Impact of Time to Treatment on Mortality After Prehospital Fibrinolysis or Primary Angioplasty

Data From the CAPTIM Randomized Clinical Trial

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Background—CAPTIM was a randomized trial comparing prehospital thrombolysis with transfer to an interventional facility (and, if needed, percutaneous intervention) with primary percutaneous coronary intervention (PCI) in patients with ST-segment–elevation myocardial infarction (STEMI). Because the benefit of thrombolysis is maximal during the first 2 hours after symptom onset, and because prehospital thrombolysis can be implemented earlier than PCI, this analysis studied the relationship between the effect of assigned treatment and the time elapsed from symptom onset.

Methods and Results—Randomization within 2 hours (n=460) or ≥2 hours (n=374) after symptom onset had no impact on the effect of treatment on the 30-day combined primary end point of death, nonfatal reinfarction, and disabling stroke. However, patients randomized <2 hours after symptom onset had a strong trend toward lower 30-day mortality with prehospital thrombolysis compared with those randomized to primary PCI (2.2% versus 5.7%, P=0.058), whereas mortality was similar in patients randomized ≥2 hours (5.9% versus 3.7%, P=0.47). There was a significant interaction between treatment effect and delay with respect to 30-day mortality (hazard ratio 4.19, 95% CI 1.033 to 17.004, P=0.045). Among patients randomized in the first 2 hours, cardiogenic shock was less frequent with lytic therapy than with primary PCI (1.3% versus 5.3%, P=0.032), whereas rates were similar in patients randomized later.

Conclusions—Time from symptom onset should be considered when one selects reperfusion therapy in STEMI. Prehospital thrombolysis may be preferable to primary PCI for patients treated within the first 2 hours after symptom onset. (Circulation. 2003;108:2851-2856.)

Key Words: angioplasty • myocardial infarction • reperfusion • thrombolysis

Intravenous thrombolysis and primary percutaneous coronary intervention (PCI) are both effective treatments for ST-segment–elevation acute myocardial infarction (STEMI). Several randomized comparisons have shown that primary PCI is associated with improved outcomes compared with in-hospital thrombolysis.1,2 However, the benefit of intravenous thrombolysis appears to depend on the time elapsed between symptom onset and initiation of treatment.3

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Prehospital thrombolysis appears safe and effective and is associated with a substantial gain in time to treatment.4 A meta-analysis of studies comparing prehospital and in-hospital thrombolysis has shown a relative reduction in short-term mortality of ≈17% with prehospital thrombolysis.4 Therefore, the Comparison of Angioplasty and Prehospital Thrombolysis In acute Myocardial infarction (CAPTIM) trial was set up to compare prehospital thrombolysis and primary PCI in patients with STEMI.5 The main results of this open-label, randomized clinical trial have been reported previously.5 No difference in the combined end point of death, reinfarction, and disabling stroke at 30 days could be demonstrated. Yet, the benefit of intravenous thrombolysis is extremely time sensitive,3,6 and when treatment is established in the first 2 hours after symptom onset, the so-called “golden hour,” survival dramatically increases.6 In this respect, it is noteworthy that the ability of certain thrombolytic agents to recanalize the infarct-related artery appears to decrease with time.7,8 Conversely, retrospective analyses of cohort and trial data have suggested that outcomes after primary PCI may be relatively independent of the time between symptom onset and reperfusion but...
are related to the time elapsed between admission and PCI.9,10 The present analysis was planned to document the patient characteristics associated with early (<2 hours) versus later (≥2 hours) presentation and to determine whether initial treatment assignment to prehospital thrombolysis or primary PCI had a differential impact on clinical outcomes in patients randomized early (<2 hours) versus later (≥2 hours) after symptom onset.

Methods

Study Organization

The trial was coordinated by the Hospices Civils de Lyon, France. Twenty-seven French tertiary hospitals and their affiliated Mobile Intensive Care Units (MICUs) participated in the study. All MICU teams included a physician and carried ECG and resuscitation equipment, including a defibrillator.

