Safety and efficacy of a pharmaco-invasive reperfusion strategy in rural ST-elevation myocardial infarction patients with expected delays due to long-distance transfers

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Aims To determine the safety and efficacy of a pharmaco-invasive reperfusion strategy utilizing half-dose fibrinolysis combined with transfer for immediate percutaneous coronary intervention (PCI) in ST-elevation myocardial infarction (STEMI) patients presenting to remote rural hospitals. Primary PCI is preferred for STEMI if performed in a timely manner. However, <20% of STEMI patients transferred for PCI in the USA have door-to-balloon times <2 h.

Methods and results Prospective data from the Level 1 MI programme were analysed. All STEMI patients presenting to the Minneapolis Heart Institute or 31 referral hospitals received aspirin, clopidogrel, and unfractionated heparin (UFH) at the presenting hospital and those presenting to hospitals ≥60 miles away also received half-dose fibrinolytic with transfer for immediate PCI. From April 2003 through December 2009, we enrolled 2634 consecutive STEMI patients in the Level 1 MI database including 660 transferred from remote hospitals utilizing pharmaco-invasive therapy and 600 patients who presented directly to the PCI centre. There were no significant differences in 30-day mortality (5.5 vs. 5.6%; $P=0.94$), stroke (1.1 vs. 1.3%; $P=0.66$) or major bleeding (1.5 vs. 1.8%; $P=0.65$), or re-infarction/ischae mia (1.2 vs. 2.5%; $P=0.088$) in patients receiving a pharmaco-invasive strategy compared with patients presenting directly to the PCI centre, despite a significantly longer door-to-balloon time.

Conclusion Within a regional STEMI system of care, half-dose fibrinolysis combined with immediate transfer for PCI may be a safe and effective option for STEMI patients with expected delays due to long-distance transfer.

Keywords STEMI • Reperfusion • Transfer • Fibrinolysis • Pharmaco-invasive

Introduction

The optimal reperfusion strategy for ST-segment elevation myocardial infarction (STEMI) is primary percutaneous coronary intervention (PCI) if it can be performed in a timely manner by experienced providers.1,2 Only 25% of hospitals in the USA are capable of providing primary PCI and most are located in urban areas. To date, less than ideal treatment options exist for STEMI patients residing in rural areas located long distances from primary PCI-capable hospitals. These include fibrinolytic therapy (which restores normal coronary flow in only 50–55% of patients) or transfer to a PCI-capable hospital for primary PCI (which can result in significant delays to reperfusion). The most recent data from the National Cardiovascular Data Registry (2005–06)
indicate that 82% of STEMI patients transferred for primary PCI had door-to-balloon times of >120 min.3

Recently, a strategy of combining fibrinolysis followed by transfer for early PCI (“pharmaco-invasive PCI”) has been shown to be an effective reperfusion strategy for STEMI patients presenting to non-PCI hospitals compared with fibrinolysis alone with an ischaemia-guided rescue PCI strategy based on current guidelines.4–7 We report the outcomes from a regional STEMI system in Minnesota utilizing a pharmaco-invasive reperfusion strategy in STEMI patients presenting to rural hospitals geographically remote from the primary PCI hospital.

Methods

The Minneapolis Heart Institute at Abbott Northwestern (MHI-ANW) Hospital in Minneapolis, Minnesota, is a tertiary, cardiovascular centre with referral relationships with 31 community hospitals throughout Minnesota and western Wisconsin. In 2003, a regional system for the management of STEMI, the “Level 1 MI programme” was initiated using a standardized protocol for transfer of STEMI patients for primary or pharmaco-invasive PCI from community hospitals up to 210 miles from the PCI hospital. Currently 11 referral hospitals are <60 miles from MHI-ANW (designated as Zone 1 hospitals) and 20 referral hospitals are 60–210 miles from MHI-ANW (designated as Zone 2 hospitals). The detailed design and early results of the Level 1 MI programme have been previously reported.8,9 Consecutive STEMI patients treated in the “Level 1 MI” regional STEMI system are enrolled in an extensive prospective registry called the “Level 1 MI” database.

