Optimal timing of staged percutaneous coronary intervention in ST-segment elevation myocardial infarction patients with multivessel disease

Xue–Dong ZHAO, Guan–Qi ZHAO, Xiao WANG, Shu–Tian SHI, Wen ZHENG, Rui–Feng GUO, Shao–Ping NIE
Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart Lung and Blood Vessel Diseases, Beijing, China

Abstract

Background Studies have shown that staged percutaneous coronary intervention (PCI) for non-culprit lesions is beneficial for prognosis of ST-segment elevation myocardial infarction (STEMI) patients with multivessel disease. However, the optimal timing of staged revascularization is still controversial. This study aimed to find the optimal timing of staged revascularization. Methods A total of 428 STEMI patients with multivessel disease who underwent primary PCI and staged PCI were included. According to the time interval between primary and staged PCI, patients were divided into three groups (≤ 1 week, 1–2 weeks, and 2–12 weeks after primary PCI). The primary endpoint was major adverse cardiovascular events (MACE), a composite of all-cause death, non-fatal re-infarction, repeat revascularization, and stroke. Cox regression model was used to assess the association between staged PCI timing and risk of MACE. Results During the follow-up, 119 participants had MACEs. There was statistical difference in MACE incidence among the three groups (≤ 1 week: 23.0%; 1–2 weeks: 33.0%; 2–12 weeks: 40.0%; \( P = 0.001 \)). In the multivariable adjustment model, the timing interval of staged PCI \( \leq 1 \) week and 1–2 weeks were both significantly associated with a lower risk of MACE [hazard ratio (HR): 0.40, 95% confidence intervals (CI): 0.24–0.65; HR: 0.54, 95% CI: 0.31–0.93, respectively], mainly attributed to a lower risk of repeat revascularization (HR: 0.41, 95% CI: 0.24–0.70; HR: 0.36, 95% CI: 0.18–0.7), compared with a strategy of 2–12 weeks later of primary PCI. Conclusions The optimal timing of staged PCI for non-culprit vessels should be within two weeks after primary PCI for STEMI patients.

Keywords: Myocardial infarction; Multivessel disease; Non-culprit lesion; Percutaneous coronary intervention; Timing

1 Introduction

For patients admitted for ST-segment elevation myocardial infarction (STEMI), timely revascularization is the most important therapeutic strategy. Although primary percutaneous coronary intervention (PCI) to target the culprit lesion has become the best strategy to improve survival of the patients with STEMI, the best management for non-culprit arteries is still controversial. Up to 50% of patients with STEMI have multivessel disease, which is strongly associated with a higher risk of major adverse cardiac events (MACE). Previous studies have suggested that staged PCI may be associated with a better outcome than multivessel primary PCI or culprit vessel only intervention. Based on these evidences, guidelines of the American Heart Association / American College of Cardiology, as well as the European Society of Cardiology, recommended that staged PCI may be an appropriate strategy for non-culprit vessels in selected patients.

However, few studies have studied the optimal timing of staged PCI in patients with STEMI and multivessel disease. In 2010, the American College of Cardiology conducted an online survey for interventional cardiology experts about the optimal timing of staged PCI in patients with multivessel disease. Of these surveyed cardiologists, 62% suggested a time period of > 2 weeks for staged PCI in patients with STEMI and multivessel disease, and renal function was the single strongest factor in the decision to stage PCI. Consistent with this recommendation, Lee, et al. found that staged PCI for a non-culprit lesion within 3 weeks might be related to occurrence of acute kidney injury; staged PCI for a non-culprit lesion over 3 weeks to 1 year had a better clinical outcome. However, Kim, et al. reported that deferred staged PCI after 1 week of index PCI was associated

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with the highest MACE compared with simultaneous multivessel PCI and early staged PCI at < 1 week.

Therefore, the optimal timing of staged PCI for non-culprit vessels is unclear. This study aimed to investigate the effect of different periods of staged PCI on the incidence of MACE and to identify the optimal timing of staged PCI in patients with STEMI and multivessel disease.

