Comparison of pre-hospital combination-fibrinolysis plus conventional care with pre-hospital combination-fibrinolysis plus facilitated percutaneous coronary intervention in acute myocardial infarction

Holger Thiele1*, Lothar Engelmann2, Kathleen Elsner1, Mathias J. Kappl1, Wulf-Hinrich Storch4, Kazem Rahimi1, Andreas Hartmann3, Dietrich Pfeiffer2, Georg D. Kneissl5, Dieter Schneider6, Thomas Möller7, Hans J. Heberling8, Ina Weise9, and Gerhard Schuler1 for the Leipzig Prehospital Fibrinolysis Group

1 Department of Internal Medicine/Cardiology, University of Leipzig—Heart Center, Strümpellstr. 39, 04289 Leipzig, Germany; 2 University of Leipzig, Leipzig, Germany; 3 Städtisches Klinikum St Georg, Leipzig, Germany; 4 Rettungsamt Leipzig, Leipzig, Germany; 5 Ambulantes Herzcentrum Elsterstr., Leipzig, Germany; 6 Kath. Krankenhaus St Elisabeth, Leipzig, Germany; 7 Ev. Luth. Diakonissen-Krankenhaus, Leipzig, Germany; 8 Städtische Klinik St Georg—Stadtkrankenhaus, Leipzig, Germany; and 9 Park-Krankenhaus Leipzig Südost GmbH, Leipzig Germany

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Aims Early and complete reperfusion is the main treatment goal in ST-elevation myocardial infarction (STEMI). The timely optimal reperfusion strategy might be a pre-hospital initiated pharmacological reperfusion with subsequent facilitated percutaneous coronary intervention (PCI). This approach has been compared with pre-hospital combination-fibrinolysis only to determine whether either one of these methods offer advantages with respect to final infarct size.

Methods and results Patients with STEMI were randomized to either pre-hospital combination-fibrinolysis (half-dose reteplase + abciximab) with standard care (n = 82) or pre-hospital combination-fibrinolysis with facilitated PCI (n = 82). Primary endpoint was the infarct size assessed by delayed enhancement magnetic resonance. Secondary endpoints were ST-segment resolution at 90 min and a composite of death, re-myocardial infarction, major bleeding, and stroke at 6 months. The infarct size was lower after facilitated PCI with 5.2% [interquartile range (IQR) 1.3–11.2] as opposed to 10.4% (IQR 3.4–16.3) after pre-hospital combination-fibrinolysis (P = 0.001). Complete ST-segment resolution was 80.0% after facilitated PCI vs. 51.9% after pre-hospital combination-fibrinolysis (P < 0.001). After facilitated PCI, there was a trend towards a lower event rate in the combined clinical endpoint (15 vs. 25%, P = 0.10, relative risk 0.57, 95% CI 0.28–1.13).

Conclusion In patients with STEMI, additional facilitated PCI after pre-hospital combination-fibrinolysis results in an improved tissue perfusion with subsequent smaller infarct size as opposed to pre-hospital combination-fibrinolysis alone. This translates into a trend towards a better clinical outcome.

KEYWORDS Acute myocardial infarction; Fibrinolysis; Pre-hospital treatment; Percutaneous coronary intervention; Facilitated angioplasty

Introduction

Patients with acute ST-elevation myocardial infarction (STEMI) benefit markedly from reperfusion. The time to reperfusion and complete reperfusion remain the key determinants either for fibrinolysis or for mechanical revascularization.1–3 Primary percutaneous coronary intervention (PCI) performed by skilled operators is superior to fibrinolysis when reperfusion starts 2–3 h after symptom onset, mainly because of a higher patency of the infarct-related artery.4–7 However, PCI has the limitation of limited availability and the inherent delay for patient transfer. The reduction of total ischaemia time by pre-hospital fibrinolysis compensates for the inferiority of fibrinolysis in comparison with primary PCI,8 particularly in patients treated very early after symptom onset.9,10 Therefore, fibrinolysis and PCI are equally recommended for patients presenting within the first 3 h after symptom onset.3

It is only logical to combine the advantages of both strategies, i.e. pre-hospital fibrinolysis with subsequent PCI and stent, in order to achieve optimal results. This “facilitated” PCI approach failed to show any benefit in early trials mainly because of bleeding complications and a higher rate of recurrent myocardial infarctions.11,12 Revised strategies using newer fibrinolytics, reduction of
concomitant anticoagulation, and improvements in technique, such as stents, may allow a combined approach.\textsuperscript{13} We conducted a city-wide trial to assess whether facilitated PCI after pre-hospital combination-fibrinolysis (half-dosereteplase + abciximab) leads to a smaller infarct size and better clinical outcome in patients with STEMI than pre-hospital combination-fibrinolysis alone.

