Patients with ST-segment elevation of myocardial infarction miss out on early reperfusion: when to undergo delayed revascularization

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Abstract

Objective There are still a high proportion of patients with ST-segment elevation myocardial infarction (STEMI) missing out early reperfusion even in the primary percutaneous coronary intervention (PCI) era. Most of them are stable latecomers, but the optimal time to undergo delayed PCI for stable ones remains controversial. Methods We investigated all STEMI patients who underwent delayed PCI (2–28 days after STEMI) during 2007–2010 in Beijing and excluded patients with hemodynamic instability. The primary outcome was major adverse cardiovascular events (MACEs). Results This study finally enrolled 5,417 STEMI patients and assigned them into three groups according to individual delayed time (Early group, 55.9%; Medium group, 35.4%; Late group, 8.7%). During 1-year follow-up, MACEs occurred in 319 patients. The incidence of MACEs were respectively 7.1%, 5.6% and 6.7% among three groups. The Medium group had less recurrent myocardial infarction plus cardiac death (hazard ratio, 0.525; 95% confidence interval, 0.294–0.938, \( P = 0.030 \)) than Late group and less repeat revascularization (hazard ratio, 0.640; 95% confidence interval, 0.463–0.883, \( P = 0.007 \)) than Early group in pairwise comparisons. We depicted the incidence of major adverse cardiovascular event (MACE) by delayed time as a quadratic curve and found the bottom appeared at day 14. Conclusions The delayed PCI time varied in the real-world practice, but undergoing operations on the second week after STEMI had greater survival benefit and less adverse events for whom without early reperfusion and hemodynamic instability.

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1 Introduction

Primary percutaneous coronary intervention (PCI) has become the first-choice reperfusion therapy for ST-segment elevation myocardial infarction (STEMI) during the past decade, but the proportion of primary PCI is still low in some countries and regions.\(^{1-4}\) Prehospital and treatment delay are major contributors to under-utilization of primary PCI, leading to performing PCI outside the recommended time-window.\(^{5,6}\) In China, only about one third (29.8–38.9%) STEMI patients received primary PCI in recent 5 years and most of else patients had to receive delayed revascularization.\(^{7}\) Current guidelines tend to widen the time-window of primary PCI to 24 hours for stable patients and recommend late coronary patency in the presence of hemodynamic or electrical instability or continuing ischemic symptoms.\(^{8,9}\) A meta-analysis included 10 trials and 3,560 STEMI latecomers, who were randomized to delayed PCI (range 1–26 days after STEMI) or optimal medical therapy (OMT), demonstrated that late revascularization improved survival (all-cause mortality) as compared with OMT during a follow-up period of 2.8 years.\(^{10}\) Subsequent meta-analysis indicated that late revascularization of an occluded infarct-related artery (IRA) could improve left ventricular systolic function and remodeling.\(^{11,12}\) However, the time of performing delayed PCI varies among...
hospitals in the real-world,\textsuperscript{[13]} and the outcomes of different operation time are still not clear. In recent years, the rapid development of Beijing health information system provides an opportunity to monitor cardiovascular disease morbidity and mortality based on routinely collected administrative data at the city level.\textsuperscript{[14,15]} Based on the validated data from this system, we planned to investigate the current situation of delayed PCI and prognosis for different operation times. These data will have a guiding significance for the management of PCI and the design of future clinical trials.