## 2 Methods

This was a retrospective study of consecutive patients with the clinical diagnosis of STEMI and multivessel disease who underwent primary PCI (interval from symptom onset to admission < 12 h) with implanted drug-eluting stent (DES) in Beijing Anzhen Hospital, Capital Medical University, Beijing, China. All demographic, clinical, angiographic, and initial or planned staged procedural data of the patients were collected from medical records by trained data technicians using a standardized questionnaire. This study was approved by the Ethics Committee of Beijing Anzhen Hospital.

### 2.1 Study populations

From January 2005 to January 2015, a total of 2674 patients with STEMI referred for primary PCI within 12 hours from symptom onset in Beijing Anzhen Hospital. According to the operation record, 1033 patients with STEMI were diagnosed with multivessel disease and implanted DES (Figure 1). Among these patients, 439 received planned staged PCI. After excluding 11 patients who were lost in the follow-up, 428 were included in this study. Two operators evaluated selection of the culprit vessel in similar conditions (Figure 1).

According to the time interval from initial to staged PCI, patients were divided into three groups as follows: staged PCI of non-culprit vessels ≤ 1 week after primary PCI \( (n = 261) \); 1 to 2 weeks after primary PCI \( (n = 112) \); and 2 to 12 weeks after primary PCI \( (n = 55) \).

### 2.2 Follow-up and study endpoints

Patients were followed-up by telephone interviews from December 2016 to January 2017. All adverse events were re-confirmed by reviewing the medical records of the patients who were followed up in our hospital. We also contacted the patients’ physicians and reviewed the hospital records of patients who were treated elsewhere. The primary endpoint of this study was MACE, a composite of all-cause death, non-fatal re-infarction, repeat revascularization, and stroke after staged PCI.

### 2.3 Definitions

All of the eligible patients were diagnosed with STEMI at admission based on clinical presentation, increased cardiac biomarkers, echocardiographic results, and 12-lead electrocardiographic findings. Multivessel disease was defined as critical stenosis (diameter of stenosis > 50%) in at least two major epicardial coronary arteries on a diagnostic coronary angiogram. Complete revascularization was defined as revascularization of all culprit and non-culprit arteries during staged PCI. Repeat revascularization was defined as subsequent revascularization of the index vessel due to ischemic symptoms or new-onset myocardial infarction by either PCI (additional stent or angioplasty) or coronary artery bypass graft (CABG).

### 2.4 Statistical analysis

Data are expressed as mean ± standard deviation for continuous data with a normal distribution, median (interquar-
tile range) for continuous variables with a skewed distribution, and percentages for categorical variables. Data were compared using one-way ANOVA or the Kruskal-Wallis rank-sum test for continuous data; χ² test or Fisher’s exact probability test for categorical variables. To evaluate the association between time interval of staged PCI and risk of MACE, a Kaplan-Meier survival curve was performed for MACE in the three groups with the log-rank test. Then we constructed a Cox proportional-hazard regression model with adjustment of potential confounding and risk factors for the prognosis. The adjusted variables included age, sex, the time from onset of symptoms to PCI, heart function and if the patients received complete revascularization. The adjusted variables were age, sex, left ventricular ejection fraction, and the interval from symptom onset to admission, other characteristics were comparable among the groups (Table 1).

3.2 Angiographic and procedural characteristics

Angiographic findings of culprit vessels and non-culprit vessels were comparable among the three groups but some of the procedural of the characteristics were of statistical significance between three groups, including PCI approach, thrombus aspiration and temporary cardiac pacing (Table 2).

