One-Year Clinical Outcome of Interventionist- Versus Patient-Transfer Strategies for Primary Percutaneous Coronary Intervention in Patients With Acute ST-Segment Elevation Myocardial Infarction

Results From the REVERSE-STEMI Study

Qi Zhang, MD; Rui Yan Zhang, MD; Jian Ping Qiu, MD; Jun Feng Zhang, MD; Xiao Long Wang, MD; Li Jiang, MD; Min Lei Liao, MD; Jian Sheng Zhang, MD; Jian Hu, MD; Zheng Kun Yang, MD; Wei Feng Shen, MD, PhD

Background—Traditional reperfusion options for patients with acute ST-segment elevation myocardial infarction (STEMI) presenting to non-primary percutaneous coronary intervention (PPCI)-capable hospitals generally include onsite fibrinolytics or emergency transfer for PPCI. A third option, involving interventionalist transfer, was examined in the REVERSE-STEMI study.

Methods and Results—A total of 334 patients with acute STEMI who presented to 5 referral hospitals with angiographic facilities but without interventionalists qualified for PPCI were randomized to receive PPCI with either an interventionalist- (n = 165) or a patient-transfer (n = 169) strategy. The primary end point of door-to-balloon (D2B) time and secondary end points of left ventricular ejection fraction and major adverse cardiac events (MACE) at 1-year clinical follow-up were compared between the 2 groups. Compared with the patient-transfer strategy, the interventionalist-transfer strategy resulted in a significantly shortened D2B time (median, 92 minutes versus 141 minutes; P < 0.0001), with more patients having first balloon angioplasty within 90 minutes (21.2% versus 7.7%, P < 0.001). This treatment strategy also was associated with higher left ventricular ejection fraction (0.60 ± 0.07 versus 0.57 ± 0.09, P < 0.001) and improved 1-year MACE-free survival (84.8% versus 74.6%, P = 0.019). Multivariate Cox proportional hazards modeling revealed that the interventionalist-transfer strategy was an independent factor for reduced risk of composite MACE (hazard ratio, 0.63; 95% CI, 0.45 to 0.88; P = 0.003).

Conclusions—The interventionalist-transfer strategy for PPCI may be effective in improving the care of patients with STEMI presenting to a non-PPCI-capable hospital, particularly in a congested cosmopolitan region where patient transfers could be prolonged.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00713557.

Key Words: myocardial infarction • angioplasty • stents • outcome and process assessment
Angiographic facilities lack interventionalists qualified for PPCI in China, where the volume of PCI has increased dramatically in recent years. The strategy of transferring patients with STEMI in large cities is still not consummate. In the RESVERSE-STEMI study, we sought to examine whether an interventionalist-transfer strategy for PPCI could further shorten door-to-balloon (D2B) time and improve 1-year clinical outcome in patients with acute STEMI.

**WHAT IS KNOWN**
- Primary percutaneous coronary intervention (PPCI) is the preferred treatment option for patients with ST-segment elevation myocardial infarction (STEMI) presenting to PPCI-capable hospitals.
- Interhospital transfer often is used for patients with STEMI who present to hospitals without PPCI capability.

**WHAT THE STUDY ADDS**
- This multicenter, prospective, randomized clinical study compares the 1-year outcomes of patients with STEMI treated by a strategy of interhospital patient transfer versus that of interventionalist transfer to regional hospital PPCI.
- The interventionalist-transfer strategy resulted in significantly shorter door-to-balloon times and better 1-year clinical outcomes.
- This novel strategy of interventionalist transfer for PPCI may improve the care of patients with STEMI presenting to a non-PPCI-capable hospital, particularly in regions where patient transfers are prolonged by delays in transport.

**Methods**

**Study Design and Patient Population**
A total of 351 consecutive patients with STEMI within 12 hours of symptom onset who presented to 5 referral hospitals with angiographic facilities but without interventionalists qualified for PPCI were enrolled between November 2005 and November 2007. Seventeen patients were excluded before randomization because of refusal of interventional treatment (n=13) or loss of consciousness on admission (n=4). The remaining 334 patients were randomized to receive PPCI using either an interventionalist-transfer group (n=165) or a patient-transfer group (n=169) strategy by a 24-hour computer-generated random-allocation system (Figure 1). One single tertiary hospital provided experienced interventionists to perform procedures in the referral hospitals or received referral patients and then performed PPCI in the tertiary-care hospital. The mean distance between referral and tertiary-care hospitals was 17.5 km (range, 10.7 to 25.4 km) (Figure 2). During the study period, 2 more qualified interventionists in the tertiary hospital were always on standby in case the local hospitals received patients with STEMI at the same time. For the interventionalist-transfer strategy, only 1 interventional cardiologist was sent from the tertiary hospital to the local hospitals. Patients were sent from a regional service center to the local hospitals and then transferred the patients to the tertiary hospital to receive PPCI. All referral hospitals had a coronary care unit and diagnostic cardiac catheterization laboratory. The cardiology interventional team, including operator, nurses, and technicians, was qualified and approved in performing elective PCI (minimum annual volume, 75 cases). For the care of patients with STEMI, a formal training program was implemented for technicians and nurses in the referral hospitals before starting the study. One of the 5 referral hospitals had cardiac surgery on site. The study protocol was approved by the hospital ethics committees of all participating centers, and written informed consent was obtained from all patients.