2 Methods

2.1 Data sources and definition

We obtained administrative data from the Beijing Hospital Discharge Information System (HDIS), which covered all secondary and tertiary nonmilitary hospitals in Beijing. So far, there has been over 162 hospitals to report their discharge abstracts through this system routinely. Hospitalization records were coded by the International Classification of Diseases 10th revision (ICD-10) and operations or procedures were coded by the International Classification of Diseases Clinical Modification of 9th Revision (ICD-9-CM-3). The coding has not changed during the study period. In our study, STEMI was coded as I21.0–I21.3, I22.0, I22.1, and I22.8 in the principal discharge diagnosis.\textsuperscript{[2]} We identified comorbidities according to codes in the secondary discharge diagnoses (up to 7 diagnoses), and identified operation records such as percutaneous coronary intervention coded as 00.66, 36.01, 36.02, 36.05, 36.06, and 36.07 and coronary artery bypass grafting (CABG) coded as 36.1 in the similar way. The Vital Registration Monitoring System, recording all in- and out-hospital deaths of Beijing residents, is managed by the Beijing Center for Disease Control and Prevention (CDC). Reported death due to ischemic heart disease (I20.XX–I25.XX, I46.XX or R96.XX–R99.XX) were extracted and identified by linking individual hospitalization data with mortality data. The follow-up methods in this study therefore was different from ones in traditional studies such as hospital visiting or telephone call. We used the whole city’s data to monitor individual each hospitalization record and the death record if happened. It could outline the track of when the AMI occurred, developed and died during monitoring periods. The accuracy and completeness of the International Classification of Diseases (ICD) code-based diagnoses/procedures were validated in our previous studies.\textsuperscript{[14,15]}

2.2 Study population

All in-hospital STEMI patients (principal diagnosis) who received PCI within 2–28 calendar days from STEMI/admission between January 2007- December 2010 at secondary and tertiary hospitals in Beijing city were included. We excluded patients who received early reperfusion including thrombosis or primary PCI in admission. We also excluded patients with hemodynamic instability or contraindications to therapy including cardiogenic shock, ventricular arrhythmias, severe heart failure, renal dysfunction or cancer. Moreover, patients with the hospital length of stay (LOS) of zero were excluded because they were possibly transferred to other hospitals or died within 24 hours of admission.\textsuperscript{[2]} Enrolled patients were divided into three groups according to the time of PCI: PCI on day 2–7 (Early group), on day 8–14 (Medium group) and on day 15–28 (Late group) after STEMI, respectively (Figure 1).

2.3 Outcome measures

The primary endpoint, that was major adverse cardiovascular events (MACEs), was a composite of cardiac death, recurrent myocardial infarction (MI) and repeat revascularization procedures. Each component was also assessed as the secondary endpoint. Cardiac death was defined as in- or out-hospital mortality due to ischemic heart disease or sudden cardiac arrest. Recurrent myocardial infarction (ReMI) referred to any documented readmission with primary di-
agnosis of acute myocardial infarction. Repeat revascularization procedures referred to performing either PCI or CABG in subsequent hospitalizations.

2.4 Statistical analysis

Descriptive data are reported as the mean ± SD or frequencies expressed as percentages. Pearson χ2/Kruskal–Wallis rank-sum tests and t-test were used for comparison among categorical and continuous variables, respectively. We compared rates of primary and secondary endpoints events using Kaplan–Meier survival curves and log-rank statistics with a two-sided alpha level of 0.05. The Cox proportional-hazard models were used to generate the covariate-adjusted hazard ratio with eleven covariates including age, gender, residential zone, index-hospital level, drugs eluting stents, MI location and presence of heart failure, diabetes, hypertension, hyperlipidemia or ischemic stroke. We used Schoenfeld residuals to test the assumptions of proportionality of the hazard ratios for covariates. The relationship between onset-to-invention intervals and the incidence of primary outcomes adjusted by age and gender was fitted as a continuous function and depicted with a quadratic regression model. All analyses were performed with SAS, version 9.4 64-bit (SAS Institute Inc., Cary, NC). A 2-tailed \( P < 0.05 \) was regarded as statistically significant in all calculations.

3 Results

3.1 Delayed PCI time

5,417 STEMI patients from 67 PCI-capable hospitals were finally enrolled after 4 years’ surveillance. Delayed PCI were performed within 2–7 days from admission (Early group) in 3,030 (55.9%) patients, as compared with 1,915 (35.4%) patients within 1–2 weeks from admission (Medium group) or 472 (8.7%) patients within 3–4 weeks from admission (Late group). The overall distribution of PCI time was left-skewed. The average time was 7 days, and over 90% patients received delayed PCI within two weeks. The peak numbers distributed at day 2 and day 7 (Figure 2A).

