents and followed-up at 1 month, 6 months and 12 months after discharge by telephone contact or outpatient visit. Repeated coronary imaging was performed within one year. We compared the procedural success rates in MV and in side branch (SB), and target lesion failure (TLF), defined as a composite of cardiac death, non-fatal myocardial infarction, definite or possible stent thrombosis and target lesion revascularization between patients with and without MV calcification.

Results A total of 185 subjects were enrolled according to the inclusion and exclusion criteria of this study. MV calcification was detected in 119 (64.3%, calcification group) and not found in 66 (35.7%, non-calcification group) patients. The angiographic success rate of MV was 95.8% in the calcification group and 97.0% in the non-calcification group (P = 0.91); the angiographic success rate of SB was 32.8% in the calcification group and 53.0% in the non-calcification group (P < 0.05). During the one-year follow-up period, TLF occurred in 14 (11.8%) patients in the calcification group and in 13 (19.7%) in the non-calcification group (P = 0.31). Multivariate regression analysis showed the same result (HR = 1.23, 95% CI: 0.76–1.52, P = 0.47). Calcification on group had higher recurrent angina than non-calcification group (13.51% vs. 17.65%, P < 0.05).

Conclusions In patients with coronary bifurcation lesion treated with provisional one stent approach, calcification of MV is associated with lower SB procedural success rate, it could increase recurrence of angina; however, it was not associated with an increased risk of TLF.

Keywords: Bifurcation lesion; Coronary artery disease; Coronary calcification; Percutaneous coronary intervention

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1 Introduction

Bifurcation lesions account for 15%–20% of all percutaneous coronary interventions (PCIs). Coronary bifurcation stenting remains technically challenging and associated with a high risk of adverse clinical events. Coronary artery calcification (CAC), on the other hand, has also been reported to be associated with increased risk of coronary dissection and procedural failure when treated with plain old balloon angioplasty, a higher incidence of in-stent restenosis and target lesion revascularization (TLR) when treated with bare-metal stent, and controversially, with higher incidence of stent thrombosis (ST) and an increased major adverse event rate when treated with drug eluting stents (DESs). However, few data exist on the combined effects of bifurcation and calcification on coronary artery disease (CAD) patients undergoing PCI. A recent study by Kim and colleagues of Korean patients reported that compared with no or mild calcification, moderate or severe calcification of coronary bifurcation lesions is associated with increased frequency of repeat revascularization. In their study, however, coronary calcification was assessed by angiography, which is considered to be an inadequate technique in the evaluation of calcification by many researchers. Our present study investigated effects of main vessel (MV) calcification on procedural and clinical outcomes of bifurcation lesion in Chinese patients who underwent provisional single-stenting intervention.

2 Methods

2.1 Study population and design

This is a multicenter, prospective, observational clinical study of patients treated with DESs for coronary bifurcation lesions. Between January 2015 and December 2017, a total of 532 patients were treated with DESs for bifurcation lesions using provisional one stent approach at 10 participating major coronary intervention centers in China. We used the following inclusion and exclusion criteria to enroll study patients: the inclusion criteria were (1) aged 18–75 years old; (2) Intravascular ultrasound (IVUS)/ optical coherence tomography (OCT) guided PCI; and (3) MV diameter ≥ 2.5 mm and side branch (SB) diameter ≥ 2.0 mm by visual estimation; the exclusion criteria were: (1) patient with in-stent restenosis or chronic total occlusion (CTO) or post coronary bypass graft (CABG); (2) patient had acute myocardial infarction (AMI) within seven days; (3) patient with more than one culprit bifurcation lesion; and (4) patient who had used drug coating balloon for SB protection (Figure 1). The ethics committees of all participating hospitals approved the study protocol, and all patients provided written informed consent. Calcification lesions were defined as IVUS or OCT findings of calcification plaques (no matter the arc and depth of calcification plaque) in the MV of the segment of bifurcation lesion.

All patients received loading doses of aspirin (300 mg), or clopidogrel (300 mg) or ticagrelor (180 mg) before PCI unless they had previously received these antiplatelet medications. Provisional one stent technique had been described previously. Briefly, a stent is implanted in the MV with the jailed wire or jailed balloon protecting the SB, followed by kissing balloon dilatation if there is at least one of the following: > type B dissection and thrombolysis in myocardial infarction (TIMI) flow < 3 at the ostial SB. An additional stent is required for the SB if any of the following issues are observed after kissing balloon inflation: > type B dissection or TIMI flow < 3 (Figure 2). All patients had IVUS or OCT evaluation prior to the procedure unless there was severely stenosis. Pre-dilation with a small balloon with low pressure (< 10 atmospheric pressure) was given when IVUS/OCT catheter could not cross the lesions. All stents used were sirolimus-eluting stents.