**Medical Treatment and Coronary Intervention**
All patients were treated with loading doses of aspirin (300 mg) and clopidogrel (300 mg) after a diagnosis of STEMI was made, but the use of platelet glycoprotein IIb/IIIa inhibitor (tirofiban) was at the discretion of physicians. PPCI, including balloon predilation and stent implantation, was performed only for infarct-related artery (IRA) with thrombolysis in myocardial infarction (TIMI) flow grade ≤2. Intracoronary stents were implanted as a final treatment option when the anatomy was suitable. Procedural success was defined as residual stenosis ≤20% after intervention; TIMI flow grade ≥2; and absence of death, emergency bypass surgery, and disabling cerebral events. After the procedure, clopidogrel (75 mg/d) was continued for at least 12 months in all patients because of the setting of MI, irrespective of implantation of either bare-metal or drug-eluting stents. Aspirin (100 mg/d) was prescribed indefinitely in all patients.

**End Points and Definitions**
The primary end point was D2B time measured from the patient’s arrival at the local hospital to first balloon inflation. The secondary end points included left ventricular ejection fraction and major adverse cardiac events (MACE), including death, recurrence of nonfatal MI, and target vessel revascularization at 1-year clinical follow-up. Death included cardiac and noncardiac death. Recurrence of nonfatal MI was defined as recurrent chest pain lasting ≥30 minutes after index procedure, associated with new Q waves or recurrent ST elevation ≥0.1 mV in at least 2 contiguous leads, and re-elevation of creatine kinase MB isoenzyme to at least twice the upper limit of normal and ≥50% above the previous value. Target vessel revascularization was defined as repeat PCI or surgical bypass for any segment of the target vessel. The occurrence of stent thrombosis according to the Academic Research Consortium (ARC) criteria was also monitored at one-year follow-up.

**Follow-Up**
Follow-up was completed by an interview of patients in the cardiology clinic or by telephone conversation with patients or their relatives every 3 months after discharge, and continued for ≥1 year. None of the hospital survivals were lost to follow-up. Relevant information regarding the patient’s state of health and medications was obtained. The follow-up process was monitored by the tertiary hospital, and 25% of the follow-up data provided by the referral hospital were checked by the tertiary hospital. In patients with MACE, a detailed, predesigned questionnaire was completed by the relevant physician. Transthoracic 2D echocardiography was performed in the local or tertiary hospitals where PCI was carried out. Left ventricular volumes and ejection fractions were determined with apical 4-chamber view using the modified Simpson method during hospitalization and at 6-month and 1-year follow-up. All MACE were continuously reviewed by the critical events committee members, who were blinded to treatment options, and echocardiographic studies were sent to a dependent core laboratory and analyzed by 2 experienced cardiologists who were blinded to randomization of the patients.

**Statistical Analysis**
Based on the results of National Registry of Myocardial Infarction-3/4 analysis with the median total D2B time reaching 180 minutes.
we hypothesized a 15% reduction in D2B time in the patient-transfer group because of the intracity transfer property and a 30% reduction in the interventionalist-transfer group. Accordingly, a total sample size of 362 patients (161 in each group) would provide 90% power to detect a difference with α=0.05, suggesting the robustness of our results.

