Timing of Staged Percutaneous Coronary Intervention for a Non-Culprit Lesion in Patients With Anterior Wall ST Segment Elevation Myocardial Infarction With Multiple Vessel Disease

Wei-Chieh Lee, MD, Bo-Jui Wu, MD, Chih-Yuan Fang, MD, Chien-Jen Chen, MD, Cheng-Hsu Yang, MD, Hon-Kan Yip, MD, Chi-Ling Hang, MD, Chiung-Jen Wu, MD, and Hsiu-Yu Fang, MD

Summary

The optimal timing of a staged percutaneous coronary intervention (PCI) for non-culprit lesions in patients with ST-segment elevation myocardial infarction (STEMI) patients with multi-vessel disease (MVD) remains controversial. We focused on patients with anterior wall STEMI with MVD and determined the clinical effects for timing of staged PCI.

From November 2005 to December 2014, 258 patients were diagnosed with anterior wall STEMI with MVD in our hospital. Among them, 37 patients received staged PCI within 3 weeks, 50 patients received staged PCI during 3 weeks to one year, and 167 patients received only primary PCI for culprit lesions. Clinical outcomes such as admission for angina or heart failure, target vessel revascularization, myocardial infarction, stroke, cardiovascular mortality, and all-cause mortality were compared among the 3 groups.

Acute kidney injury (AKI) after PCI occurred in 18.9% of the 3-week group, 0% of the one-year group, and 7.6% of the control group \( (P = 0.005) \). Of the one-year and 3-year clinical outcomes, the one-year group had better results, such as fewer major adverse cardiac cerebral events \( (P = 0.028, \ P = 0.023) \), and lower recurrent MI \( (P = 0.065; \ P = 0.018) \), cardiovascular mortality \( (P = 0.043; \ P = 0.020) \), and all-cause mortality \( (P = 0.047; \ P = 0.005) \).

In patients with anterior wall STEMI with MVD, staged PCI for a non-culprit lesion over 3 weeks to one year had a better clinical outcome. Staged PCI for a non-culprit lesion within 3 weeks may be related to the occurrence of AKI, may lead to worse clinical outcomes, and did not decrease the occurrence of angina or post-MI heart failure. \( \) (Int Heart J 2016; 57: 417-423)

Key words: Multiple vessel coronary artery disease, Non-culprit lesion

Primary percutaneous coronary intervention (PCI) has become the preferred reperfusion strategy in ST segment elevation myocardial infarction (STEMI) if a first medical contact to reperfusion time of < 90 minutes (< 60 minutes in early presenters [ESC guidelines]) can be achieved. \(^1\) \(^2\) Approximately 40% of patients undergoing primary PCI have multiple vessel disease (MVD) with at least one additional severe lesion in an artery other than the culprit vessel. \(^3\) Patients with MVD have worse outcomes, with more than a 2-fold increase in death at 1 year compared with patients who have single-vessel disease. \(^4\) Multiple-vessel PCI may offer advantages over a strategy of culprit lesion-only PCI because plaque instability may be a widespread process throughout the coronary vessels. \(^5\) Moreover, complete revascularization has been associated with an improved long-term clinical outcome in patients with stable coronary artery disease (CAD). \(^6\) However, in the acute phase of STEMI with regional myocardial compromise, intervention of a non-culprit lesion may result in unnecessary hemodynamic compromise and may cause worse clinical results. Given the extended duration of the intervention, increased contrast load, and off-hours timing, additional adverse peri-procedural events may occur and cause unnecessary problems. Therefore, the strategy of non-culprit vessel PCI in patients with STEMI and MVD remains controversial. Current guideline recommendations encourage culprit lesion-only PCI in patients with STEMI and MVD (excluding cardiogenic shock). \(^1\) \(^3\) In fact, patients and clinicians are often more comfortable with complete revascularization than with medical therapy for angiographically significant residual coronary stenoses, especially when it supplies a large territory. Therefore, staged PCI for a non-culprit vessel is a reasonable strategy for these patients. Some meta-analysis studies \(^7\) \(^8\) have
explained the benefit of staged PCI, but the timing of the staged PCI has not been well explored. The clinical outcomes of staged PCI for different territory STEMI with MVD has not been discussed before.