Patients

Patients were recruited between June 30, 1997, and September 30, 2000. Patients were eligible for inclusion within 6 hours after the onset of symptoms of STEMI, ie, characteristic pain lasting for at least 30 minutes, or pain lasting for <30 minutes but still present and not responsive to nitrates, with ECG ST-segment elevation of at least 0.2 mV in 2 or more contiguous leads or left bundle-branch block. Patients with hemorrhagic diathesis or any contraindication to thrombolysis, severe renal or hepatic insufficiency, aortofemoral bypass or any condition that could hamper femoral artery access, cardiogenic shock, or a history of CABG or who were receiving oral anticoagulants were excluded. Patients were not eligible if the duration of transfer to the hospital was expected to exceed 1 hour.

Randomization and Treatment Strategies

Eligible patients were randomly assigned at the site of initial management (usually at home or at their workplace) to prehospital recombinant tissue plasminogen activator (rtPA) with transfer to an interventional facility or primary PCI by use of a 24-hour computerized randomization service. Prehospital thrombolysis patients received a 5000-U intravenous heparin bolus, 250 to 500 mg of aspirin (orally or intravenously), and an intravenous bolus of 15 mg of alteplase (rtPA), followed by an infusion of 0.75 mg per kilogram of body weight (not to exceed 50 mg) over a 30-minute period and then 0.50 mg/kg (not to exceed 35 mg) over the next 60 minutes, up to a maximal total dose of 100 mg. All patients were then transported to the hospital. The decision to perform angiography in the hospital was left to the judgment of the investigator.

Primary PCI patients received a 5000-U intravenous heparin bolus and 250 to 500 mg of aspirin (orally or intravenously) and were transported immediately to the hospital for PCI. The protocol advised that in patients with stenoses of the left main stem or critical 3-vessel disease, CABG should be strongly considered. When the infarct-related artery had Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow, the decision to perform PCI was left to the operator.

The primary end point was a composite of death, nonfatal reinfarction, and nonfatal disabling stroke within 30 days. Severe hemorrhage was defined as intracranial hemorrhage or bleeding that caused hemodynamic compromise or required blood transfusion.

Statistical Analysis

Continuous data are presented as medians with interquartile ranges unless otherwise stated. Selected baseline characteristics and clinical end points were compared between treatment groups by Fisher’s exact test for discrete variables, and the t test for continuous variables. Relative risks (RRs) and 95% CIs were used to compare treatments with regard to major clinical end points. Kaplan-Meier survival curves were used to analyze time to death during the follow-up period. Interaction between time to treatment and randomized treatment assignment was examined in a Cox model in which these 2 variables and their interaction were entered. All tests of significance were 2-tailed, and analysis was done on an intention-to-treat basis.

The study was approved by an institutional review board serving all participating hospitals. All patients provided written informed consent to participation before randomization.

Results

Overall, 840 patients were enrolled in the trial: 419 were randomized to prehospital thrombolysis and 421 to primary PCI. Of these 840 patients, 460 were included within 2 hours after symptom onset and 374 from 2 to 6 hours after symptom onset. Data regarding delays were missing or incomplete in 6 patients. The baseline characteristics of the patients randomized early and late differed (Table 1). Patients randomized within 2 hours were younger, more frequently males, and had a lower baseline heart rate than patients randomized later. Initial treatment and in-hospital management were comparable in both groups, but patients randomized early more frequently received statins (59.6% versus 50.4%, P = 0.010). Outcomes were similar in both groups (Table 1), with the exception of severe hemorrhage (more frequent in patients randomized later after symptom onset) and cardiogenic shock before admission (more frequent in patients randomized early than in those randomized later after symptom onset; 1.8% versus 0.3%, respectively; P = 0.048). Time to treatment was consistently shorter in the lysis group than in the PCI group (median difference of 55 minutes before 2 hours and 63 minutes among patients randomized later; Table 2).