Data are presented as mean±SD unless otherwise indicated. Continuous variables were compared using the Student t test or Wilcoxon rank sum test, and categorical variables were compared using the Fisher exact test. A 2-sided P<0.05 was accepted as significance. The MACE-free survival rate at 1-year follow-up was estimated with the Kaplan-Meier method, and the difference was assessed by the log-rank test. Univariate analysis and multivariable Cox proportional hazards modeling were used to determine the crude and adjusted hazard ratios of the interventionalist-transfer strategy for composite MACE at 1-year follow-up both in the overall population and in the subgroups. In detail, the multivariable Cox model regressed treatment effect, through the backward method with P for removal of <0.1, on all baseline demographic, clinical, and angiographic covariates, including age, sex, diabetes, hypertension, hypercholesterolemia, smoking, previous MI, previous PCI, heart rate, systolic blood pressure and Killip class at presentation, location of culprit vessel, degree of coronary artery disease, TIMI flow of the IRA before and after procedure, use of glycoprotein IIb/IIIa inhibitor, D2B time, and distance from a referral hospital to the tertiary hospital. Finally, the type of transfer strategy was modeled as an independent binary variable, and hazard ratios and 95% CIs were calculated. Data management and statistical analyses were conducted using SPSS version 10.0 (SPSS Inc; Chicago, IL) software.

Results

Baseline Characteristics and Medications
Baseline characteristics were not significantly different between the interventionalist- and patient-transfer groups, and medications at the end of 1-year follow-up were similar (Table 1). In the interventionalist- and patient-transfer groups, 78 (47.3%) and 85 (50.3%) patients were self-transferred to the referral hospitals, respectively (P=0.58), and the remaining patients were brought in by ambulance.
D2B Time and PPCI

Table 1. Baseline Characteristics and Medications

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interventionalist-Transfer Group (n=165)</th>
<th>Patient-Transfer Group (n=169)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65.1±10.3</td>
<td>63.9±11.1</td>
<td>0.41</td>
</tr>
<tr>
<td>Male sex</td>
<td>100</td>
<td>97</td>
<td>0.55</td>
</tr>
<tr>
<td>Aged &gt;65 years</td>
<td>73</td>
<td>71</td>
<td>0.68</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>35</td>
<td>41</td>
<td>0.51</td>
</tr>
<tr>
<td>Hypertension</td>
<td>117</td>
<td>125</td>
<td>0.53</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>56</td>
<td>62</td>
<td>0.60</td>
</tr>
<tr>
<td>Current smoker</td>
<td>68</td>
<td>59</td>
<td>0.24</td>
</tr>
<tr>
<td>Previous MI</td>
<td>31</td>
<td>23</td>
<td>0.20</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>13</td>
<td>11</td>
<td>0.63</td>
</tr>
<tr>
<td>HR at presentation, beats/min</td>
<td>101±22</td>
<td>89±28</td>
<td>0.11</td>
</tr>
<tr>
<td>Anterior infarction</td>
<td>110</td>
<td>103</td>
<td>0.28</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>99</td>
<td>98</td>
<td>0.71</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>133±28</td>
<td>123±31</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Table 2. Time to Reperfusion Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interventionalist-Transfer Group (n=165)</th>
<th>Patient-Transfer Group (n=169)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Door to balloon, min</td>
<td>92 (85±20)</td>
<td>141 (147±29)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Door to balloon &lt;90 min, n (%)</td>
<td>35 (21.2)</td>
<td>13 (7.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as median (mean±SD), unless otherwise indicated. NA indicates not available.

*Numbers at 1-year follow-up are indicated in parenthesis.

D2B Time and PPCI

With the interventionalist-transfer strategy, the D2B time was significantly reduced (median, 92 minutes versus 141 minutes; P<0.0001), and more patients had first balloon angioplasty within 90 minutes (21.2% versus 7.7%, P<0.0001) (Table 2). The treatment delay with the patient-transfer strategy (median, 49 minutes) was mainly due to extra time consumed on waiting for ambulance arrival at the local hospital (median, 21 minutes) and transferring the patient from emergency department to the catheterization laboratory in the tertiary hospital (median, 15 minutes).

Both the interventionalist- and the patient-transfer groups did not differ significantly with respect to use of tirofiban (66.1% versus 56.2%) and angiographic features, except for more TIMI flow grade 3 of the IRA in the interventionalist-transfer group (17.6% versus 10.1%, P<0.05). Stent implantation of the IRA during PPCI (80.6% versus 84.6%) or elective PCI before discharge was similar in the 2 groups. Drug-eluting stents were implanted in 96.2% and 100% of patients in the interventionalist- and patient-transfer groups, respectively, during PPCI (P=0.10).