2.2 IVUS/OCT imaging

IVUS imaging (40-MHz IVUS catheter, Boston Scientific Corp, Natick, Mass; 40-MHz IVUS catheter, Volcano Therapeutics, Inc, California, USA) and OCT imaging (C7-XR system, LightLab Imaging Ic., Westford, Massachusetts) was performed before all interventions and after intracoronary administration of 0.1 mg nitroglycerin. The probe was advanced into the distal reference segment and an imaging run was performed back to coronary ostium using a motorized transducer pullback (0.5 mm/s) system of IVUS.
Figure 2. A case of LAD bifurcation lesion undergone single-stenting in calcification group. (A): Coronary angiography showed a Medina type 1, 1, 1 bifurcation lesion (red arrow) in the LAD; (B): IVUS detected calcification in the main vessel with an arc > 180°; (C): after single stent, the residual stenosis of MV is less than 20%, the residual stenosis of SB ostium is more than 50%; and (D): angiography at 12 months no significant changes in both main vessel and side branch. IVUS: intravascular ultrasound; LAD: left anterior descending; MV: main vessel.

The OCT catheter was pulled back at a speed of 20 mm/s to guarantee sufficient time to acquire images of a 54–mm long segment (frame density: 10 frames/mm). OCT images were acquired after removing all blood adequately from the imaging site. Non-occlusive flushing was performed using continuously injected contrast medium via an automated power injector. When poor image quality was obtained, the pullback was repeated subsequently for modification of the flushing intensity or probe position. OCT images were analyzed online and offline. Intravascular imaging was recorded continuously into digital media for offline analysis. OCT images were analyzed using Lightlab software (v1.13, Lightlab Imaging Incorporated, USA). IVUS imaging were analyzed using QIVUS post-processing software (v3.1, Medis Medical Imaging Bv, the Netherlands). Qualitative and quantitative analysis were performed by independent observers according to current consensus on standards for acquisition, measurement, and reporting of IVUS or OCT studies. Calcium was brighter than adventitia with acoustic shadowing of the underlying tissue in IVUS imaging. The calcium component was detected on OCT using validated criteria. We classified calcium according the max calcified arc as arc ≤ 90°, 90° < arc ≤ 180°, 180°< arc ≤ 270°, and > 270° subgroups. Reference segments were defined as the most normal-looking cross sections proximal and distal to the lesion.

2.3 Data collection

Data were collected using a Web-based clinical trial management system “ResMan”. Additional information was obtained from the medical records or by telephone contacts. All outcome data reported from the participating centers were reviewed by an independent clinical event adjudicating committee. Coronary angiograms were reviewed and analyzed quantitatively by an independent core laboratory at Chinese PLA general hospital cardiology center using an automated edge-detection system (Centricity CA1000, GE; Waukesha, WI, USA). All pre-procedural angiograms were analyzed before the introduction of the coronary guide wire by independent observers without the knowledge of clinical or IVUS data. The reference diameter of MV was defined as the average of the proximal and distal reference lumen diameters. The reference diameter of SB was the distal reference lumen diameter. Minimum lumen diameter (MLD) was measured in multiple projections with results recorded from the view that demonstrated the smallest diameter. All
bifurcation lesions were classified according to the Medina classification, and Medina types 1,1,1, 1,0,1 and 0,1,1 lesion was defined as true bifurcation lesions. The evaluation by angiography was performed by identifying the view displaying the widest opening and demonstrating the side branch most clearly. Quantify coronary analysis (QCA) was performed by two cardiovascular physicians who were blind to the study results.