The left anterior descending (LAD) artery is the most important coronary artery and usually has a large myocardial territory. The timing of staged PCI for non-culprit vessel revascularization of anterior wall STEMI with MVD remains unknown. The best timing of staged PCI and its benefit requires additional evaluation. With technical and device improvements, physicians could deal with more complex cases and would want to complete revascularization of all coronary vessels within a short-term period. The majority of cardiologists suggest a timeframe of ≥ 15 days in STEMI patients for staging of the second PCI after the initial revascularization during the same hospitalization. In elective stable patients, the majority of cardiologists again recommend a timeframe of ≥ 15 days for the second PCI after the initial revascularization, and other cardiologists recommend PCI within 2 weeks. Based on the clinical symptoms, disease severity, and physician suggestions, short-term (the same hospitalization within one month) and long-term (different hospitalization between 30 days and one year) strategies for reperfusion of a non-culprit vessel were developed.

In our study, we focused on patients with anterior wall STEMI with MVD and determined the clinical effects for timing of staged PCI in this group.

METHODS

Patient collection and groups: From November 2005 to December 2014, 1751 STEMI patient charts were reviewed. A total of 1110 (63.3%) patients had MVD and 843 (48.1%) had at least one severe coronary artery disease, with a stenotic percentage greater than 70%. Among them, 258 patients were diagnosed with anterior wall STEMI with MVD and received primary PCI for the culprit lesion such as LAD after we excluded patients who presented with cardiogenic shock. Patients were divided into 3 groups: 3-week, one-year, and control according to the timing of stage PCI. The 3-week group included patients who received staged PCI for the non-culprit lesion within 3 weeks. The one-year group consisted of patients who received staged PCI between 3 weeks and one year. The control group included patients who did not receive staged PCI. Based on the clinical symptoms, disease severity, and physician suggestions, reperfusion strategies for non-culprit vessels were divided into short-term or long-term period.

The demographics, risk factors, severity of MI, timing of primary PCI, characteristics of coronary artery disease, and post-MI medication were compared among the 3 groups. According to the chart review, the occurrence of stroke, myocardial infarction, target lesion revascularization (TLR), cardiovascular death, and all-cause death were collected. The Institutional Review Committee on Human Research of our institution approved the study protocol.

Procedure and protocol: The PCI strategies for STEMI patients with MVD were defined as follows: The culprit-vessel only PCI (culprit PCI) strategy was defined as PCI confined to culprit vessel lesions only. The staged PCI strategy was defined as PCI confined to culprit vessel lesions only, after which > 1 lesions in a non-culprit vessel were treated during planned secondary procedures. The timing of staged PCI procedures was defined as within 3 weeks or between 3 weeks and one year.

Definitions: Advanced heart failure (HF) was defined as a New York Heart Association (NYHA) functional class greater than or equal to 3. The definition of major adverse cerebral cardiac events (MACCEs) included myocardial infarction, TLR, stroke, and cardiovascular mortality. Typical angina was characterized by at least one of the following: 1) chest pain occurring at rest or during minimal exertion and usually lasting less than 20 minutes (if nitroglycerin is not administered); 2) severe flank pain of new onset (ie, within one month); or 3) a crescendo pattern of chest pain (more severe, prolonged, or increased frequency compared to previously experienced). Acute decompensated heart failure was defined as the sudden or gradual onset of the symptoms of heart failure necessitating emergency room visits or hospitalizations for the use of intravenous diuretic agents (a dose more than two times the usual oral dose).

Acute kidney injury (AKI) was defined by the Kidney Disease Improving Global Outcomes (KDIGO) study in 2012 and specific criteria exist for the diagnosis of AKI. AKI can be diagnosed if any one of the following is present: 1) increase in the level of serum creatinine by ≥ 0.3 mg/dL within 48 hours; or 2) increase in the level of serum creatinine to ≥ 1.5 times baseline, which has occurred within the prior 7 days; or 3) urine volume < 0.5 mL/kg/hour for 6 hours.

Study endpoints: The primary endpoint of this study was visits to emergency departments or re-admission for angina or HF, which was examined at 30 days and one year after primary PCI. The secondary endpoints were MACCEs, such as TVR, recurrent MI, cardiovascular mortality, and all-cause mortality at 30 days, one year and 3 years after primary PCI.