3.3 Events at follow-up

Patients with acute coronary syndrome (ACS) were followed for an average of 4.0 years (interquartile range: 1.6–6.9 years). A total of 119 (24.5%) participants with 151 MACE events were recorded during the follow-up, including all-cause death (n = 22), cardiac death (n = 8), myocardial infarction (n = 25), repeat revascularization (n = 85), and stroke (n = 11). There was statistical difference in MACE among the three groups with log-rank test (≤ 1 week: 23.0%; 1–2 weeks: 33.0%; 2–12 weeks: 40.0%; P = 0.001) (Figure 2). However, there was no statistical difference in MACE between time interval ≤ 1 week and 1–2 weeks (P = 0.311). In the Cox proportional hazards multivariate analysis, the timing interval of staged PCI ≤ 1 week and 1–2 weeks were both significantly associated with a lower risk of MACE [hazard ratio (HR): 0.40, 95% confidence intervals (CI): 0.24–0.65; HR: 0.54, 95% CI: 0.31–0.93, respectively]. The associations between different periods of staged PCI and components of MACE were also evaluated (Figure

| Table 1. Baseline characteristics of the study populations. |
|----------------------------------------------------------|
| Group 1 (< 1 week, n = 261) | Group 2 (1–2 weeks, n = 112) | Group 3 (2–12 weeks n = 55) | P value |
|-----------------------------|-------------------------------|-----------------------------|---------|
| Age, yrs | 57.3 ± 10.0 | 61.6 ± 10.5 | 56.4 ± 11.0 | < 0.001 |
| Female | 37 (14.2%) | 26 (23.2%) | 6 (10.9%) | 0.050 |
| Current smoker | 180 (69.0%) | 68 (60.7%) | 31 (56.4%) | 0.105 |
| Hypertension | 103 (39.5%) | 50 (44.6%) | 23 (41.8%) | 0.644 |
| Diabetes | 59 (22.6%) | 33 (29.5%) | 13 (23.6%) | 0.364 |
| Dyslipidemia | 54 (20.7%) | 17 (15.2%) | 12 (21.8%) | 0.415 |
| Prior MI | 20 (7.7%) | 5 (4.5%) | 3 (5.5%) | 0.488 |
| PCI history | 20 (7.7%) | 4 (3.6%) | 3 (5.5%) | 0.317 |
| LVEF | 57.2 ± 8.6 | 54.4 ± 8.4 | 55.8 ± 8.2 | 0.040 |
| Killip class II-IV | 95 (36.4%) | 49 (43.8%) | 22 (40.0%) | 0.401 |
| Medications | | | | |
| Aspirin | 260 (99.6%) | 111 (99.1%) | 55 (100%) | 0.207 |
| Clopidogrel/Ticagrelor | 260 (99.6%) | 111 (99.1%) | 55 (100%) | 0.693 |
| Statins | 253 (96.9%) | 110 (98.2%) | 55 (100%) | 0.113 |
| Beta-blockers | 148 (56.7%) | 71 (63.4%) | 34 (61.8%) | 0.440 |
| ACEI/ARBs | 157 (60.2%) | 71 (63.4%) | 34 (61.8%) | 0.837 |

Data were presented as mean ± SD or n (%). ACEI/ARBs: angiotension converting enzyme inhibitors / angiotensin II receptor blocker; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention.
Table 2. Angiographic and procedural characteristics.

