Transfer for Primary Angioplasty Versus Immediate Thrombolysis in Acute Myocardial Infarction

A Meta-Analysis

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Background—The benefit of primary percutaneous coronary intervention (PCI) over thrombolysis has been clearly demonstrated in acute myocardial infarction (AMI). However, the best therapeutic strategy for a patient with AMI presenting to acute care services without catheterization facilities remains under debate. Our objective was to gather all available information from clinical trials comparing transfer of patients experiencing AMI for angioplasty versus immediate thrombolysis.

Methods and Results—We performed a meta-analysis of all data available from published randomized trials and from presentations in scientific sessions of major cardiology congresses comparing the 2 strategies. The primary end point was the combined criteria (CC) of death/reinfarction/stroke as defined in each trial. Relative risk (RR) evaluated the treatment effect. We identified 6 clinical trials including 3750 patients. Transfer time was always <3 hours. The CC was significantly reduced by 42% (95% confidence interval [CI] 29% to 53%; \( P < 0.001 \)) in the group transferred for primary PCI compared with the group receiving on-site thrombolysis. When CC parameters were considered separately, reinfarction was significantly reduced by 68% (95% CI, 34% to 84%; \( P < 0.001 \)) and stroke by 56% (95% CI, −15% to 77%; \( P = 0.015 \)). There was a trend toward reduction in all-cause mortality of 19% (95% CI, −3% to 36%; \( P = 0.08 \)) with transfer for PCI.

Conclusion—Even when transfer to an angioplasty center is necessary, primary PCI remains superior to immediate thrombolysis. Organization of ambulance systems, prehospital management, and adequate PCI capacity appear now to be the key issues in providing reperfusion therapy for AMI. (Circulation. 2003;108:1809-1814.)

Key Words: angioplasty ■ thrombolysis ■ catheterization ■ myocardial infarction

Since percutaneous intracoronary intervention (PCI) has become widely available, a large number of trials have compared thrombolytic and percutaneous reperfusion strategies for the treatment of acute myocardial infarction (AMI). The meta-analysis from Weaver et al1 of 10 randomized trials indicated that primary PCI is superior to thrombolysis, resulting in a significant reduction in mortality, death/reinfarction, and stroke. A subsequent updated comprehensive analysis of randomized trials comparing thrombolysis with primary PCI in AMI has confirmed these findings.5 On the basis of these trials, primary PCI is widely regarded as the reperfusion strategy of choice in AMI. Many of the studies on which this premise is based, however, have limitations that could have favored primary PCI because the trials were performed at centers where both thrombolysis and PCI facilities were available on site; thus, at the time of randomization, both treatment arms were ready available. Furthermore, the PCI procedures were generally performed at high-volume centers with experienced operators achieving high success rates.

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In reality, only a minority of patients experiencing AMI present directly to PCI centers, where perhaps the trial conclusions can be applied. In “real” life, the majority of patients, even in well-resourced countries, present initially to their emergency ambulance service and/or to local hospitals rather than to an angioplasty center. In this situation, the clinical decision needs to be made between early thrombolysis or transfer to a PCI center with delayed, but more complete, reperfusion.

The clinically relevant question with regard to reperfusion strategy must therefore take into account the delay in triage and transfer for primary PCI, if available, when judging it against rapid thrombolysis. We identified 6 recent trials addressing this issue, but the individual studies have yielded inconsistent results. Of the 6 trials, 3 significantly favor transfer for PCI,3–5 and 3 show nonsignificant trends or no difference for primary PCI.6–8 Two of these were limited by sample size, one being a feasibility study6 and the other...
hampered by low recruitment.\textsuperscript{7} In the third, there was a worrying trend toward increased mortality with transfer for PCI (4.8\% with primary PCI versus 3.8\% with thrombolysis, \(P=\text{not significant})\textsuperscript{,8} This unresolved clinical problem has widespread implications for clinical care and healthcare infrastructure. Given the discrepant results, along with the low power of some of the studies to detect a difference, we performed a combined analysis of “transfer” trials to increase the statistical power in addressing the important question of the optimal reperfusion strategy for AMI in patients who present to acute care services without immediately available PCI facilities.