2.4 Study outcomes and definitions

Clinical follow-up was performed during outpatient visits or through telephone contact at 1 month, 6 months and 12 months. Adverse events were monitored throughout the entire study period. The procedural outcome included the procedural success rates in MV and in SB. The primary clinical outcome was target lesion failure (TLF), defined as a composite of cardiac death, non-fatal myocardial infarction (MI), definite or possible ST, as detected by follow-up coronary angiography (CAG) or IVUS or OCT, and TLR. Target vessel revascularization (TVR) was defined as revascularization of the MV or SB. The secondary clinical endpoint was the occurrence of recurrence of angina during follow-up. Academic Research Consortium’s definitions of MI, cardiac death, TVR, angiographic and procedural success, and recurrence angina were used. Multiple lesions included multiple-vessel disease (defined as ≥ 70% stenosis in at least 1 major epicardial vessel and ≥ 50% stenosis in at least 1 other major vessel) or ≥ 2 lesions separated by at least a 5-mm normal segment in the target vessel. The diameter of the stenosis in the SB ostium was calculated by the following equation: 100 × (reference diameter of distal SB-minimum lumen diameter of SB ostium) /reference diameter of distal SB. SB compromise was defined as thrombolysis in TIMI flow grade < 3 during the procedure or the acute or chronic total occlusion of SB. The definition of angiographic success was final TIMI 3 flow and < 20% residual stenosis in the MV and < 50% residual stenosis in the SB. Procedural success was defined as angiographic success plus no cardiac death, ST-segment elevation MI, or emergency CABG surgery during the hospital stay.

2.5 Statistical analysis

For statistical analysis of continuous variables, we used t-test and presented the results as mean ± SD. Differences among groups were evaluated using the Chi-square test for categorical data. Cox proportional hazards regression with adjustment for covariates was used to assess clinical outcomes. The variables which had a P-value ≤ 0.05 in univariate Cox regression analysis were included in the multivariate Cox regression analysis: lesion location (left main vs. non-left main bifurcation), additional stent for SB (with vs. without), side branch pre-dilatation, diabetes mellitus, history of cerebrovascular accident, history of PCI, left main disease, multivessel disease, use of non-compliant balloon after stenting, and true bifurcation. We performed statistical analyses using SAS 9.2 (SAS Institute Inc., Cary, NC, USA). All tests were 2-tailed, and P < 0.05 was considered statistically significant.

3 Results

3.1 Patient characteristics

As shown in Table 1, there were no significant differences regarding age, sex, current smoking, whether having acute coronary syndrome (ACS), chronic kidney disease (CKD), prior MI, or hypertension between patients with or without MV calcification. Low density lipoprotein chole-

| Table 1. Baseline clinical characteristics in patients with or without MV calcification. |
|-----------------------------------------------|-------------------------------|-----------------------------|
| **Calcification group** | **Non-calcification group** | **P-value** |
| **n = 119** | **n = 66** | |
| Age, yrs | 62.3 ± 9.7 | 58.1 ± 10.9 | 0.554 |
| Male | 90 (75.63%) | 54 (81.82%) | 0.332 |
| ACS | 96 (80.67%) | 59 (89.39%) | 0.123 |
| Current smoker | 35 (29.41%) | 25 (37.88%) | 0.239 |
| DM | 44 (36.97%) | 14 (21.21%) | < 0.05 |
| Hypertension | 80 (67.23%) | 35 (53.03%) | 0.056 |
| LDL-c, mmol/L | 2.29 ± 0.79 | 2.25 ± 0.84 | 0.729 |
| CKD | 13 (10.92%) | 2 (3.03%) | 0.060 |
| Prior MI | 3 (2.52%) | 2 (3.03%) | 0.838 |
| LVEF | 59.15 ± 9.11 | 59.82 ± 6.26 | 0.729 |

Data are presented as mean ± SD or n (%). ACS: acute coronary syndrome; CKD: chronic kidney disease; DM: diabetes mellitus; LDL-c: low density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; MI: myocardial infarction; MV: main vessel.
Download (118%) were also similar between the two groups. Diabetes mellitus was more prevalent in the calcification group than that in non-calcification group ($P < 0.05$). The majority (78%) of the patients had ACS.

The angiographic and procedural characteristics of patients with or without MV calcification are summarized in Table 2. Compared with patients in the non-calcification group, patients in the calcification group had increased rate of bifurcation lesions located in left anterior descending (LAD) and decreased rate in left circumflex (LCX), were more likely to have true bifurcation, with higher rate of SB ostium stenosis > 50%. Rotational atherectomy (ROTA) and cutting balloon (CB) were more often used to treat the MV in calcification group patients.

### 3.2 Procedural outcomes

The angiographic success rate of MV was 95.8% in the calcification group and 97.0% in the non-calcification group ($P = 0.91$). There were no significant differences regarding MV procedural complications including dissection, hematoma, Final TIMI flow grade < 3 and Residual stenosis > 20% between the two groups. The angiographic success rate of SB was 32.8% in the calcification group and 53.0% in the non-calcification group ($P < 0.05$), driven mainly by the higher rate of final TIMI flow grade < 3 in SB in the calcification group (Table 3).