| Group 1 (<1 week, n = 261) | Group 2 (1–2 weeks, n = 112) | Group 3 (2–12 weeks n = 55) | P value |
|----------------------------|-------------------------------|----------------------------|---------|
| Infarct location            |                               |                            |         |
| Anterior MI                 | 117 (44.8%)                   | 50 (44.6%)                 | 21 (38.2%) |
| Inferior MI                 | 125 (47.9%)                   | 53 (47.3%)                 | 29 (52.7%) |
| Lateral MI                  | 4 (1.5%)                      | 1 (0.9%)                   | 1 (1.8%)  |
| Multiple MI                 | 15 (5.7%)                     | 8 (7.1%)                   | 4 (7.3%)  |
| Site of culprit vessel      |                               |                            |         |
| RCA                        | 130 (49.8%)                   | 53 (47.3%)                 | 33 (60.0%) |
| LM                         | 1 (0.4%)                      | 0 (0.0%)                   | 1 (1.8%)  |
| LAD                        | 89 (34.1%)                    | 42 (37.5%)                 | 19 (34.5%) |
| LCX                        | 41 (15.7%)                    | 17 (15.2%)                 | 2 (3.6%)  |
| Site of non-culprit vessel  |                               |                            |         |
| RCA                        | 106 (40.6%)                   | 43 (38.4%)                 | 14 (25.5%) |
| LM                         | 4 (1.5%)                      | 2 (1.8%)                   | 3 (6.0%)  |
| LAD                        | 152 (58.2%)                   | 61 (54.5%)                 | 28 (50.9%) |
| LCX                        | 142 (54.4%)                   | 60 (53.6%)                 | 37 (67.3%) |
| Three-vessel disease       | 141 (54.0%)                   | 52 (46.4%)                 | 25 (45.5%) |
| Radial artery access       | 211 (80.8%)                   | 85 (75.9%)                 | 29 (52.7%) |
| Thrombus aspiration        | 181 (69.3%)                   | 65 (58.0%)                 | 26 (47.3%) |
| IABP                       | 46 (17.6%)                    | 19 (17.0%)                 | 9 (16.4%)  |
| Temporary cardiac pacing   | 6 (2.3%)                      | 10 (8.9%)                  | 0 (0.0%)  |
| Slow/No reflow             | 10 (3.8%)                     | 6 (5.4%)                   | 1 (1.8%)  |
| Complete revascularization | 181 (69.3%)                   | 82 (73.2%)                 | 39 (70.9%) |

Data were presented as n (%). IABP: intra-aortic balloon pump; LAD: left anterior descending coronary artery; LCX: left circumflex artery; LM: left main; MI: myocardial infarction; RCA: right coronary artery.

Figure 2. Unadjusted mortality curves during follow-up for patients undergoing staged PCI in three different periods. MACE, major adverse cardiovascular events.

3). Compared with timing interval of staged PCI 2–12 weeks, the timing interval ≤1 week and 1–2 weeks were both significantly associated with a lower risk of repeat revascularization (HR: 0.41, 95% CI: 0.24–0.70; HR: 0.36, 95% CI: 0.18–0.70) (Table 3).

4 Discussion

In our study, the clinical benefits of staged PCI were compared over three common revascularization periods in non-culprit vessel PCI with a relatively long-term follow-up. We found that performing staged PCI within two weeks especially in one week was associated with a lower risk of MACE, mainly attributed to a lower risk of repeat revascularization compared with a strategy of two weeks later of primary PCI. This result suggests that the optimal timing for non-culprit lesions should be limited within two weeks after undergoing primary PCI.

Because there is no specific guideline for the optimal timing period for staged PCI, cardiologists often make decisions based on clinical experience (safety and efficacy) and requests of the patients (convenience and costs). In our study, most of the patients (87.1%) underwent staged PCI within two weeks, especially within one week (61.0%). Therefore, our findings are consistent with the preference of cardiologists.
Figure 3. Cox regression analysis for timing of staged PCI. In multivariable analysis, an independent association was found between staged PCI 2-12 weeks and MACE. CI: confidence interval; HR: hazard ratio; MACE: major adverse cardiovascular events.

Table 3. Multivariable Cox model for long-term MACE.

| Variable                          | HR (95% CI)     | P value |
|----------------------------------|-----------------|---------|
| Staged time                      |                 |         |
| 1–2 weeks                        | 1.10 (0.63–1.92)| 0.736   |
| 2–12 weeks                       | 2.77 (1.51–5.08)| 0.001   |
| Sex                              | 1.46 (0.82–2.61)| 0.203   |
| Age                              | 1.00 (0.97–1.02)| 0.802   |
| LVEF ≥ 50%                       | 0.73 (0.43–1.24)| 0.242   |
| Interval from symptom onset to admission > 2 h | 1.66 (0.84–3.27) | 0.144   |
| Complete revascularization        | 0.74 (0.45–1.23)| 0.246   |

CI: confidence interval; HR: hazard ratio; LVEF: left ventricular ejection fraction; MACE: major adverse cardiovascular events.