A standardized protocol with pre-printed standing orders was implemented at each hospital. Each patient received aspirin 325 mg p.o., clopidogrel 600 mg p.o., unfractionated heparin (UFH) 60 U/kg i.v. load (maximum 4000 U), 12 U/kg/h i.v. infusion (max 1000 U/h), and a beta-blocker (unless contraindicated) in the emergency department at the presenting hospital. Patients who presented to the PCI hospital (MHI-ANW) or were transferred from a Zone 1 hospital (<60 miles away) underwent primary PCI as the reperfusion method. Patients transferred from Zone 2 hospitals (≥60 miles) received half-dose fibrinolytic followed by emergency transfer for immediate PCI (pharmaco-invasive PCI). The decision regarding which fibrinolytic to use was based on the individual hospital formulary but was tenecteplase (TNK) most frequently. Contraindications to fibrinolysis included: active bleeding, significant closed head injury within 3 months, suspected aortic dissection, ischaemic stroke within 3 months, known intracranial neoplasm or prior intracranial haemorrhage, and out of hospital cardiac arrest with prolonged CPR. Femoral access was used for coronary angiography in nearly all cases.

Patients with STEMI or new left bundle branch block within 24 h of symptom onset were included in the MHI Level 1 MI programme and database. No patients were excluded from the protocol unless the physician determined that reperfusion therapy was inappropriate due to an underlying co-morbid condition, such as advanced cancer or end-stage dementia. All patients (including those with advanced age, out-of-hospital cardiac arrest, and cardiogenic shock) were included in the data analysis. Data were prospectively entered into a registry and included clinical, laboratory, electrocardiogram, angiographic, and follow-up information. Clinical outcome data at 30 days and 1 year were abstracted from the electronic medical record. In addition, all patients were contacted by telephone at 1 year to inquire about clinical events. Angiographic data included the culprit coronary artery, number of vessels with coronary artery disease, thrombolysis in myocardial infarction (TIMI) flow before and after intervention, and ejection fraction using American College of Cardiology National Cardiovascular Data Registry definitions.10 All data collection forms, discharge summaries, and angiographic reports were reviewed by one of the authors (D.M.L. or T.D.H.) to ensure accuracy.

Recent ischaemia was defined as recurrent ischaemic pain at rest (believed to be cardiac in origin) associated with electrocardiographic changes. Recurrent infarction was defined according to the Joint European Society of Cardiology/American College of Cardiology definition of myocardial infarction.11 Major bleeding was defined according to the TIMI definitions for bleeding.10

For the purposes of comparison, we established five patient groups (Figure 1). Group A (n = 600)—primary PCI patients who presented directly to the PCI hospital (MHI-ANW). Group B (n = 1163)—primary PCI patients transferred from hospitals located <60 miles (Zone 1) from the PCI hospital. Group C (n = 32)—pharmaco-invasive PCI patients transferred from hospitals located <60 miles (Zone 1) from the PCI hospital with anticipated delays due to inclement weather. Group D (n = 660)—pharmaco-invasive PCI patients transferred from hospitals located ≥60 miles (Zone 2) from the PCI hospital. Group E (n = 179)—primary PCI patients transferred from ≥60 miles (Zone 2).

Statistics

The prespecified primary groups of comparison were patients presenting directly to the PCI hospital treated with primary PCI (Group A) and those transferred from hospitals >60 miles away who received pharmaco-invasive PCI (Group D). We also compared patients receiving primary PCI at both the PCI hospital and Zone 1 (Group A + B) with those receiving a pharmaco-invasive approach (Group C + D) in both Zone 1 and Zone 2. Categorical variables are reported as the number of patients (%) with the characteristic, except for door-to-balloon and length of stay (LOS) values which are reported as the median, and the 25 and 75th percentiles. χ2 or Fisher’s exact tests were used to assess the statistical significance of categorical variables among combinations of groups. Length of stay and door-to-balloon values were transformed using ln(value + 1) to more closely approximate a normal distribution, and compared with t-tests.