Follow-Up Outcomes

During 1-year clinical follow-up, 10 patients in the interventionalist-transfer group and 18 in the patient-transfer group died; death occurred during the first 30 days in 6 and 10 patients, respectively. Recurrence of nonfatal MI occurred in 5 and 11 patients at 30 days and in 9 and 18 patients at 1-year follow-up in the interventionalist- and patient-transfer groups, respectively (Table 3). The 1-year MACE-free survival was significantly improved with interventionalist-transfer strategy (84.8% versus 74.6%, P=0.019) (Figure 3). Left ventricular ejection fraction was significantly higher in the interventionalist-transfer group than in the patient-transfer group during hospitalization and at 6-month and 1-year follow-up (Figure 4). The multivariate Cox proportional hazards model showed that D2B time (>90 minutes) continued to predict MACE at 1 year (hazard ratio, 2.24; 95% CI, 1.27 to 3.96; P=0.02), and the interventionalist-transfer strategy was an independent factor for reduced risk of MACE in overall patients (hazard ratio, 0.63; 95% CI, 0.45 to 0.88; P=0.003) and significantly improved 1-year clinical outcomes in patients with Killip class III to IV, multivessel disease, anterior infarction, female sex, and aged >65 years (Figure 5). However, distance from a referral hospital to tertiary center (<20 km) did not enter the final model (P=0.51).

Discussion

How to optimize the STEMI caring system in a large metropolitan region remains different from the system for a
rural geography of hospitals separated by >50 miles.¹ In the current study, we evaluated the effects of an interventionalist-transfer strategy for PPCI in Shanghai, China, where 17 million inhabitants and 31 hospitals qualified for PPCI existed at the time of the study. The results of this study demonstrated that interventionalist-transfer strategy is superior to patient-transfer strategy in reducing D2B and improving 1-year clinical outcome for patients with STEMI undergoing PPCI.

**Primary PCI and Transfer Strategy**

Over the past decade, PPCI has been recommended as the default reperfusion strategy,²⁻⁴,¹² and various models have been proposed in the system of care for patients with STEMI.¹³,¹⁴ For those presenting to a PPCI-capable hospital with experienced interventional cardiologists, clinical pathways with bypassing cardiac ward stay⁵⁻⁷ and direct ambulance-to-catheterization laboratory transfer⁷ have been implemented to shorten the D2B time. However, in real-world practice, only a minority of patients with STEMI are admitted directly to PPCI-capable hospitals,¹³ and PPCI may not be available in many hospitals because of geographical reasons and lack of PCI-qualified physicians.⁴,¹⁴,¹⁶ For patients presenting to non-PPCI-capable hospitals, an interhospital patient-transfer strategy was suggested.¹⁸

The REVERSE-STEMI study was conducted to prospectively compare the effects of PPCI with an interventionalist-transfer strategy versus a routine patient-transfer approach for patients with STEMI who present to a non-PPCI-capable hospital. Of note, all local hospitals in the current study were equipped with angiographic facilities and PCI materials and had nurses and paramedic personnel adequately trained to provide care for patients with STEMI and their acute problems. With interventionalist-transfer strategy, the experienced interventionalists in a tertiary hospital were on standby 24 hours/day, 7 days/week, and they could go directly to the local hospitals by taxi or private automobile once they received an emergency call. At the same time, the patient started to be loaded with aspirin and clopidogrel, or intravenous glycoprotein IIb/IIIa inhibitor (tirofiban) if necessary. Likewise, patients could be sent to the catheterization laboratory and an arterial sheath may be inserted in the index hospital before the arrival of an experienced interventionalist.

In this study, an increased rate of TIMI flow grade 3 of the IRA at initial angiogram in the interventionalist-transfer group may be, at least in part, related to earlier use of tirofiban.⁷,¹⁹ Such a strategy has resulted in significantly

### Table 3. Clinical Outcomes at One-Year Follow-Up

<table>
<thead>
<tr>
<th>Variables</th>
<th>Interventionalist-Transfer Group (n=163)</th>
<th>Patient-Transfer Group (n=169)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, n (%)</td>
<td>10 (6.1)</td>
<td>18 (10.7)</td>
<td>0.17</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>9 (5.5)</td>
<td>16 (9.5)</td>
<td>0.21</td>
</tr>
<tr>
<td>Non-cardiac death</td>
<td>1 (0.6)</td>
<td>2 (1.2)</td>
<td>0.58</td>
</tr>
<tr>
<td>Non-fatal reinfarction, n (%)</td>
<td>9 (5.5)</td>
<td>18 (10.7)</td>
<td>0.11</td>
</tr>
<tr>
<td>TVR, n (%)</td>
<td>8 (4.8)</td>
<td>10 (5.9)</td>
<td>0.81</td>
</tr>
<tr>
<td>PCI, n (%)</td>
<td>8 (5.0)</td>
<td>9 (5.3)</td>
<td>0.84</td>
</tr>
<tr>
<td>CABG</td>
<td>0</td>
<td>1 (0.6)</td>
<td>0.32</td>
</tr>
<tr>
<td>MACE, n (%)</td>
<td>25 (15.2)</td>
<td>43 (25.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Stent thrombosis, n (%)</td>
<td>4 (2.4)</td>
<td>5 (3.0)</td>
<td>0.76</td>
</tr>
<tr>
<td>Definite</td>
<td>2 (1.2)</td>
<td>2 (1.2)</td>
<td>0.98</td>
</tr>
<tr>
<td>Possible</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>0.99</td>
</tr>
<tr>
<td>Probable</td>
<td>1 (0.6)</td>
<td>2 (1.2)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Data are presented as n (%). PCI indicates percutaneous coronary intervention; TVR, target vessel revascularization; CABG, coronary artery bypass grafting; and MACE, major adverse cardiac events.