Methods

Study Objectives and Design
The primary aim of the meta-analysis was to compare immediate local thrombolytic drug treatment with transfer for primary PCI in the treatment of AMI. AMI was defined according to the inclusion criteria of the trials concerned. It was recognized that there would be significant heterogeneity in the studies in both the pharmacological and mechanical reperfusion arms. Thrombolytic agents and speed of administration were likely to be different. Equally, transfer times for patients randomized to primary PCI were likely to be variable. On the other hand, by combining the studies, even if case-specific data were not available, the statistical power to detect a difference in treatment effect would be greatly increased.

Trial Search Strategy
We conducted a Medline database search (National Library of Medicine, Bethesda, Md) of the literature to identify all randomized trials comparing primary PCI with thrombolysis in AMI from January 1985 to September 2002. In addition, we searched for papers presented at major cardiac conferences during the same time period. Finally, the Cochrane Database was searched and national and international colleagues were consulted. From these trials, specific transfer studies were identified, defined as those in which randomization took place outside the PCI center. In addition, all apparently nontransfer trial methodologies were scrutinized to establish whether patients in the primary PCI arm were transferred to the PCI center after randomization, potentially making them eligible for inclusion.

Study Inclusion Criteria
Trials had to make a randomized comparison between local thrombolysis and transfer for primary PCI at the point of initial contact or at community hospitals. Clinical outcome data had to be available on mortality, reinfarction, and stroke, or a combination of these criteria. We excluded trials or trial arms that specifically addressed transfer for PCI after thrombolysis as distinct from primary PCI per se.

End Points and Definitions
The primary end point was the 30-day composite of death, reinfarction, or stroke. The individual end points were also assessed separately.

Statistical Analysis
The results from each trial were those obtained on an intention-to-treat basis. The meta-analysis was performed using the relative risk (RR) as parameter of efficacy with a fixed effect model. Different techniques were used (the combined logarithm of the relative risk, both exact and approximate, Mantel-Haentzel, Cochran, and Peto\textsuperscript{9,10}) in the analysis. The results obtained from the different methods were similar, and therefore only the results from the combined logarithm of the RR with the corresponding 95\% confidence interval (CI) are presented in this analysis. Association and heterogeneity tests were performed for each meta-analysis. The probability value for significance of association and heterogeneity test was set at 0.05. Graphic representation of RR and their 95\% CI were performed with use of a logarithmic scale.

In the case of absence of an event in 1 group of patients, a pseudocount method was used to calculate the RR, adding a value of 0.25 event in each group. Finally, the number of patients needed to be treated to avoid one event (NNT) was calculated for each end point using the overall weighted risk difference (NNT=\(1/|\text{absolute risk difference}|\))

A robustness analysis testing the publication bias (ie, the nonpublication of neutral trials) was performed with a group of 500 patients (the same size as the largest trials in this analysis) in each treatment group with an event rate of 15\% for the combined end point, 6\% for reinfarction, and 2\% for stroke in the lysis groups. Given the difficulties in allocating an effect amplitude to the hypothetical trials they were to be given a treatment effect, neutral trials (RR=1) were used.