A propensity-score method was used to identify comparable patients treated with the pharmaco-invasive approach and those receiving PPCL in Groups A and D. Multivariable logistic regression analysis, including all baseline characteristics, was performed to calculate the predicted probability of receiving pharmaco-invasive (propensity score) for each patient. A nearest-neighbour 1:1 matching algorithm was used to match subjects on the basis of the logit of the propensity score.

A stepwise logistic multivariable analysis was performed to look for independent factors related to 30-day mortality. The model had a c-statistic of 0.88, indicating excellent discrimination and a Hosmer–Lemeshow test statistic of 12.77 (P = 0.12), indicating that the model had good fit.

A P-value of 0.05 or less was considered statistically significant and all reported P-values are two-sided. All analyses were performed with Stata Version 11.0 (College Station, TX, USA).

Results

From April 2003 to December 2009, we enrolled 2634 consecutive STEMI patients in the Level 1 MI database of whom 600 presented to the PCI hospital (MHI-ANW), 1195 to Zone 1 hospitals
60 miles, and 839 to Zone 2 hospitals >60 miles from the PCI hospital (Figure 1). Primary PCI was the reperfusion strategy for 1942 (73.7%) including the 600 patients who presented to the PCI hospital (MHI-ANW) directly, 1163 transferred from hospitals located <60 miles (Zone 1), and 179 transferred from hospitals located >60 miles (Zone 2) from the PCI hospital. A pharmaco-invasive reperfusion strategy with half-dose fibrinolysis (97% TNK, 3% reteplase) was used in 692 (26.3%) patients including 660 from Zone 2 hospitals located >60 miles away and 32 from Zone 1 hospitals with weather-related transfer delays.

Baseline clinical characteristics are shown in Table 1. Primary PCI-treated patients presenting directly to the PCI hospital or transferred from Zone 1 hospitals (Group A and B) were compared with pharmaco-invasive PCI-treated patients transferred from Zone 1 or 2 hospitals (Group C and D). The pharmaco-invasive-treated patients were slightly older; otherwise, there were no statistically significant differences in baseline clinical characteristics.

Clinical outcome parameters are shown in Table 2. Median door-to-balloon times were 62 (44, 83) min for those presenting directly to the PCI hospital (Group A), 94 (80, 116) min for primary PCI patients transferred from Zone 1 hospitals (Group B), and 122 (100, 147) min for pharmaco-invasive-treated patients transferred from Zone 2 hospitals (Group D). The median door-to-needle time (arrival at the presenting hospital emergency department to administration of fibrinolytic) was 29 (20, 42) min for patients receiving fibrinolytic therapy prior to transfer.

Pre-PCI patency (TIMI 2 or 3 flow) was found in 73.6% of the pharmaco-invasive PCI-treated patients vs.40.3% in primary PCI patients (P < 0.001). Angiographic data comparing Group A vs. Group D are shown in Table 3. The time in minutes from fibrinolysis to angiography in Group D patients was <60 in 13%, 61–90 in 36%, 91–120 in 28%, 121–180 in 17%, and >180 in 6%.

A pre-specified prospective comparison of patients presenting directly to the PCI hospital, treated with primary PCI (Group A) with patients transferred from hospitals >60 miles from the PCI hospital (Zone 2) who received pharmaco-invasive PCI showed no significant differences with respect to 30-day mortality (5.5 vs. 5.6%; P = 0.94), stroke (1.3 vs. 1.1%; P = 0.66), recurrent ischaemia/myocardial infarction (2.5 vs. 1.2%; P = 0.088), or TIMI major bleeding (1.8 vs. 1.5%; P = 0.65). In addition, comparing the total group of patients treated with primary PCI (Group A and B) who presented to the PCI centre or were transferred from <60 miles (Zone 1) with the total group treated with pharmaco-invasive PCI (Group C and D) also showed no significant difference in 30-day mortality (5.6 vs. 5.8%; P = 0.67), stroke (0.9 vs. 1.2%; P = 0.48), recurrent ischaemia/myocardial infarction (1.5 vs. 1.3%; P = 0.67) or TIMI major bleeding (1.4 vs. 1.6%; P = 0.76).