There are several potential advantages to performing early staged PCI. First, acute optimization of myocardial blood supply may increase myocardial salvage in hibernating myocardium or border areas of infarction, improving left ventricular ejection fraction (LVEF) although with conflicting views.[11–13] Second, complete revascularization of the non-culprit arteries in the early phase may be helpful for building of the collateral circulation and improving regeneration of the infarcted myocardium, for recovery from acute myocardial infarction.[14,15] Myocardial reperfusion within one week, before completion of adverse remodeling after myocardial infarction, improves long-term clinical outcomes. Deferred intervention of non-culprit arteries may induce prolonged dual antiplatelet therapy, which may increase the risk of bleeding.[16] Hemorrhagic events have major negative prognostic implications in patients with stable and acute coronary syndromes.[17] Third, the procedure for most patients who underwent a staged PCI of the non-culprit lesions within one week after primary PCI was performed before initial discharge from hospital. In-hospital staged PCI may reduce readmission rates, resource use, and cost.

Randomized trials such as DANAMI-3-PRIMULTI study[18] and COMPARE-ACUTE study[19] emphasize the importance of fractional flow reserve (FFR) to guide the strategy of revascularization. Although studies shows that earlier reperfusion of non-culprit vessels was associated with better prognosis compared with infarct artery only treatment, FFR or other noninvasive examinations[20] may not be appropriate at the time of primary PCI considering the patient’s status at the acute phase of STEMI and issues of the index PCI procedure (additional contrast volume and prolonged procedure time).[21] Thus, after stabilization of hemodynamics, early staged PCI facilitates a series of functional examinations, which are noninvasive or invasive, to confirm the role of non-culprit lesions in myocardial ischemia and to guide the procedure.[22] An early staged PCI strategy provides not only more time to evaluate the risks and benefits of additional revascularization for non-culprit arteries, but also timely reperfusion of ischemic myocardium.

Although some studies have compared the strategy of staged PCI versus complete[23–25] or culprit-only revascularization,[26–28] a conclusion of the optimal timing cannot be drawn from published studies, because different timing frames of staged PCI were reported in different studies and rarely detailed. Our findings about optimal timing of staged PCI are supported by a recently published study of Korea.[10] This study showed that deferred staged PCI for one week after index PCI was associated with the highest MACE.
compared with simultaneous multivessel PCI. However, our finding is inconsistent with opinions of most (62%) interventional cardiology experts in an online survey that was conducted by the American College of Cardiology in 2010.[8] These experts suggested a time period of > 2 weeks for staged PCI in patients with STEMI and multivessel disease for considering renal function. Therefore, we also assessed the change in serum creatinine levels from admission to before discharge. Compared with patients who only received primary PCI during the index hospitalization, those who received complete staged PCI during the index hospitalization did not have a higher rate of contrast nephropathy (diagnosed as a > 50% rise in plasma creatinine levels) (7.5% vs. 7.2%, \( P = 0.899 \)).

This study has some limitations. First, because this was a retrospective, observational study, there was selection bias, unmeasured confounders, and a lack of adequate risk adjustment. As we observed a relatively high mortality rate in 1–2 weeks group and this might be attributed to the group’s population characteristics, older age, more women, lower LVEF, and a higher level of Killip class. Second, our study was lacking data of the Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score, which indicates the complexity of coronary anatomy and prognosis of patients after the procedure. Third, information on functional examinations of coronary arteries was not collected because it was unavailable in records. This information might be an important clinical indicator for comprehensively evaluating the prognosis.

In conclusion, our study shows that, for patients with STEMI and multivessel disease, the optimal timing period of staged PCI for non-culprit vessels should be within two weeks, especially within one week after primary PCI. Deferred staged PCI within 2–12 weeks of primary PCI might be associated with a higher risk of MACE compared with early staged PCI. Although the findings of this study are important for clinical practice, further prospective, observational studies and large-scale, randomized trials are still required to confirm these findings.

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