Results

Trials Included Patient Characteristics and Study Designs
Six transfer trials were identified with a design, including randomization to immediate thrombolysis or transfer for primary PCI in which randomization took place outside the PCI center.\textsuperscript{3,4,5} The trial names, acronyms, patient characteristics, and details of the pharmacologic and transfer for mechanical reperfusion groups are shown in the Table. In the Maastricht and PRAGUE trials, there was a third arm combining thrombolytic and PCI treatments. In line with the inclusion criteria, these arms were excluded. Enrollment criteria of chest pain (<6 or <12 hours) with ST elevation or new left bundle branch block on the electrocardiogram were used throughout; and although the AIR-PAMI trial specifically selected higher-risk patients, it was the smallest trial and accounted for only 3\% of the pooled total number of patients. Trial design was broadly similar in all studies; however, there were some key differences. With regard to time and site of randomization, in the Maastricht study, PRAGUE, and AIR-PAMI, randomization was at local hospitals. In approximately 28\% of the DANAMI-2 patients, randomization was at a PCI center. Analyses were performed with and without these nontransfer patients to avoid the potential problems of subgroup analysis. Importantly, in the CAPTIM trial, patients were randomized before arrival at the hospital, allowing a comparison of optimal prehospital thrombolysis versus transfer for primary PCI. Although the difference in trial design in CAPTIM would be a limitation in the combined analysis, it fit the inclusion criteria and excluding it would leave the analysis without a trial of optimal early thrombolysis, thus introducing bias in favor of PCI. On this basis, the benefits were felt to outweigh the limitations and this trial was included. All trials used t-PA in the thrombolytic arms apart from PRAGUE and PRAGUE-2, which used streptokinase. The time delays resulting from transfer are indicated in the Table. The use of a 30-day end point of death, reinfarction, or stroke was also consistent, except in the small Maastricht trial in which death/reinfarction at 42 days was reported, although the stroke data were also available and therefore incorporated into the meta-analysis. In PRAGUE-2, the 30-day mortality rate was the primary end point; however, the death/reinfarction/stroke
composite data at 30 days were also available. Reinfarction was defined as recurrent chest pain, and all studies required electrocardiographic changes and/or an elevation in cardiac enzymes. The definition of stroke varied between the trials and ranged from any neurologic event lasting more than 24 hours to events causing significant disability.

### Death/Reinfarction/Stroke

A reduction in the combined end point at 30 days with PCI was found to be significant individually only for PRAGUE, DANAMI-2, and PRAGUE-2. Combining the 6 trials, however, there was a marked and highly significant reduction in RR favoring transfer for primary PCI (Figure 1) with no evidence of heterogeneity ($P=0.67$). Excluding the nontransferred patients (randomized in PCI centers) from DANAMI-2 did not change the findings (RR = 0.58; 95% CI, 0.47 to 0.71; $P<0.001$). The overall 30-day NNT was 19 for the combined criteria. The robustness analysis showed that 11 trials had to be added to obtain a nonsignificant result of the meta-analysis for the combined end point. Because the symptom onset time varied between studies, between <6 hours (Maastricht, PRAGUE-1, CAPTIM) and <12 hours (Air Pami, DANAMI-2, PRAGUE-2), and the thrombolytic agent used varied (streptokinase in PRAGUE-1 and PRAGUE-2, tPA in Maastricht, Air-Pami, CAPTIM, and DANAMI-2), in both cases, separate repeat combined analyses for the 2 groups of trials were performed with regard to the combined end point. In both cases, the subgroups gave very similar relative risks, 0.59 (95% CI, 0.41 to 0.85) for <6 hours versus 0.57 (95% CI, 0.45 to 0.72) for <12 hours and 0.5 (95% CI, 0.35 to 0.70) for streptokinase versus 0.62 (95% CI, 0.49 to 0.78) for tPA, and there was no heterogeneity of relative risk between the subgroups ($P=0.88$ for symptom onset, $P=0.31$ for thrombolytic).