In the propensity score matched cohort, all baseline characteristics exhibited excellent balance between Groups A and D. Of the 1260 patients, 75 were omitted due to an unknown baseline characteristic, with only 1 patient removed due to not achieving a suitable match. Of note, there was no difference in the 30-day mortality between the matched groups after adjustment for the propensity score, confirming our primary analyses. A multivariate analysis identified age, out-of-hospital cardiac arrest, and cardiogenic shock as independent predictors of 30-day mortality (Table 4).

Kaplan–Meier 1-year survival curves comparing primary PCI (Group A and B) treated patients with pharmaco-invasive PCI...
Table 1  
Baseline clinical characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>n</th>
<th>PPCI (A)</th>
<th>PCI (B)</th>
<th>Zone 1 (A)</th>
<th>Zone 1 (B)</th>
<th>Total (A)</th>
<th>Total (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Age ≥ 75</td>
<td>Male</td>
<td>Hyperlipidaemia</td>
<td>Hypertension</td>
<td>Diabetes</td>
<td>History of MI</td>
</tr>
<tr>
<td>Group E</td>
<td>PPCI, Zone 2</td>
<td>151</td>
<td>151 (25.2)</td>
<td>151 (25.2)</td>
<td>151 (25.2)</td>
<td>151 (25.2)</td>
<td>151 (25.2)</td>
<td>151 (25.2)</td>
</tr>
<tr>
<td>Group D</td>
<td>PI, Zone 2</td>
<td>160</td>
<td>160 (24.2)</td>
<td>160 (24.2)</td>
<td>160 (24.2)</td>
<td>160 (24.2)</td>
<td>160 (24.2)</td>
<td>160 (24.2)</td>
</tr>
<tr>
<td>Group C</td>
<td>PI, Zone 1</td>
<td>405</td>
<td>405 (23.0)</td>
<td>405 (23.0)</td>
<td>405 (23.0)</td>
<td>405 (23.0)</td>
<td>405 (23.0)</td>
<td>405 (23.0)</td>
</tr>
<tr>
<td>Group B</td>
<td>PPCI, Zone 1</td>
<td>254</td>
<td>254 (21.8)</td>
<td>254 (21.8)</td>
<td>254 (21.8)</td>
<td>254 (21.8)</td>
<td>254 (21.8)</td>
<td>254 (21.8)</td>
</tr>
<tr>
<td>Group A</td>
<td>PPCI, PCI hospital</td>
<td>618</td>
<td>618 (25.2)</td>
<td>618 (25.2)</td>
<td>618 (25.2)</td>
<td>618 (25.2)</td>
<td>618 (25.2)</td>
<td>618 (25.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>61.2 ± 14.6</td>
<td>61.8 ± 14.6</td>
<td>61.7 ± 14.6</td>
<td>63.3 ± 12.6</td>
<td>63.2 ± 13.5</td>
<td>63.1 ± 14.5</td>
</tr>
</tbody>
</table>