When outcomes were examined with reference to the time to randomization (Table 2), the latter had no impact on the effect of treatment on the primary end point or on reinfarction or disabling stroke. However, time to randomization influenced the outcome of treatment comparison on 30-day mortality; within 2 hours of symptom onset, there was a strong trend toward a higher mortality in the PCI group (5.7% versus 2.2%, RR 2.62, 95% CI 0.95 to 7.24, P = 0.058), whereas after 2 hours, deaths tended to be less frequent in the PCI group (3.7% versus 5.9%, RR 0.64, 95% CI 0.25 to 1.61, P = 0.47; P = 0.039 for heterogeneity). Log-rank analysis (Figure) confirmed a nonsignificant trend toward a lower 30-day mortality for patients randomized within 2 hours of symptom onset and treated with thrombolysis than for patients treated with PCI (P = 0.053). In patients randomized after 2 hours, there was no difference in survival. Similar trends were found for cardiovascular mortality after stratification according to time to randomization: within 2 hours of symptom onset, cardiovascular mortality was 2.2% and 5.2% in patients treated with thrombolysis and primary PCI, respectively (P = 0.089), whereas it was 5.9% and 3.2% in patients randomized later (P = 0.321; P = 0.034 for heterogeneity between groups). In the first 2 hours, cardiogenic shock was less frequent with lytic therapy than with primary PCI, mostly because of a lower incidence of shock developing during transport to the hospital; in this subset, cardiogenic shock occurred between randomization and admission in 3.6% of patients randomized to PCI but in none of the patients randomized to prehospital thrombolysis (P = 0.007). In patients randomized later, the rates were very low and were similar in both groups (0% versus 0.5%, respectively).
Analysis for interaction between treatment effect and time to randomization (based on 36 events in 834 patients) confirmed a significant interaction between treatment and delay with respect to 30-day mortality (hazard ratio 4.19, 95% CI 1.033 to 17.004, \( P = 0.045 \)).

**Discussion**

The present study shows that patients treated early and late differ in terms of baseline characteristics and suggests reduced 30-day mortality after prehospital thrombolysis compared with primary PCI in STEMI patients randomized within 2 hours after pain onset, whereas for those randomized later, no difference in outcome between reperfusion strategies was seen.

There is conclusive evidence from clinical trials that reduction of mortality by fibrinolytic therapy in STEMI is related to the time elapsed between onset of symptoms and beginning of treatment.\(^3\) Meta-analysis of randomized, placebo-controlled trials of thrombolysis has shown that the survival benefit of lytic therapy is substantially higher during the first 2 hours after symptom onset\(^6\) and thereafter decreases rapidly. Moreover, at least with non-fibrin-specific thrombolytic agents, thrombolysis is more effective for re-canalizing the infarct vessel when patients are treated early.\(^7,8,11\) Similar decreased efficacy over time of newer agents has also been reported.\(^12\)

With primary PCI, such a steep decrease in survival benefit with increasing time to treatment has not been demonstrated.\(^9,10\) The reason that increasing time between symptom onset and reperfusion therapy would have different effects on survival in patients treated with thrombolysis or with primary PCI is still unclear. Interestingly, among patients treated

| TABLE 1. Baseline Characteristics, In-Hospital Management, and Outcomes of Patients According to Time Between Symptom Onset and Randomization |

<table>
<thead>
<tr>
<th>Time Between Symptom Onset and Randomization</th>
<th>&lt;2 h (n=460)</th>
<th>≥2 h (n=374)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>56 (24–86)</td>
<td>60 (28–91)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Male gender</strong></td>
<td>402 (87.4)</td>
<td>283 (75.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Current smoker</strong></td>
<td>243 (53.3)</td>
<td>175 (47.8)</td>
<td>0.059</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>52 (11.4)</td>
<td>49 (13.2)</td>
<td>0.456</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>145 (31.7)</td>
<td>138 (37.2)</td>
<td>0.105</td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td>226 (49.5)</td>
<td>197 (53.2)</td>
<td>0.294</td>
</tr>
<tr>
<td><strong>Prior myocardial infarction</strong></td>
<td>34 (7.4)</td>
<td>27 (7.3)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Prior angioplasty</strong></td>
<td>24 (5.2)</td>
<td>16 (4.3)</td>
<td>0.626</td>
</tr>
<tr>
<td><strong>Heart rate, bpm</strong></td>
<td>74 (25–180)</td>
<td>76 (41–153)</td>
<td>0.041</td>
</tr>
<tr>
<td><strong>Systolic blood pressure, mm Hg</strong></td>
<td>125 (60–193)</td>
<td>128 (68–190)</td>
<td>0.602</td>
</tr>
<tr>
<td><strong>Anterior infarction</strong></td>
<td>190 (41.8)</td>
<td>151 (40.9)</td>
<td>0.831</td>
</tr>
<tr>
<td><strong>Time to treatment, min</strong></td>
<td>120 (40–260)</td>
<td>225 (120–1275)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Treatment assignment: prehospital thrombolysis</strong></td>
<td>231 (50.2)</td>
<td>187 (50.0)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