### Mortality

The mortality outcomes varied between trials. The Maastricht trial was neutral for mortality with 5 deaths in each group. In CAPTIM, there was a nonsignificant trend toward increased

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**Death/Reinfarction/Stroke**

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion Criteria</th>
<th>No. PCI</th>
<th>Time to PCI (From Randomization)</th>
<th>No. Lytic</th>
<th>Time to Lytic (From Randomization)</th>
<th>Lytic Agent</th>
<th>Trial Weight, %</th>
<th>Primary End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAASTRICHT*</td>
<td>Pain &gt;30 min and &lt;6 h ST elevation</td>
<td>75</td>
<td>85</td>
<td>75</td>
<td>10</td>
<td>tPA</td>
<td>6</td>
<td>Test safety and feasibility of acute transfer for PCI</td>
</tr>
<tr>
<td>PRAGUE-1†</td>
<td>Pain &lt;6 h ST elevation or new LBBB</td>
<td>101</td>
<td>80</td>
<td>99</td>
<td>10</td>
<td>SK</td>
<td>7</td>
<td>Death, re-MI, or stroke (30 days)</td>
</tr>
<tr>
<td>AIR-PAMI‡</td>
<td>Pain &lt;12 h with ST elevation/new LBBB, plus 1 or more high-risk criteria</td>
<td>71</td>
<td>122</td>
<td>66</td>
<td>19</td>
<td>By center. If tPA, bolus plus 72 h heparin infusion</td>
<td>4</td>
<td>Death, re-MI, or disabling stroke (30 days)</td>
</tr>
<tr>
<td>CAPTIM§</td>
<td>Pain &gt;30 min and &lt;6 h ST elevation/new LBBB</td>
<td>421</td>
<td>82</td>
<td>419</td>
<td>23</td>
<td>tPA</td>
<td>15</td>
<td>Death, re-MI or stroke (30 days)</td>
</tr>
<tr>
<td>DANAMI-2</td>
<td></td>
<td>Pain &lt;12 h with ST elevation</td>
<td>790</td>
<td>NA</td>
<td>782</td>
<td>NA</td>
<td>tPA</td>
<td>43</td>
</tr>
<tr>
<td>PRAGUE-2¶</td>
<td>AMI &lt;12 h</td>
<td>429</td>
<td>97</td>
<td>421</td>
<td>17</td>
<td>SK</td>
<td>25</td>
<td>Mortality (30 days)</td>
</tr>
</tbody>
</table>

LBBB indicates left bundle-branch block; MI, myocardial infarction.

*Prospective, randomized comparison between thrombolysis, rescue percutaneous transluminal coronary angioplasty (PTCA) and primary PTCA in patients with extensive myocardial infarction admitted to a hospital without PTCA facilities: a safety and feasibility study.5

†Multicenter randomized trial comparing transport to primary angioplasty versus immediate thrombolysis versus combined strategy for patients with acute myocardial infarction presenting to a community hospital without a catheterization laboratory. The PRAGUE Study.3

‡The Air Primary Angioplasty in Myocardial Infarction study.7 In Air-PAMI, high-risk criteria were age >70, HR >100/min, SBP <100 mm Hg, Killip class II/III, ECG LBBB, or anterior MI.

§Comparison of primary angioplasty and prehospital thrombolysis in the acute phase of myocardial infarction.8

¶The Danish multicenter randomized study on thrombolytic therapy vs acute coronary angioplasty in acute myocardial infarction. (DANAMI-2).4

††PRAGUE-2. Long-distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction.5
mortality with primary PCI. The other trials indicated non-significant trends toward reduced mortality with primary PCI. Taking the trials together, there was a trend toward reduced mortality with primary PCI, which did not reach statistical significance (Figure 2) with no evidence of heterogeneity ($P=0.56$). However, when excluding the CAPTIM patients who were randomized outside the hospitals, mortality was significantly reduced in the pooled analysis of the other 5 trials (RR 0.76; 95% CI, 0.59 to 0.98; $P=0.035$), suggesting that death is significantly reduced with primary PCI in patients who present to the hospital for reperfusion therapy.

**Reinfarction**

A consistent reduction in reinfarction at 30 days with primary PCI was shown in all studies, except PRAGUE-2 for which reinfarction data as an individual end point was not available although the composite of reinfarction/stroke was reduced with primary PCI. However, this only reached statistical significance (Figure 3) with no evidence of heterogeneity ($P=0.65$). The 30-day NNT was 33. The robustness analysis showed that 10 trials had to be added to obtain a nonsignificant result of the meta-analysis for reinfarction.