Statistical analysis: All statistical analyses were performed using SPSS 22.0 software (SPSS, Inc., Chicago, IL). The data are expressed as percentages and the mean ± standard deviation. Continuous variables were compared using analysis of variance (ANOVA). Continuous variables among the 3 groups were analyzed by one-way analysis of variance with Bonferroni correction. A Kaplan–Meier survival curve was performed for TLR and MACCEs in the 3 groups. P values below 0.05 were considered statistically significant.

RESULTS

Baseline characteristics of study patients (Table I): The average age of the 3-week group was 63.08 ± 12.17 years, and 83.8% of the patients were male. The average age of the one-year group was 60.32 ± 9.19 years, and 90.0% of the patients were male. The average age of the control group was 63.61 ± 12.92 years, and 86.0% of the patients were male. The average age of the patients was significantly lower in the one-year group (P = 0.244). Baseline characteristics were similar among the 3 groups, except for statin use (64.9% versus 90.0% versus 67.8%; P = 0.006). The percentage of LDL concentrations more than 100 mg/dL was 50.0% in the 3-week group, 73.9% in the one-year group, and 64.0% in the control group (P = 0.089).

Smaller prevalences of diabetes mellitus (40.5% versus 30.0% versus 39.2%; P = 0.461), hypertension (67.6% versus
60.0% versus 66.1%; \( P = 0.689 \), advanced HF (10.8% versus 2.0% versus 12.3%; \( P = 0.103 \)), and previous stroke (8.1% versus 4.0% versus 11.7%; \( P = 0.254 \)) were observed in the one-year group, and a smaller prevalence of current smokers (54.1% versus 56.0% versus 47.4%; \( P = 0.461 \) ) was observed in the control group. A smaller prevalence of Killip III patients was observed in the one-year group (21.6% versus 10.0% versus 18.1%; \( P = 0.491 \)). A shorter chest pain-to-reperfusion time was observed in the one-year group (328.23 ± 264.86 minutes versus 291.04 ± 196.46 minutes versus 343.01 ± 304.28 minutes; \( P = 0.541 \)). Lower fasting sugar (150.10 ± 62.27 mg/dL versus 142.79 ± 51.30 mg/dL versus 160.79 ± 93.94 mg/dL; \( P = 0.438 \) ), higher LDL (111.06 ± 43.36 mg/dL versus 126.63 ± 33.37 mg/dL versus 117.47 ± 29.59 mg/dL; \( P = 0.191 \) ), and higher peak troponin-I (47.95 ± 47.61 ng/mL versus 60.89 ± 54.34 ng/mL versus 51.23 ± 58.03 ng/mL; \( P = 0.622 \) ) levels were noted in the one-year group.

The control group had a higher prevalence of double-vessel coronary disease and the 3-week group had a greater percentage of triple-vessel coronary artery disease. The percentage of patients in whom the non-culprit lesion involved the left circumflex artery was 83.8% in the 3-week group, 72.0% in the one-year group, and 72.5% in the control group (\( P = 0.343 \)). The corresponding percentages of patients in whom the non-culprit lesion involved the right coronary artery were 83.8% in the 3-week group, 90.0% in the one-year group, and 73.7% in the control group (\( P = 0.033 \)).
among the 3 groups (2.7% versus 0% versus 0.6%; membrane oxygenation use was not significantly different (32.4% versus 16.0% versus 9.9%; balloon pumping (IABP) use was higher in the 3-week group characteristics were similar among the 3 groups. Intra-aortic 10.26% versus 82.12 ± 10.05% versus 82.30 ± 12.27%; not statistically different between the 3 groups (83.96 ± 3 groups. The stenotic percentage of non-culprit vessels was 3 weeks) groups. The stenotic percentage of non-culprit vessels was 3 weeks) groups. The stenotic percentage of non-culprit vessels was not statistically different among the 3 groups. Pre-PCI angiography and method of primary PCI (Table II): Pre-PCI and post-PCI angiographic characteristics were similar among the 3 groups. Intra-aortic balloon pumping (IABP) use was higher in the 3-week group (32.4% versus 16.0% versus 9.9%; P = 0.002). Extracorporeal membrane oxygenation use was not significantly different among the 3 groups (2.7% versus 0% versus 0.6%; P = 0.323). The methods of PCI were not statistically different among the 3 groups. The stenotic percentage of non-culprit vessels was not statistically different between the 3 groups (83.96 ± 0.26% versus 82.12 ± 10.05% versus 82.30 ± 12.27%; P = 0.631). In the 3-week group, 11.1% of the patients received stage PCI for LCX and RCA, 30.6% received stage PCI for only an LCX lesion, and 58.3% received stage PCI for only an RCA lesion. In the one-year group, 14.6% of the patients received stage PCI for LCX and RCA, 35.4% received stage PCI for only an LCX lesion, and 50.0% received stage PCI for only an RCA lesion. There was no significant difference in stage PCI for non-culprit lesions between the 3-week group and one-year group (P = 0.834).