**Medications and procedures**

| **ACE inhibitor** | 213 (49.3) | 189 (54.0) | 0.196 |
| **Aspirin** | 431 (96.6) | 346 (96.4) | 0.849 |
| **\( \beta \)-blocker** | 386 (90.8) | 301 (88.3) | 0.282 |
| **Heparin** | 434 (97.3) | 347 (96.7) | 0.678 |
| **Statin** | 266 (59.0) | 181 (50.4) | 0.010 |
| **Ticlopidine/clopidogrel** | 305 (68.4) | 241 (67.1) | 0.705 |
| **Angioplasty up to day 30** | 196 (42.6) | 158 (42.2) | 0.944 |
| **Urgent angioplasty** | 90 (20.4) | 60 (16.7) | 0.203 |
| **CABG** | 6 (1.4) | 3 (0.8) | 0.738 |

**Clinical outcomes**

| **Primary combined end point** | 32 (7.0) | 28 (7.5) | 0.789 |
| **Death** | 18 (3.9) | 18 (4.8) | 0.608 |
| **Reinfarction** | 12 (2.7) | 10 (2.8) | 1.000 |
| **Disabling stroke** | 3 (0.7) | 1 (0.3) | 0.632 |
| **Recurrent ischemia** | 27 (6.2) | 18 (5.1) | 0.540 |
| **Severe hemorrhage** | 1 (0.2) | 9 (2.5) | 0.007 |
| **Cardiogenic shock (from randomization to hospital discharge)** | 15 (3.3) | 15 (4.2) | 0.578 |
| **Cardiogenic shock (from randomization to hospital admission)** | 8 (1.8) | 1 (0.3) | 0.048 |

Values are number of patients (%) or median (interquartile range, 25th and 75th percentiles).
early, all cardiogenic shocks that developed between random-
ization and hospital admission were observed in patients in
the primary PCI group, which suggests that the 1-hour
additional delay imposed by primary PCI may have facili-
tated the development of cardiogenic shock in those patients.

In CAPTIM, the difference in time to treatment between
prehospital thrombolysis and primary PCI was \( \approx 1 \) hour.\(^5\)
Given the strong time dependency of the benefit of lytic
therapy, it is not surprising that a reduction of 1 hour of this
delay would be beneficial to patients given early
thrombolysis but not to those treated later. In other words,
“losing 1 hour” to implement a strategy of hospital transfer
for primary PCI has a different impact on survival when
patients are seen early as opposed to late. Early, prehospital
thrombolysis appears to be a legitimate option that may be
associated with better survival than primary PCI. Random-
ized trials comparing in-hospital thrombolysis with primary
PCI have generally demonstrated the superiority of primary
PCI,\(^2,13,14\) even when the latter required transportation to
another hospital.\(^1,15,17\)

The present findings of a different outcome of the com-
parison between thrombolysis and primary PCI as a function
of time from onset of symptoms are consistent with results
from the PRAGUE II trial, in which in-hospital thrombolysis
achieved identical 30-day mortality compared with primary
PCI within the first 3 hours after symptom onset (7.4% versus
7.3%, respectively), whereas mortality was lower with PCI
among patients randomized later.\(^18\) In the Zwolle randomized
trial of thrombolysis versus primary PCI, the latter was
associated with lower adverse event rates regardless of

### TABLE 2. Incidence of Primary and Secondary End Points According to Randomized Treatment Assignment and Time Between
Symptom Onset and Randomization