Figure 2. The distribution of delayed PCI time. (A): showed the relationship between operation time and the incidence of 1-year MACEs. The relationship between operation time and incidence of MACE adjusted by demographic and clinical characteristics was depicted as a ‘U’ shape. The bottom occurred on the second week from STEMI onset. Also, the distribution of operation time was left-skewed and the number of delayed PCI reached the top on the day 2 and day 7 (Figure 2A).
The distribution of time also varied across hospitals and institutions. We sorted and quartered the hospitals due to their annual interventional quantity. Hospitals in quartile 1 (high-volume centers) performed the delayed PCI earlier than ones in quartile 4 (6.2 ± 3.8 days vs. 9.2 ± 5.6 days, \( P < 0.001 \)). We then observed the distribution of time by gender, age and hospital level (Figure 2B-D). The time trends in different subgroups were similar but the proportions were different. The proportion of Late group in female were significantly higher than that in male. The proportion of Early group in young patients (age ≤ 75 years-old) or tertiary hospitals were significantly higher than those in the younger patients or secondary hospitals. Multinomial logistic regression analysis suggested the delay of PCI was associated with advanced age (> 75 years old), index-admission in secondary hospitals and heart failure (all \( P < 0.05 \)) after adjusting potential risk factors including gender, comorbidities and MI location.

### 3.2 Patients

Baseline characteristics were not well balanced among the study groups (Table 1). Patients in Late group tended to be older, more females, more patients from suburban areas, more index-admission in secondary hospitals or more transferring for PCI compared to those in Early or Medium group. The prevalence of comorbidities including hypertension, hyperlipidemia and diabetes were similar among three groups but the proportion of heart failure was higher in Late group. In addition, the proportion of implanting drug eluting stents (DES) was higher in Early group than the other two groups.

### Table 1. Baseline patient characteristics.

|                      | Early group (\( n = 3030 \)) | Medium group (\( n = 1915 \)) | Late group (\( n = 472 \)) | \( P \) value |
|----------------------|-------------------------------|-------------------------------|--------------------------|--------------|
| Age, yrs             | 58.98 ± 11.54                 | 59.84 ± 11.68                 | 61.58 ± 11.91           | < 0.001      |
| Female               | 608 (20.1%)                   | 403 (21.0%)                   | 119 (25.2%)             | 0.037        |
| Residential zone*    |                               |                               |                          | < 0.001      |
| Urban area           | 1869 (67.3%)                  | 1105 (62.6%)                  | 252 (58.7%)             |              |
| Suburban area        | 908 (32.7%)                   | 660 (37.4%)                   | 177 (41.3%)             |              |
| Tertiary hospitals   | 2369 (78.2%)                  | 1263 (66.0%)                  | 257 (54.4%)             | < 0.001      |
| Transfer for PCI     | 90 (3.0%)                     | 221 (11.5%)                   | 198 (41.9%)             | < 0.001      |
| LOS, days            | 9.17 ± 4.68                   | 13.38 ± 5.35                  | 17.52 ± 8.57            | < 0.001      |
| Anterior-wall MI     | 1648 (54.4%)                  | 1071 (55.9%)                  | 258 (54.7%)             | 0.089        |
| DES*                 | 1730 (57.1%)                  | 814 (42.5%)                   | 91 (19.3%)              | < 0.001      |
| Heart Failure        | 591 (19.5%)                   | 321 (16.8%)                   | 125 (26.5%)             | < 0.001      |
| Hypertension         | 1717 (56.7%)                  | 1084 (56.6%)                  | 289 (61.2%)             | 0.157        |
| Hyperlipidemia       | 1303 (43.0%)                  | 785 (41.1%)                   | 204 (43.2%)             | 0.385        |
| Diabetes Mellitus    | 886 (29.2%)                   | 585 (30.5%)                   | 151 (32.0%)             | 0.370        |
| Ischemic stroke      | 50 (1.7%)                     | 37 (1.9%)                     | 18 (3.8%)               | 0.007        |

Data were presented as \( n \) (%) or mean ± SD. *Urban area referred to Xicheng, Dongcheng, Haidian, Chaoyang, Fengtai and Shijingshan district, Beijing. Suburban area referred to Mentougou, Fangshan, Daxing, Changping, Shunyi, Tongzhou, Yanqing, Huairou, Miyun and Pinggu district, Beijing. *Partial operation records regarding stents (18.9%) and procedures (8.9%) were not complete. This table shows the comparison of baseline characteristics among three groups.