PPCI, primary percutaneous coronary intervention; PCI, percutaneous coronary intervention; PI, pharmaco-invasive; MI, myocardial infarction; CABG, coronary artery bypass graft; LBBB, left bundle branch block.
<table>
<thead>
<tr>
<th></th>
<th>Group A, PPCI, PCI hospital, n = 600</th>
<th>Group B, PPCI, Zone 1, n = 1163</th>
<th>Total PPCI, A + B, n = 1763</th>
<th>Group C, PI, Zone 1, n = 32</th>
<th>Group D, PI, Zone 2, n = 660</th>
<th>Total, PI, C + D, Zone 2, n = 692</th>
<th>Group E, PPCI, Zone 2, n = 179</th>
<th>P-value, A vs. D</th>
<th>P-value, PPCI vs. PI, A + B vs. C + D</th>
<th>P-value, Zone 2, D vs. E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Door-to-balloon</td>
<td>62 (44, 83)</td>
<td>94 (80, 116)</td>
<td>86 (68, 108)</td>
<td>112.5 (102, 141.5)</td>
<td>122 (100, 147)</td>
<td>121 (100, 146)</td>
<td>131 (107, 169)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chest pain-to-balloon</td>
<td>171.5 (118, 314)</td>
<td>190 (141, 304)</td>
<td>185 (135, 307)</td>
<td>238 (177.5, 379.5)</td>
<td>209.5 (160, 313.5)</td>
<td>210.5 (160.5, 316)</td>
<td>272 (192, 435)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mortality hospital</td>
<td>30 (5.0)</td>
<td>57 (4.9)</td>
<td>87 (4.9)</td>
<td>2 (6.3)</td>
<td>35 (5.3)</td>
<td>37 (5.4)</td>
<td>17 (9.5)</td>
<td>0.81</td>
<td>0.68</td>
<td>0.039</td>
</tr>
<tr>
<td>Mortality 30 days</td>
<td>33 (5.5)</td>
<td>66 (5.7)</td>
<td>99 (5.6)</td>
<td>3 (9.4)</td>
<td>37 (5.6)</td>
<td>40 (5.8)</td>
<td>19 (10.6)</td>
<td>0.94</td>
<td>0.87</td>
<td>0.017</td>
</tr>
<tr>
<td>Re-MI 30 days</td>
<td>10 (1.7)</td>
<td>10 (0.9)</td>
<td>20 (1.1)</td>
<td>1 (3.1)</td>
<td>7 (1.1)</td>
<td>8 (1.2)</td>
<td>2 (1.1)</td>
<td>0.35</td>
<td>0.96</td>
<td>0.95</td>
</tr>
<tr>
<td>Re-MI/ischaemia 30 days</td>
<td>15 (2.5)</td>
<td>12 (1.0)</td>
<td>27 (1.5)</td>
<td>1 (3.1)</td>
<td>8 (1.2)</td>
<td>9 (1.3)</td>
<td>2 (1.1)</td>
<td>0.088</td>
<td>0.67</td>
<td>0.92</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>11 (1.8)</td>
<td>14 (1.2)</td>
<td>25 (1.4)</td>
<td>1 (3.1)</td>
<td>10 (1.5)</td>
<td>11 (1.6)</td>
<td>3 (1.7)</td>
<td>0.65</td>
<td>0.76</td>
<td>0.88</td>
</tr>
<tr>
<td>Stroke 30 days</td>
<td>8 (1.3)</td>
<td>7 (0.6)</td>
<td>15 (0.9)</td>
<td>1 (3.1)</td>
<td>7 (1.1)</td>
<td>8 (1.2)</td>
<td>2 (1.1)</td>
<td>0.66</td>
<td>0.48</td>
<td>0.95</td>
</tr>
<tr>
<td>Length of stay</td>
<td>3 (2.5)</td>
<td>3 (2.4)</td>
<td>3 (2.4)</td>
<td>3 (2.4)</td>
<td>3 (2.4)</td>
<td>3 (2.5)</td>
<td>0.0017</td>
<td>0.050</td>
<td>0.0334</td>
<td></td>
</tr>
<tr>
<td>AICD implanted</td>
<td>18 (3.0)</td>
<td>54 (4.6)</td>
<td>72 (4.1)</td>
<td>0 (0)</td>
<td>19 (2.9)</td>
<td>19 (2.8)</td>
<td>6 (3.4)</td>
<td>0.90</td>
<td>0.11</td>
<td>0.74</td>
</tr>
</tbody>
</table>

PPCI, primary percutaneous coronary intervention; PCI, percutaneous coronary intervention; PI, pharmaco-invasive; MI, myocardial infarction AICD, automated implantable cardioverter defibrillator.

*PI group is significantly shorter.
Group C and D-treated patients are shown in Figure 2 and were nearly identical.

Intracranial haemorrhage occurred in two patients (0.3; 95% confidence interval, 0–0.7%) treated with high-dose fibrinolysis. Both patients survived neurologically intact. Although the LOS in the pharmaco-invasive group was statistically significant, the median LOS was 3 days for each group and, therefore, unlikely to be clinically relevant. There was also no difference in the requirement for automatic implantable cardiac defibrillators between any of the groups.