**Stroke**

In the Maastricht study, stroke was neutral with 2 events in each group; however, in the other trials, there was a nonsignificant trend toward a reduction with primary PCI. Combining the data indicated a very marked and statistically significant reduction in stroke with PCI (Figure 4) with no evidence of heterogeneity ($P=0.47$). The 30-day NNT was 86. The robustness analysis showed that 9 trials had to be added to obtain a nonsignificant result of the meta-analysis for stroke.

**Discussion**

The 6 trials comprising this meta-analysis represent the new style of trials of reperfusion strategies for AMI in patients who do not present immediately to a PCI center. This meta-analysis indicates that even when transport is required, primary PCI remains a superior strategy to local thrombolysis. The transport time to the PCI center in the DANAMI-2 trial was always less than 3 hours. In the remaining 5 trials, however, the additional time to treatment with PCI compared with local thrombolysis ranged from 70 to 103 minutes. Despite the fact that transfer clearly adds delays to reperfusion, patients still had better outcomes. Furthermore, if the CAPTIM trial is excluded, thereby considering only patients who have already presented to the hospital, transfer for primary PCI confers a significant mortality benefit.

The findings are in keeping with the observation that time to reperfusion is much less critical with primary PCI than thrombolysis.$^{11-13}$ This view is further supported by the subgroup analysis of the recent PRAGUE-2 data in which patients treated within 3 hours of chest pain experienced similar mortality of 7.4% with thrombolysis and 7.3% with primary PCI, whereas at 3 to 12 hours, primary PCI was strongly and significantly favored with a mortality of 6% compared with 15.3% with thrombolysis ($P<0.02$).5

The French CAPTIM trial, however, is important because it compares transfer for primary PCI with optimal prehospital thrombolysis.$^8$ Overall, the trial was neutral and at odds with the other trials, including the recent DANAMI-2 trial.$^4$ Important differences in designs could explain the results of CAPTIM; enrollment was within 6 hours of chest pain (compared with 12 hours in DANAMI-2) and time to thrombolysis was short with prehospital administration. Subsequently, shock occurred in 2.1% of the patients transferred for primary PCI and none of the prehospital thrombolysis group ($P=0.004$). Furthermore, patients in the thrombolytic arm were all transferred to tertiary care centers and managed relatively invasively, with 26% undergoing rescue PCI after admission (compared with no transfer and conservative management of the thrombolytic patients in DANAMI-2). These features suggest that the benefits of both reperfusion strategies could have been combined in many patients in the CAPTIM thrombolytic group, and the favorable findings support further the concept that early thrombolysis with rapid transfer and aggressive management after admission remains an effective reperfusion strategy when compared with primary PCI.

Funnel plots of the trials for the combined (Figure 5) and individual end points indicated a fairly symmetric distribution.
of relative risks around the overall RR and convergence toward the pooled effect when the weight of the trials increases, suggesting that publication or selection bias are unlikely. Furthermore, the robustness analyses showed that the results of this meta-analysis are robust and that nonpublication bias of negative trials is unlikely.

With regard to the generalizability of the conclusions of this combined analysis to other established or proposed primary PCI programs, it should be noted that the vast majority of patients underwent primary PCI at established angioplasty centers. Although in the DANAMI 2 study, 3 of the 5 PCI centers had not performed primary PCI before study participation, in the 5 other studies, the PCI centers, most often high-volume centers, were already experienced in primary angioplasty before the study. From the standpoint of the combined analysis, it cannot therefore be assumed that primary angioplasty in low-volume centers by low-volume operators, particularly without prior experience of the technique, could achieve the overall success seen in this analysis.