Short-term and long-term clinical outcomes of study patients (Table III): The occurrence of acute kidney injury (AKI) was significantly higher in the 3-week group (18.9% versus 0% versus 7.8%; P = 0.005). During the 30-day follow-up period, 4 patients in the 3-week group suffered from cardiovascular mortality. Among them, 3 patients experienced AKI. On the other hand, 7 patients in the 3-week group experienced AKI. Among them, 3 patients suffered from cardiovascular mortality. During the 30-day follow-up period, 10 patients in the control group suffered from cardiovascular mortality. Among them, 5 patients experienced AKI. On the other hand, 13 patients in the control group experienced AKI, 5 of whom suffered from cardiovascular mortality.

At the 30-day follow-up, re-admission for recurrent angina or heart failure, MACCE, recurrent MI, TVR, cardiovascular mortality, and all-cause mortality were higher in the 3-week group. No significant differences were observed. Considering the one-year and 3-year clinical outcomes, the one-year group had better results, such as lower incidences of MACCEs (P = 0.028, P = 0.023; respectively), recurrent MI (P = 0.065; P = 0.018; respectively), cardiovascular mortality (P = 0.043; P = 0.020; respectively), and all-cause mortality (P = 0.047; P = 0.005; respectively). Recurrent MI often occurred in the culprit vessel. All 30-day recurrent MI of the 3-week group and control group occurred in the culprit vessel. During the one-year follow-up period, recurrent MI of the culprit vessel occurred in the cul...
66.7% of the patients in the 3-week group, and in 55.6% of the patients in the control group. During the 3-year follow-up period, recurrent MI of the culprit vessel occurred in 66.7% of the patients in the 3-week group and in 60% of the patients in the control group.

**Kaplan-Meier curve of one-year symptom-free survival and 3-year MACCE (Figure 1 and Figure 2):** The Kaplan-Meier curve of one-year symptom-free survival was not significantly different among the 3 groups (Figure 1) and the Kaplan-Meier curve of the 3-year MACCE was not significantly different among the 3 groups (Figure 2) ($P = 0.989$, $P = 0.539$; respectively). However, the 3-week group had worse clinical results when compared with the one-year group ($P = 0.061$).
**DISCUSSION**

Primary PCI of the culprit coronary artery is the standard of care for patients presenting with acute STEMI, but the literature is conflicting regarding the benefit of PCI for significant stenosis in non-Infarct arteries after successful primary PCI. Current guidelines state that, “Primary PCI should not be performed in a non-infarct artery at the time of primary PCI in patients with STEMI who are hemodynamically stable”,” “PCI is reasonable in a non-infarct artery at a time separate from primary PCI in patients with intermediate- or high-risk findings on noninvasive testing”, and “PCI for STEMI should be limited to the culprit lesion, except in patients with cardiogenic shock”. However, current guidance does not mention the best timing for staged PCI for severe stenosis of a non-infarct artery. The majority of cardiologists suggest a timeframe of ≥ 15 days in STEMI patients and elective stable patients for staging of the second PCI after the initial revascularization. Contrast exposure and the severity of the infarction could influence clinical outcome even if complete revascularization is achieved within a short-term period. In our study, the clinical benefits of staged PCI over different periods were evaluated.