### 3.3 Clinical outcomes

During the one-year follow-up period, TLF, including cardiac death, definite or probable ST, and TVR occurred in 14 (11.8%) patients in the calcification group and in 13 (19.7%) in the non-calcification group ($P = 0.38$, Table 4). Analysis using Cox multivariate regression also showed that MV calcification did not significantly increase the risk of TLF (HR = 1.23, 95% CI: 0.76–1.52, $P = 0.47$).

| Table 2. Angiographic and procedural characteristics of patients with or without MV calcification. |
|-------------------------------------------------|-------------------|------------------|----------|
| Bifurcation location | Calcification group | Non-calcification | $P$-value |
| | $n = 119$ | $n = 66$ |          |
| LM | 41 (34.45%) | 29 (43.94%) | 0.203 |
| LAD | 72 (60.50%) | 19 (28.79%) | < 0.01 |
| LCX | 3 (2.52%) | 12 (18.18%) | > 0.05 |
| RCA | 3 (2.52%) | 6 (9.09%) | 0.12 |
| True bifurcation | 81 (68.07%) | 34 (51.52%) | < 0.05 |
| SB ostium stenosis > 50% | 81 (68.07%) | 34 (51.52%) | < 0.05 |
| No. of diseased vessels | | | |
| 1 | 60 (50.42%) | 39 (59.09%) | 0.257 |
| 2 | 37 (31.09%) | 16 (24.24%) | 0.324 |
| 3 | 22 (18.49%) | 11 (16.67%) | 0.757 |
| PCI Procedure | | | |
| FKA | 17 (14.29%) | 5 (7.58%) | 0.177 |
| Guidance of IVUS | 96 (80.67%) | 47 (71.21%) | 0.141 |
| Guidance of OCT | 23 (19.33%) | 19 (28.79%) | 0.141 |
| MV ROTA | 13 (10.92%) | 0 | < 0.05 |
| MV using cutting balloon | 35 (29.41%) | 9 (13.64%) | < 0.05 |
| SB using cutting balloon | 12 (10.08%) | 4 (6.06%) | 0.510 |
| SB general balloon protection | 27 (22.69%) | 9 (13.64%) | 0.136 |
| SB wire protection | 65 (54.62%) | 32 (48.48%) | 0.518 |
| SB predilation | 9 (7.56%) | 1 (1.52%) | 0.081 |
| Remote site intervention | 46 (38.66%) | 21 (31.82%) | 0.354 |
| MV Stent | | | |
| Total stent length, mm | 34.9 ± 16.58 | 32.22 ± 14.47 | 0.268 |
| Maximal stent diameter, mm | 3.23 ± 0.45 | 3.25 ± 0.48 | 0.724 |

Data are presented as mean ± SD or n (%). FKB: final kissing balloon angioplasty; IVUS: intravascular ultrasound; LAD: left anterior descending; LCX: left circumflex; LM: left main; MV: main vessel; OCT: optical coherence tomography; RCA: right coronary artery; ROTA: rotational atherectomy; SB: side branch.
Table 3. Procedural outcomes in patients with or without MV calcification.

|                          | Calcification group | Non-calcification group | P-value |
|--------------------------|---------------------|-------------------------|---------|
| Angiographic success in MV | 114 (95.8%)         | 64 (97.0%)              | 0.91    |
| MV dissection            | 6 (5.0%)            | 1 (1.5%)                | 0.422   |
| MV hematoma              | 1 (0.8%)            | 0 (0%)                  | 0.455   |
| Final TIMI flow grade < 3 in MV | 2 (1.7%)         | 2 (3.0%)                | 0.601   |
| Residual stenosis > 20% in the MV | 1 (0.9%)       | 0 (0%)                  | 0.764   |
| Angiographic success in SB | 37 (31.1%)          | 35 (53.0%)              | <0.01   |
| SB dissection            | 3 (2.5%)            | 1 (1.5%)                | 0.939   |
| SB closure during procedure | 1 (0.8%)           | 1 (1.5%)                | 0.671   |
| Final TIMI flow grade < 3 in SB | 12 (10.1%)         | 1 (1.5%)                | <0.05   |
| Residual stenosis > 50% in SB ostium | 69 (58.0%)      | 29 (43.9%)              | 0.067   |

Data are presented as mean ± SD or n (%). MV: main vessel; SB: side branch; TIMI: thrombolysis in myocardial infarction.