<table>
<thead>
<tr>
<th></th>
<th>&lt;2 h</th>
<th>( \geq 2 ) h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prehospital Lysis</td>
<td>Primary PCI</td>
</tr>
<tr>
<td>Randomization to treatment, min</td>
<td>95 (40–175)</td>
<td>150 (82–260)</td>
</tr>
<tr>
<td>Primary end point</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>17 (7.4)</td>
<td>15 (6.6)</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>5 (2.2)</td>
<td>13 (5.7)</td>
</tr>
<tr>
<td>Disabling stroke</td>
<td>9 (4.0)</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td></td>
<td>3 (1.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Secondary end points</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent ischemia</td>
<td>16 (7.1)</td>
<td>11 (5.1)</td>
</tr>
<tr>
<td>Severe hemorrhage</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Cardiogenic shock (from randomization to discharge)</td>
<td>3 (1.3)</td>
<td>12 (5.3)</td>
</tr>
<tr>
<td>Cardiogenic shock (from randomization to admission)</td>
<td>0 (0.0)</td>
<td>8 (3.6)</td>
</tr>
</tbody>
</table>

Values are number of patients (%) or median (interquartile range; 25th and 75th percentiles).

*\( P \) for heterogeneity.
whether patients were treated early (<2 hours) or late.\textsuperscript{19} However, this comparison involved in-hospital rather than prehospital thrombolysis. Given the shorter time to treatment with prehospital than with in-hospital thrombolysis (usually in the range of at least 45 minutes\textsuperscript{4,20,21}), outcomes may conceivably be improved after prehospital thrombolysis, especially for patients treated early.

In CAPTIM, 70% of the patients treated by thrombolysis underwent PCI up to day 30, and 33% had urgent PCI\textsuperscript{1} (26% labeled “rescue PCI” because of persistent ischemia). Therefore, CAPTIM really compares primary PCI to a strategy of prehospital thrombolysis, transfer to an interventional center, and subsequent PCI. This strategy is therefore very different from thrombolysis per se and probably explains why the results achieved by prehospital thrombolysis in CAPTIM are very different from studies reported in the meta-analysis of prehospital versus hospital thrombolysis.\textsuperscript{4} Some studies have suggested that combining early thrombolysis with subsequent PCI in the setting of STEMI may be a very effective strategy,\textsuperscript{22–24} particularly because it would reduce the time to optimal myocardial reperfusion\textsuperscript{25} compared with primary PCI and may reduce the risk of recurrent infarction compared with in-hospital thrombolysis. This may be especially true of a strategy of prehospital thrombolysis, subsequent angiography, and, if needed, percutaneous intervention, which in a previous matched case-control study appeared to achieve in-hospital outcomes similar to those of primary angioplasty.\textsuperscript{23} The strategy of combining early thrombolysis with subsequent percutaneous intervention is currently being investigated in several trials.

There are several limitations to the present analysis. This is a subgroup analysis of a trial that did not show an overall survival difference between the 2 strategies. Time to treatment appears to affect mortality and several secondary end points but not the primary end point of the trial. However, there is biological plausibility to the finding that time elapsed between symptom onset and treatment would influence mortality (which is consistent with experimental findings on infarct size reduction\textsuperscript{26}) but not the risk of reinfarction or stroke, which would be expected to be less dependent on time elapsed since symptom onset. The choice of 2 hours as a cutoff point for this subgroup analysis is not arbitrary but is consistent with the finding that in placebo-controlled trials, the mortality reduction afforded by thrombolysis appeared to be far greater within this time interval after symptom onset.\textsuperscript{3,6} Overall, the unspecified subgroup analysis, the use of a portion of the primary end point (30-day mortality), the small number of end points, and the borderline nominal significance test ($P=0.058$) make this analysis hypothesis generating rather than hypothesis testing. Importantly, patients with cardiogenic shock before randomization were excluded. In these patients, primary PCI may be a better option in terms of survival than thrombolysis.\textsuperscript{27–29} Finally, in the present study, treatment was initiated in a prehospital setting, which may not be feasible in all environments. Whether these results apply to in-hospital thrombolysis for patients treated early during the course of their symptoms is uncertain.

Conclusions

In this trial, STEMI patients randomized within 2 hours after symptom onset to prehospital thrombolytic therapy had a strong trend toward lower mortality and had a markedly lower rate of cardiogenic shock than patients treated with primary PCI. This difference was not apparent among patients randomized later. This suggests that time since onset of symptoms should be considered when one selects reperfusion therapy. Prehospital thrombolysis with transfer to an interventional facility and, if needed, percutaneous intervention is a valid treatment option and may even be preferable to primary PCI for patients treated early after symptom onset.

Acknowledgments

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