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Figure 3. MACE-free survival rate at 1-year clinical follow-up. MACE indicates major adverse cardiac events.
reduced D2B time and decreased rate of MACE at 1 year. For patients with Killip class III to IV, multivessel disease, anterior infarction, female sex, and advanced age (>65 years), the interventionalist-transfer strategy also exerted a significant beneficial effect on clinical outcomes compared with the patient-transfer strategy. Multivariate analysis revealed that the interventionalist-transfer strategy was an independent factor for reduced risk of composite MACE at 1-year follow-up.

Limitations and Perspectives
This study has several limitations. First, it was powered on D2B time. Nevertheless, the results demonstrated significant differences in clinical outcomes at 1-year follow-up between the 2 treatment strategies. This observation further substantiates the concept that time to treatment is an important prognostic determinant for patients with acute STEMI undergoing PPCI.5,20 Second, the interventionalist-transfer strategy required PCI facilities or materials and nurses or paramedics adequately trained to deliver care for patients with STEMI and their acute problems in the local hospitals. Because fundamental interventionalists in the local hospitals often have insufficient training for PPCI during their fellow course, the interventionalist-transfer strategy may provide an onsite training in the index hospital by the qualified interventionalists from the tertiary centers.4 Although onsite surgical backup was not available in 4 of the 5 referral hospitals, the safety and feasibility of PPCI in hospitals without onsite cardiac surgical backup have been demonstrated by previous studies.21–24 Third, compared with findings in contemporary

| Killip III-IV | 0.66 | 0.51-0.89 | 0.01 |
| Killip I-II | 0.87 | 0.61-1.29 | 0.12 |
| Single vessel disease | 0.82 | 0.66-1.06 | 0.21 |
| Multivessel disease | 0.68 | 0.55-0.85 | 0.04 |
| Non-diabetes | 0.89 | 0.71-1.14 | 0.18 |
| Diabetes | 1.01 | 0.68-2.40 | 0.45 |
| Non-anterior STEMI | 0.83 | 0.61-1.10 | 0.09 |
| Anterior STEMI | 0.74 | 0.59-0.93 | 0.02 |
| Female | 0.71 | 0.51-0.92 | 0.02 |
| Male | 0.91 | 0.72-1.44 | 0.11 |
| Age > 65y | 0.72 | 0.53-0.98 | 0.03 |
| Age ≤ 65y | 0.76 | 0.58-1.26 | 0.17 |
| All patients | 0.63 | 0.45-0.88 | 0.003 |

Figure 4. Left ventricular ejection fraction during hospitalization and at 6-month and 1-year follow-up.

Figure 5. The effect of different transfer strategies on composite major adverse cardiac events in subgroups. HR indicates hazard ratio; STEMI, ST-segment elevation myocardial infarction.
studies,14-26 and the proportion of patients with a D2B time <90 minutes was still relatively low in the interventionalist-transfer group; and glycoprotein IIb/IIIa inhibitors were not used in the patient-transfer group during ambulance transport. Recent studies have shown that prehospital initiation of tirofiban in the ambulance was safe and beneficial for patients with acute STEMI undergoing PCI.37 Finally, the current interventionalist-transfer strategy may be a tentative option in shortening D2B time for patients with STEMI and in physician training in a single city with hospitals located close to one another. This model may not be applied to rural geographic settings with long transfer distances.30,31

In the future, an improved ambulance network with direct field triage of patients with STEMI and an automated system to transmit ECGs or detailed instructions to paramedic personnel may lead to a rapid transfer of patients with possible STEMI to hospitals with a 24-hours/day, 7-days/week PCI service, further shortening D2B time and improving the STEMI caring system in a large metropolitan region like Shanghai.32,33

Conclusions
PPCI with an interventionist-transfer strategy may be a useful approach to improve the care of patients with STEMI presenting to a non-PPCI-capable hospital, particularly in a congested metropolitan region where patient transfers could be prolonged.

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Disclosures
None.

References


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