Table 4. One-year clinical outcomes in patients with or without MV calcification.

|                          | Total n = 185 | Calcification group n = 119 | Non-calcification group n = 66 | P-value |
|--------------------------|--------------|----------------------------|--------------------------------|---------|
| Follow-up examination    |              |                            |                                |         |
| Angiography              | 131 (70.81%) | 82 (68.90%)                | 49 (74.24%)                    | 0.445   |
| Coronary artery CT       | 33 (17.84%)  | 18 (15.13%)                | 15 (22.73%)                    | 0.196   |
| IVUS or OCT              | 35 (18.92%)  | 23 (19.32%)                | 12 (18.18%)                    | 0.996   |
| Total TLF                | 22 (11.89%)  | 12 (10.08%)                | 10 (15.15%)                    | 0.308   |
| Cardiac death            | 5 (2.70%)    | 2 (1.68%)                  | 3 (4.55%)                      | 0.250   |
| Definite or probable ST  | 8 (4.32%)    | 5 (4.20%)                  | 3 (4.55%)                      | 0.912   |
| TVR                      | 9(4.86%)     | 5(4.20%)                   | 4(6.06%)                       | 0.573   |
| Recurrent angina         | 25 (13.51%)  | 21 (17.65%)                | 4 (6.06%)                      | <0.05   |

Data are presented as mean ± SD or n (%). IVUS: intravascular ultrasound; MV: main vessel; OCT: optical coherence tomography; TVR: target vessel revascularization; ST: stent thrombosis.

The recurrent angina occurred more often in the calcification group than that in the non-calcification group (P < 0.05) (Table 4).

4 Discussion

Our present study results show that in patients with coronary bifurcation lesion treated with provisional one stent approach, calcification of MV is associated with lower SB procedural success rate, it could increase recurrence of angina; but the occurrences of TLF at 1-year follow-up was comparable between those with and those without MV calcification.

PCI of bifurcation lesions is still technically challenging and associated with lower success rates, even with the recently developed dedicated bifurcation stents. Earlier studies showed that bifurcation lesions were also associated with increased risk of ST. CAC is an integral process in atherogenesis, and in spite of development of technologies for atheroablation, such as rotational atherectomy and aortic atherectomy, CAC is still associated with lower procedural success rate of PCI. Currently, the one-stent strategy with provisional SB stenting is considered by most interventional cardiologists as the default strategy for most coronary bifurcation lesions. However, researches are undertaking to identify specific patient group who would benefit more from other strategy beyond the provisional one-stent approach. Our present study may provide some insights for these efforts by evaluating the efficacy and feasibility of provisional one-stent approach in patients with bifurcation lesion and MV calcification.

We found that calcification of MV is associated with lower SB procedural success rate, this might be one of the important reasons for the higher rate of recurrent angina in the calcification group. The clinical outcome results of our present study are, to a large extent, in consistent with those reported by Kim, et al. In Kim’s study, the clinical endpoint composed cardiac death, non-fatal MI and TLR. Moderate or severe calcification was associated with increased risk of TLR, but not cardiac death, MI and ST.

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Whereas in our study, the clinical endpoint composed cardiac death, definite or possible ST and TVR, and our results showed no significant differences in terms of cardiac and ST.

In the present study, IVUS or OCT was used to detect and define CAC. Angiography often underestimates calcification.\(^\text{[9,10]}\) Actually, CAC was observed by CAG in only 50 of the 119 patients with MV calcification detected by IVUS or OCT (data not shown).

### 4.1 Study strength and limitations

The strength of our present study includes the multicenter, prospective design, the unified use of provisional one-stent approach in all patients, the high rate of follow-up coronary imaging, and the use of IVUS/OCT to detect CAC. The major limitation of the present study is the relatively small sample size and short follow-up time. In addition, the crude division of calcification into 2 categories (with and without) may weaken the quantitative analysis of its relationship to study endpoints. Therefore, the results of our present study should be interpreted with caution and need to be tested in larger studies.

### 4.2 Conclusions

In patients with coronary bifurcation lesion treated with provisional one stent approach, calcification of MV is associated with lower SB procedural success rate, it could increase recurrence of angina; but comparable MV procedural success rate; however, it was not associated with an increased risk of cardiac death, stent thrombosis, and target vascular revascularization within one year.

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