DES: drug eluting stent; LOS: length of hospitalization stays; MI: myocardial infarction; PCI: percutaneous coronary intervention.

### 3.3 Outcomes

At 1 year, the rate of major adverse cardiovascular event (MACE) from Medium group was the lowest among study groups (Figure 3A and Table 2), as well as in the landmark analysis (Figure 3B). The 1-year cumulative rate of MACE was 5.61% among patients in Medium group, as compared with 7.10% among patients in Early group (\( P = 0.045 \) by the log-rank test) or 6.71% among patients in Late group (\( P = 0.326 \) by the log-rank test). The adjusted hazard ratios (HR) by the multivariate Cox regression analysis were 0.769 [95% confidence interval (CI): 0.592–0.998, \( P = 0.048 \)] for Medium group versus Early group. In addition, the age was another risk factor for 1-year MACE (HR: 1.013; 95% CI: 1.002–1.024, \( P = 0.018 \)).

For the secondary endpoints, the cumulative rate of repeat revascularization was 3.67% among patients in Medium group, as compared with 5.48% among patients in
Figure 3. Kaplan-Meier curves for primary and secondary endpoints. (A): showed the Kaplan-Meier curves for 1-year MACE. There were significantly fewer MACEs in Medium group than other two groups at one year. Over time, the difference among three groups did not significantly changed. As most of events occurred within the first month, we further analyzed the primary endpoint with landmark analysis (B). Only patients free 28-day MACEs were enrolled in order to adjusting the impacts of early events. (C–F): showed the Kaplan-Meier curves for secondary endpoints including repeat revascularization (C), recurrent myocardial infarction (D), cardiac death (E) and recurrent myocardial infarction plus cardiac death (F). MACE: major adverse cardiovascular event; STEMI: ST-segment elevation myocardial infarction.

Early group ($P = 0.006$ by the log-rank test, Figure 3C). The cumulative rates of recurrent MI ($P = 0.146$ by the log-rank test, Figure 3D), cardiac death ($P = 0.011$ by the log-rank test, Figure 3E) and cardiac death plus recurrent MI ($P = 0.044$ by the log-rank test, Figure 3F) were lower among patients in Medium group, as compared with those among patients in Late group. The Medium group still had less cardiac death plus recurrent MI (HR, 0.525; 95% CI: 0.294–0.938, $P = 0.030$) than Late group and less repeat revascularization (HR, 0.640; 95% CI: 0.463–0.883, $P =$
Table 2. Primary and secondary outcomes.

| Outcome                          | Early group | Medium group | Late group |
|----------------------------------|-------------|--------------|------------|
| MACE                             | 194 (7.1%)* | 96 (5.6%)    | 29 (6.7%)  |
| Cardiac death                    | 22 (0.8%)   | 14 (0.8%)    | 9 (2.1%)*  |
| Recurrent MI                     | 57 (2.0%)   | 33 (1.8%)    | 13 (3.0%)  |
| Repeat revascularization         | 146 (5.5%)* | 61 (3.7%)    | 12 (3.0%)  |
| Cardiac death + recurrent MI     | 76 (2.5%)   | 45 (2.4%)    | 19 (4.0%)* |

Data were presented as n (%) or mean ± SD. P values were calculated by the log-rank test. The cumulative event rates were calculated by Kaplan–Meier analysis. *Referred to there was a significant difference (P < 0.05 by the log-rank test) in the corresponding endpoint events between Medium group and Early group. #referred to there was a significant difference (P < 0.05 by the log-rank test) in the corresponding endpoint events between Medium group and Late group.

MACE refers to major adverse cardiovascular event including cardiac death, recurrent MI or repeat revascularization. MACE: major adverse cardiovascular event; MI: myocardial infarction.

In advanced age (> 75 years-old) subgroup, the 1-year cumulative rate of MACE was 5.6% among patients in Medium group, as compared with 11.7% among patients in Early group (P = 0.032 by the log-rank test) or 9.8% among patients in Late group (P = 0.215 by the log-rank test). The HR was 0.460 (95% CI, 0.222–0.954; P = 0.037) for Medium group versus Early group.