Of the 839 patients who presented initially to hospitals ≥ 60 miles (Zone 2) from the PCI hospital, 179 (21.3%) did not receive a fibrinolytic and were transferred for primary PCI. The median door-to-balloon time in this group was 131 (107, 169) min. Contraindication to fibrinolysis was the most common reason for exclusion from pharmaco-invasive therapy (Table 5). These patients had higher in-hospital (9.5 vs. 5.3%, P = 0.039) and 30-day mortality (10.6 vs. 5.6%, P = 0.17) compared with patients transferred from Zone 2 with pharmaco-invasive PCI. They were, however, higher risk patients as they were older with more risk factors (hypertension, prior history of MI, CABG, or PCI) and more likely to have had an out-of-hospital cardiac arrest (11.7 vs. 7.0%; P = 0.037), which was considered to be a relative contraindication to fibrinolysis.

**Discussion**

ST-elevation myocardial infarction patients who present to geographically isolated hospitals located long distances from a primary PCI-capable hospital frequently have delays to PCI of >120 min. For these patients, our results indicate that a pharmaco-invasive PCI strategy utilizing half-dose fibrinolysis, in addition to clopidogrel 600 mg and UFH, within the context of an organized regional network, maybe an equally effective and safe reperfusion strategy with results similar to those for patients presenting directly to a PCI-capable hospital.

Approximately 60 million people (20% of the US population) live >60 miles from a hospital capable of performing PCI.12 Within this population it is expected that ~175 000 patients per year will have a STEMI and because of geographical location these patients may not have access to timely PCI. Even in Denmark with an organized transfer system and shorter transfer distances, 65% of transferred STEMI patients experienced a system delay to reperfusion of >120 min.13 Reperfusion options for this group of STEMI patients include the following: (i) full-dose fibrinolysis and admission to the non-PCI hospital with ischaemia-guided transfer for rescue PCI, (ii) full-dose fibrinolysis with routine transfer for ischaemia-guided rescue PCI, (iii) transfer for primary PCI, (iv) full- or reduced-dose fibrinolysis followed by immediate transfer for early or delayed PCI (pharmacoinvasive).14

Primary PCI is the preferred reperfusion strategy when compared with fibrinolysis in STEMI patients if it can be performed in a timely manner by experienced centres. However, most would agree that the benefit of primary PCI over fibrinolysis is reduced when there is a significant delay related to transfer.15–17 A recent study by Lambert et al.18 showed that STEMI patients, who are transferred for primary PCI, as recommended by guidelines, with delays to reperfusion >90 min have significantly greater 30-day mortality.

An alternative strategy, in principle, is combining the advantage of fibrinolysis availability with the improved reperfusion with PCI. The results of early randomized clinical trials, comparing the combination of fibrinolysis followed by immediate PCI with primary PCI alone, were disappointing.19–22 It is important to note that the majority of the patients enrolled in these trials was randomized at or within short distances to a PCI centre where primary PCI remains the optimal reperfusion strategy. However, a recent retrospective analysis of the two largest trials, ASSENT IV and FINESSE, offered new insights regarding this group of STEMI patients.14,23,24 Facilitated PCI seemed to show a benefit in certain subgroups such as high-risk patients who presented early to spoke hospitals.

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### Table 3 Angiographic characteristics

<table>
<thead>
<tr>
<th>Culprit artery</th>
<th>Group A, ANW PPCI, (n = 600)</th>
<th>Group D, Zone 2 PI, (n = 660)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left main</td>
<td>5 (0.8)</td>
<td>6 (0.9)</td>
<td>0.89</td>
</tr>
<tr>
<td>LAD</td>
<td>195 (32.5)</td>
<td>219 (33.2)</td>
<td>0.80</td>
</tr>
<tr>
<td>LCx</td>
<td>73 (12.2)</td>
<td>79 (12.0)</td>
<td>0.92</td>
</tr>
<tr>
<td>RCA</td>
<td>203 (33.8)</td>
<td>244 (37.0)</td>
<td>0.25</td>
</tr>
<tr>
<td>Graft</td>
<td>24 (4.0)</td>
<td>16 (2.4)</td>
<td>0.11</td>
</tr>
<tr>
<td>No culprit</td>
<td>53 (8.8)</td>
<td>55 (8.3)</td>
<td>0.75</td>
</tr>
<tr>
<td>No culprit and negative markers</td>
<td>26 (4.3)</td>
<td>26 (3.9)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