Acute coronary syndromes are manifested by prominent systemic derangements in these processes, with multiple inflamed lesions at once, compared with stable angina. The potential advantages of the completeness of revascularization in the short term are possible, decreasing the occurrence of recurrent MI and recurrent angina. The potential disadvantages are possible lengthening of the cumulative hospital stay, increased contrast load (and thus increased risk of contrast-induced nephropathy), haemodynamic instability in the acute setting, and potentially disastrous complications of a non-infarct artery PCI. In addition, treating a non-infarct artery that is causing stenosis could jeopardize healthy areas of myocardium when the recovering areas of injured myocardium are at their weakest after STEMI. One randomized study reported that in haemodynamically stable patients with multi-vessel disease, staged multi-vessel PCI within 60 days had a significantly lower 12-month mortality rate than patients undergoing PCI for only the culprit vessel PCI. One observational study showed a higher 30-day mortality and one-year mortality in early-staged PCI (the time of staged PCI) when compared to late-staged PCI (the time of staged PCI more than one month after primary PCI) when compared to late-staged PCI (the time of staged PCI more than one month and less than 6 months after primary PCI). To the best of our knowledge, no studies have discussed the timing of staged PCI in different territories of STEMI.

The percentage of statin use was higher in the one-year group, which was related to the fact a greater percentage of the patients had higher concentrations of serum LDL. Statins could influence long-term outcome, but may not affect short-term outcome and AKI. Furthermore, the percentage of statin use was the same between the 3-week group and control group. However, no better clinical benefit existed in the 3-week group when compared to the control group.

MI resulting from coronary artery disease is a leading cause of death in the United States, where more than 1 million people have AMIs each year. Patients with MVD and at least one additional severe lesion in an artery other than the culprit vessel during primary PCI are increasing. In our study, 63.3% of patients had MVD and 48.1% of patients had at least one severe coronary artery disease, with a stenotic percentage greater than 70%. An anterior wall MI is a significant predictor of in-hospital death in all STEMI. Therefore, the timing of staged PCI for anterior wall STEMI with MVD is important. In our study, the patients with anterior wall STEMI with MVD were divided into 3 groups according to the period of staged PCI and whether they received staged PCI or not. Some differences were observed in baseline characteristics among the 3 groups, but only post-MI statin use was significantly different. Pre- and post-PCI angiographic characteristics were similar among the 3 groups. A higher Syntax score and greater stenotic severity of the non-culprit vessel still presented in the 3-week group, even if no significant difference was noted between the 3 groups. The percentage of IABP use was higher in the 3-week group. This study was not a prospective randomized study, and some selection bias occurred. Furthermore, this may be related to clinicians wanting to do more intervention for a non-infarct lesion in the short-term because of a worse clinical condition or existing supportive device. However, this strategy did not result in more benefit for the patients, but it seemed to cause unnecessary harm to patients during injured myocardium recovery. In our study, the occurrence of AKI related contrast exposure and the severity of infarction was higher in the 3-week group. The incidence of recurrent admission for angina or heart failure did not decrease in the 30-day and one-year follow-up periods. In addition, the one-year group had better results, such as less MACCE, recurrent MI, cardiovascular mortality, and all-cause mortality in the one-year and 3-year follow-up periods. Therefore, we need to reconsider the need for stage PCI for non-culprit vessels within a short-term period.

Even if this study was a retrospective single-center study with observational analysis and a small number of patients, valuable experience concerning the timing of staged PCI in the patients with STEMI and MVD was gained. Staged PCI seemed to be performed after the patient’s clinical condition had stabilized and needs to be prevented in the short term because of the high incidence of AKI if the patients presented with an unstable clinical condition. Furthermore, the timing of staged PCI for the patients with STEMI requires a large randomized study for additional evaluation.

**Study limitations:** First, our study was a retrospective single-center study with observational analysis. The clinical results of this study are valuable because it is the first study to evaluate the clinical results of the timing of staged PCI. Second, some selection bias presented in the choice of staged PCI because of different clinical conditions. Third, the percentage of statin use could influence long-term outcome, but may not influence short-term outcome and the incidence of AKI.

**Conclusions:** In patients with anterior wall STEMI with MVD, staged PCI for a non-culprit lesion during 3 weeks to one year had better clinical outcomes. Staged PCI for a non-culprit lesion within 3 weeks may be related to AKI occurrence, causing worse clinical outcomes, and did not decrease the occurrence of angina and post-MI heart failure.

**Disclosures**

**Conflict of interest:** The authors declare that they have no conflicts of interest.
Human rights statements and informed consent: All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revisions. Informed consent was obtained from all patients who were in the study.

REFERENCES