4 Discussion

Our study focused on the patients who were in the "gray zone" of procedural timing recommended by guidelines. These patients usually missed out the best time for early reperfusion therapy and did not show evident hemodynamic instability. We found lower event rate among patients undergoing PCI on the second week, especially in side of reducing repeat revascularizations. In addition, we found the advanced age was associated with the delay of time and elder patients had more survival benefits in Medium group. As we known, this study is the first one addressing the issue of time distribution and survival benefit regarding delayed PCI based on the whole-area unselected population.

Previous studies have proven that a portion of ischemic myocardium succumbs to necrosis in a time-dependent and rapid way. At the phase of rapid progression of ischemic myocardium to necrosis, the earlier reperfusion therapy is performed, the greater the amount of myocardium can be saved. Whereas there is a large amount of viable myocardium presenting in the area at risk in latecomers with STEMI. For example, the residual flow in the infarct-related artery of those presenting 12–48 hours after symptoms onset could increase to about 50%. Residual anterograde blood flow may assure a low level of perfusion for stunned or hibernated myocardium and extend the salvageable time-window to several days later. Sim et al. evaluated the efficacy of PCI in 2,344 stable patients with STEMI presenting 12 to 72 hours after symptom onset and found that PCI was associated with significant improvement in the 12-month clinical outcome. Our study found that there were a large amount of patients receiving delayed PCI in current clinical practice, although the time was different. The pathologic theory thought that myocardial edema subsided and myocardial scarring started to form on the second week after myocardial infarction. This was consistent with our result that there was a significant reduction in MACEs in Medium group. In contrast, the Occluded Artery Trial (OAT) explored outcomes with PCI over medical therapy in stable patients randomized to 3–28 calendar days following an index myocardial infarction. They found no interaction between time to randomization defined as a continuous or categorical variable with a cut-point of 7 days post-MI and treatment effect. We thought it was possibly due to too wide time span in grouping. If we merged latter two group (after 1 week) into one group, the results were similar as the Late group had more recurrent MI and cardiac death than the former ones.

As expected, the amount of procedures was higher on day 2 and day 7 during all periods. Current guidelines suggested that the ischemia-driven strategy with primary PCI could extend to 48 hours for a part of symptomatic latecomers. Others would like wait one week or longer to re-
ceive revascularization until out of hemodynamic instability or high thrombus burden. Of note, there was a trend toward less revascularization when delayed PCI was performed after one week, which might be associated with excess distal embolization or reperfusion injury in premature procedures.\cite{15,16} It deserved to concern about the cost-effectiveness for repeat revascularization.

This study has several limitations. It is an observational cohort study with longitudinal administrative data analyzed. Assignment for revascularization procedure was not through randomization, which could be effected by either physician decision or patients’ preference. Randomized controlled trials were, however, hard to conduct as huge ethical hurdle and recruitment difficulty in clinical settings. For example, the OAT study showed that only two patients per year per center were enrolled on average throughout the research, reflecting a under-representation population.\cite{22} In contrast, real-world study could avoid those difficulties and exhibit clear situations. Furthermore, a small portion of STEMI patients could readmit to military affiliated hospitals and be monitored out of range.

In conclusion, performing delayed PCI on the second week after onset for STEMI latecomers who missed early reperfusion and hemodynamic stability is relatively feasible and safe in the routine clinical practice. Our data suggested that it could improve survival benefits, especially for elder patients, in reducing repeat revascularizations or recurrent MI plus cardiac death. We recommend further clinical trials to validate this benefit.