TIMI flow pre:
- Flow: 0/1: 354 (59.7) vs. 171 (26.4), < 0.001
- Flow: 2/3: 239 (40.3) vs. 477 (73.6)

TIMI flow post:
- Flow: 0/1: 18 (3.0) vs. 18 (2.8), 0.80
- Flow: 2/3: 576 (97.0) vs. 629 (97.2)
- Ejection fraction: 46.6 ± 13.4 vs. 46.8 ± 13.5, 0.81

**Table 4 Multivariable model for predictors of death at 30 days (Group A + Group D)**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Coefficient (SE)</th>
<th>Odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>−8.327 (0.935)</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Agea</td>
<td>0.064 (0.012)</td>
<td>1.89 (1.49, 2.40)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Out of hospital cardiac arrest</td>
<td>2.002 (0.366)</td>
<td>7.40 (3.61, 15.17)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>2.512 (0.305)</td>
<td>12.33 (6.77, 22.43)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Odds ratio is per 10 year increment in age.

ANW: Abbott Northwestern Hospital; PCI: primary percutaneous coronary intervention; PI: pharmaco-invasive; LAD: left anterior descending; LCx: left circumflex; RCA: right coronary artery.
Several recent randomized clinical trials have demonstrated the benefit of fibrinolysis followed by immediate transfer for an early PCI (pharmaco-invasive) strategy compared with fibrinolysis with an ischaemia-guided, rescue PCI strategy in STEMI patients presenting initially to non-PCI hospitals. The CARESS-in-AMI trial included high-risk STEMI patients ($n = 600$) who were admitted to non-PCI hospitals in France, Italy, or Poland. All patients received half-dose reteplase, abciximab, heparin, and aspirin and were randomized to immediate transfer for PCI or admission to the local hospital and transfer for rescue PCI if needed. The primary outcome, a composite of death, re-infarction or refractory ischaemia at 30 days, occurred in 11% of the early PCI group compared with 17.2% in the standard care/rescue PCI group (hazard ratio, 0.21–0.87; $P = 0.004$). In the TRANSFER-AMI trial, high-risk STEMI patients ($n = 1059$) presenting to non-PCI hospitals in Canada were treated with full-dose fibrinolysis and then randomized to either immediate transfer to a PCI hospital with PCI performed within 6 h vs. standard treatment with rescue PCI if needed or delayed angiography. In the early PCI group the median time from randomization to PCI was 2.8 h. The primary endpoint, a composite of death, re-infarction, recurrent ischaemia, new or worsening congestive heart failure, or cardiogenic shock within 30 days, occurred in 11% of the early routine PCI group compared with 17.2% in the standard treatment group (relative risk with early PCI, 0.64; 95% CI, 0.47–0.87; $P = 0.004$).

In the NORDISTEMI trial, STEMI patients ($n = 266$) living in rural areas with $>90$ min transfer delays were treated with full-dose TNK, aspirin, enoxaparin, and clopidogrel and then randomized to immediate transfer for PCI or to standard management in the local hospital with an ischaemia-guided rescue PCI strategy. The primary outcome, a composite of death, re-infarction, stroke, or new ischaemia at 12 months was 21% in the early PCI group vs. 27% in the standard treatment group (hazard ratio: 0.72; 95% CI: 0.44–1.18; $P = 0.19$). Even though the primary endpoint did not reach significance, the composite of death, re-infarction, or stroke at 12 months was significantly reduced in the early PCI group (6 vs. 16%, hazard ratio: 0.36, 95% CI: 0.16–0.81, $P = 0.01$).