The present combined analysis has a number of limitations. Although the literature was thoroughly searched, all recent international cardiac conferences were scrutinized and foreign colleagues from other interventional centers were consulted, it is possible that trials or trial arms fitting our inclusion criteria were overlooked. The present analysis has used time from randomization to treatment because this parameter has the most complete data in the various trials and has practical significance to clinical decision-making when patients present to the hospital. The inclusion of CAPTIM with early thrombolysis to avoid potential bias in favor of PCI has been discussed, and indeed this was the case because the combined analysis of the other trials indicated a significant mortality benefit with PCI, which was not the case when CAPTIM was included. With regard to time from symptom onset to treatment, there was significant variation between the trials, but all patients presented within 6 or 12 hours of the onset of pain (Table). There was also inevitable clinical heterogeneity between the trials with regard to study design, transfer delays, and thrombolytic agent (although the subgroup analysis for different symptom onset times and thrombolytic agents did not indicate any heterogeneity of RRs between subgroups), and the conclusions are also limited to 30-day outcome.

With regard to the statistical model used for the combined analysis, a fixed-effect model was used in view of the lack of statistical heterogeneity between the trials. Given the clinical heterogeneity, however, the analysis was also repeated using a random effect model, and there were no significant differences between the results with the 2 models. Despite these various limitations, however, the trials were in most cases underpowered and the combined analysis allows more robust conclusions.

Overall, it now appears that primary PCI is the preferred method of revascularization for AMI in most circumstances even if not immediately available on site. Defining the next standard of care in AMI management will not, however, simply involve a decision between thrombolysis or primary PCI, but development of the optimal combination of pharmacological and percutaneous revascularization strategies. Early trials combining fibrinolysis and subsequent mechanical intervention were negative, as well as the Maastricht and PRAGUE-3 trial arms, which specifically addressed transfer for PCI after thrombolysis; however, the recent Plasminogen-activator Angioplasty Compatibility Trial (PACT) study
suggested myocardial function preservation with fibrinolysis preceding intervention. The use of thrombolytics to facilitate PCI continues to be debated and is being evaluated in the large Safety and Efficacy of a New Thrombolytic (ASSENT)-4 trial.

There is now less debate with regard to GP IIb/IIIa facilitation of primary PCI in which 5 randomized studies have shown a significant 30-day reduction in death/MI/urgent revascularization with GP IIb/IIIa antagonists, 18–21 and the maximum benefit is achieved with the earliest administration.18,22,23 The absence or negligible use of GP IIb/IIIa antagonists in the primary PCI arms of the 6 studies of our meta-analysis could have reduced the magnitude of benefit observed with primary PCI in the present study despite an already impressive reduction of events. It appears clear, therefore, that facilitation of primary PCI has an important role and future studies will further investigate the role of more aggressive pharmacological treatments combining reduced doses of fibrinolytics and full-dose treatment with GP IIb/IIIa antagonists in the Facilitated Intervention with Enhanced reperfusion Speed to Stop Events (FINESSE) and Addressing the Value of primary Angioplasty after Combination therapy or Eptifibatide monotherapy in acute Myocardial Infarction (ADVANCE MI) trials. Finally, the fast expanding use of drug-eluting stents with a loading dose and prolonged prescription of the thienopyridine clopidogrel should further widen the difference between thrombolysis and primary PCI in reperfusion of acute MI.

Conclusion

On the basis of the 6 trials analyzed, prognosis of AMI is improved when patients are transferred for primary PCI, including the attendant delay, rather than treated with local thrombolytic therapy. To benefit from these findings and offer a transfer for primary PCI service, healthcare systems need to consolidate and organize rapid, safe ambulance networks, and, if possible, early pharmacologic facilitation, in addition to PCI centers able to meet with the demand.

References

4. The Danish multicenter randomized study on thrombolytic therapy versus acute coronary angioplasty in acute myocardial infarction (DANAMI-2). Presented at the 51st Annual Scientific Sessions of the American College of Cardiology: Atlanta, GA; March 2002.