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References

1 Dai X, Kaul P, Smith SC Jr, et al. Predictors, treatment, and outcomes of STEMI occurring in hospitalized patients. *Nat Rev Cardiol* 2016; 13: 148–154.
2 Alexander T, Mullasari AS, Joseph G, et al. A system of care for patients with ST-segment elevation myocardial infarction in India: the tamil nadu-ST-segment elevation myocardial infarction program. *JAMA Cardiol* 2017; 2: 498–505.
3 Zhang Y, Huo Y. Early reperfusion strategy for acute myocardial infarction: a need for clinical implementation. *J Zhejiang Univ Sci B* 2011; 12: 629–632.
4 Krumholz HM, Herrin J, Miller LE, et al. Improvements in door-to-balloon time in the United States, 2005 to 2010. *Circulation* 2011; 124: 1038–1045.
5 Nielsen PH, Terkelsen CJ, Nielsen TT, et al. System delay and timing of intervention in acute myocardial infarction (from the Danish Acute Myocardial Infarction-2 [DANAMI-2] trial). *Am J Cardiol* 2011; 108: 776–781.
6 Peng YG, Feng JJ, Guo LF, et al. Factors associated with prehospital delay in patients with ST-segment elevation acute myocardial infarction in China. *Am J Emerg Med* 2014; 32: 349–355.
7 Huo Y. Current status and development of percutaneous coronary intervention in China. *J Zhejiang Univ Sci B* 2010; 11: 631–633.
8 Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; 33: 2569–2619.
9 Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/ AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/ AHA Guideline for the Management of ST-Elevation Myocardial Infarction. *J Am Coll Cardiol* 2016; 67: 1235–1250.
10 Abbate A, Biondi-Zoccai GG, Appleton DL, et al. Survival and cardiac remodeling benefits in patients undergoing late percutaneous coronary intervention of the infarct-related artery: evidence from a meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2008; 51: 956–964.
11 Appleton DL, Abbate A, Biondi-Zoccai GG, et al. Late percutaneous coronary intervention for the totally occluded infarct-related artery: a meta-analysis of the effects on cardiac function and remodeling. *Catheter Cardiovasc Interv* 2008; 71: 772–781.
12 Malek LA, Silva JC, Bellenger NG, et al. Late percutaneous coronary intervention for an occluded infarct-related artery in patients with preserved infarct zone viability: a pooled analysis of cardiovascular magnetic resonance studies. *Cardiol J* 2013; 20: 552–559.
13 Zhang SY, Hu DY, Sun YH, et al. Current management of patients with ST elevation myocardial infarction in Metropolitan Beijing, China. *Clin Invest Med* 2008; 31: E189–97.
14 Xie W, Li G, Zhao D, et al. Relationship between fine particulate air pollution and ischaemic heart disease morbidity and mortality. *Heart* 2015; 101: 257–263.
15 Zhang Q, Zhao D, Xie W, et al. Recent trends in hospitalization for acute myocardial infarction in Beijing: increasing overall burden and a transition from ST-segment elevation to non-ST-Segment elevation myocardial infarction in a population-based study. *Medicine (Baltimore)* 2016; 95: e2677.
16 McDermott K, Maynard C, Trivedi R, et al. Factors associated with presenting > 12 hours after symptom onset of acute
myocardial infarction among Veteran men. BMC Cardiovasc Disord 2012; 12: 82.

17 Schömig A, Mehilli J, Antoniucci D, et al. Mechanical reperfusion in patients with acute myocardial infarction presenting more than 12 hours from symptom onset: a randomized controlled trial. JAMA 2005; 293: 2865–2872.

18 Schömig A, Ndrepepa G, Kastrati A, et al. Late myocardial salvage: time to recognize its reality in the reperfusion therapy of acute myocardial infarction. Eur Heart J 2006; 27: 1900–1907.

19 Sawyer DB, Loscalzo J. Myocardial hibernation: restorative or preterminal sleep?. Circulation 2002; 105: 1517–1519.

20 Sim DS, Jeong MH, Ahn Y, et al. Benefit of percutaneous coronary intervention in early latecomers with acute ST-segment elevation myocardial infarction. Am J Cardiol 2012; 110: 1275–1281.

21 Menon V, Pearte CA, Buller CE, et al. Lack of benefit from percutaneous intervention of persistently occluded infarct arteries after the acute phase of myocardial infarction is time independent: insights from Occluded Artery Trial. Eur Heart J 2009; 30: 183–191.

22 Galiuto L, Paraggio L, Liuzzo G, et al. Predicting the no-reflow phenomenon following successful percutaneous coronary intervention. Biomark Med 2010; 4: 403–420.