In all three of these randomized trials there was no significant increase in major bleeding. These three trials were included in a recent meta-analysis which demonstrated that routine early PCI following fibrinolysis, in patients presenting to non-PCI hospitals, leads to a significant reduction in re-infarction, recurrent ischaemia, and the combined endpoint of death and re-infarction at 30 days with no significant increase in bleeding complications. Based on these results, the 2010 European Society of Cardiology and the European Association for Cardio-Thoracic Surgery (ESC-EACTS) guidelines on myocardial revascularization has made a class Ia recommendation for transfer of all post-fibrinolysis STEMI patients to...
a PCI-capable hospital for immediate rescue PCI if fibrinolysis is unsuccessful or coronary angiography within 3–24 h and delayed PCI as needed.\textsuperscript{15}

The Strategic Reperfusion Early After Myocardial Infarction (STREAM) trail, currently enrolling patients, is an open label, prospective randomized international multicentre trial comparing primary PCI with a pharmaco-invasive strategy with full dose (patients < 75 years) or half-dose (patients > 75 years) TNK in STEMI patients presenting < 3 h from symptom onset if PCI is not feasible within 60 min. In this protocol, patients who receive fibrinolysis undergo diagnostic angiography and PCI in 6–24 h if there is resolution of ST-elevation or rescue PCI if reperfusion fails within 90 min.\textsuperscript{24}

Our data from real-world experience, which included all STEMI patients without exclusions, are consistent with these randomized clinical trials and confirm the safety and efficacy of a pharmaco-invasive PCI strategy for rural STEMI patients in the USA who do not have timely access to primary PCI. Our protocol differed from the ongoing STREAM trial in that we included patients with symptoms up to 24 h, and used half-dose fibrinolysis for all age groups, and PCI was performed as early as possible.

The exact pharmacologic regimen and timing of PCI following fibrinolysis remains unclear. As our regional STEMI network expanded in 2003 and 2004,\textsuperscript{8,9} it was uncertain whether patients transferred from non-PCI centres > 60 miles from the PCI centre would achieve total door-to-balloon times < 120 min. Therefore, after careful consideration of the available data including the design of the CARESS-in-AMI study, the MHI MI Committee elected to use one-half dose of TNK in addition to aspirin, clopidogrel, and IV UFH for patients in Zone 2 (61–120 miles from the PCI centre). This decision was based on the TNK patency results described in TIMI 10A and 10B\textsuperscript{27,28} and the synergistic effects of clopidogrel with fibrinolytic agents described in CLARITY and COMMIT.\textsuperscript{29,30} This decision was then followed by careful quality assurance, patient-by–patient, and month-to-month to monitor both the safety and efficacy results which have been reported here. With regard to the timing of PCI following fibrinolysis, ESC guidelines currently recommend angiography 3–24 h following fibrinolysis. Based on the design of our system, the majority (64%) of patients from Zone 2 receives angiography 60–120 min post-fibrinolysis. A significant number of patients in the randomized controlled trials comparing pharmaco-invasive PCI with standard therapy have also received PCI this early. For example, in TRANSFER-AMI ~5% of patients receive PCI < 60 min and 25% < 120 min following fibrinolysis; in CARESS-in-AMI, ~5% < 60 min, 22% < 90 min, and 40% < 120 min following fibrinolysis. While our results do not provide new information regarding the ideal regimen or the timing of PCI, they do support the safety of this approach.

\section*{Study limitations}

This study has several limitations. First of all, the results were obtained within the context of an organized STEMI system of care requiring significant resources, including physician and nurse training, and similar results may not be attainable in other regions that do not have such a system. Another limitation is that this is a registry investigation rather than a randomized, controlled trial. However, recent experience has shown that it is difficult to enroll STEMI patients in randomized trials because of the lack of research support in rural hospitals. In addition, registry data have the distinct advantage of including a higher risk patient population not included in randomized trials.\textsuperscript{31,32} The TIMI flow data were based on the interpretation by the interventional cardiologist and not independently reviewed by a core laboratory; however, this is not the main focus of this study and our results are consistent with many other randomized controlled trials demonstrating improved pre-PCI patency in patients receiving fibrinolysis prior to PCI.

\section*{Conclusion}

Pharmaco-invasive therapy utilizing half-dose fibrinolysis, clopidogrel, and UFH, combined with emergent transfer for immediate PCI, may be a safe and effective reperfusion strategy for STEMI patients with expected delays due to long distances to a PCI centre. Using a standardized protocol within a regional STEMI system of care, we have effectively eliminated urban–rural disparities in the treatment of STEMI.

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