Methods
From 20 December 2000 to 31 March 2004, we randomly assigned patients with STEMI to pre-hospital combination-fibrinolysis with subsequent standard care or pre-hospital combination-fibrinolysis with subsequent facilitated PCI. The trial was conducted in the city of Leipzig, Germany. All seven hospitals (four without and three with PCI facilities) and the six mobile care units, staffed with a physician and equipped with portable electrocardiographic equipment, participated in the trial. Criteria for inclusion were the presence of symptoms for at least 30 min but <6 h and ST-segment elevation of at least 0.1 mV in two or more extremity leads or at least 0.2 mV in two or more pre-cordial leads. Criteria for exclusion were the usual contraindications to fibrinolysis, such as haemorrhagic stroke, ischaemic stroke <3 months, active bleeding, non-compressible vascular punctures, history of major trauma or surgery <30 days, active peptic ulcer, neoplasms, uncontrolled hypertension >200 mmHg, suspected aortic dissection, cardiogenic shock, and pregnancy. The study was approved by the local Ethics Committee.

Study protocol
After confirmation of the diagnosis by the emergency physician, informed consent was obtained from the patient. Contact was made with the study centre which used a computerized randomization method in order to allocate the patients to one of the treatment arms: pre-hospital combination-fibrinolysis or facilitated PCI. All patients received 500 mg of aspirin, heparin (60 U/kg, maximum 5000 U), and abciximab (0.25 mg/kg), followed by a half-dose of reteplase (two boluses of 5 U, 30 min apart) intravenously. In patients assigned to pre-hospital combination-fibrinolysis, intravenous heparin infusion was continued within the first 30 min after hospital arrival for a period of 24 h with the dose adjusted to achieve an activated partial-thromboplastin time between 50 and 70 s. Abciximab was given intravenously by 0.125 mg/kg per minute (maximum 10 mg/min) for 12 h. Pre-defined criteria for rescue PCI were persistent angina and/or incomplete ST-segment resolution of <50% at 90 min. In case of re-infarction or recurrent ischaemia, urgent PCI was recommended. Repeated fibrinolysis was discouraged. Otherwise, elective coronary angiography was recommended before hospital discharge, and the decision to undertake angioplasty was left to the discretion of the operator.

Patients randomly assigned to facilitated PCI were transported immediately to a catheterization laboratory. The hospital staff was informed prior admission. PCI was performed according to local standards, in case of a totally occluded infarct-related artery, culprit lesion stenosis of >50%, and reduced flow grade of less than 3, according to the thrombolysis in myocardial infarction (TIMI) classification. Stenting of the culprit lesion was recommended unless the vessel had a diameter of <2.0 mm. Clopidogrel (300 mg orally, followed by 75 mg per day for at least 4 weeks) was mandatory. Aspirin was given indefinitely at a dose of 100 mg per day. The sheath was removed when the activated clotting time was <180 s and manual compression of the puncture site till haemostasis was performed. Abciximab was given continuously at standard dose for 12 h.

The following times were recorded: initial onset of angina, emergency call, arrival of the mobile care unit, injection of the first reteplase bolus, start of patient transfer, arrival at hospital, and first balloon inflation.

Angiographic analysis included initial and final TIMI-flow grade of the culprit vessel, assessed offline in the angiographic core laboratory by two blinded observers with averaging of the TIMI-flow, if not in agreement.

Magnetic resonance imaging
Myocardial infarct size was determined by magnetic resonance imaging (MRI) at 6-month follow-up. Imaging was performed on a 1.5 T scanner (Philips Intera CV, Best, The Netherlands). Left ventricular function was assessed by a standard steady-state free precession technique.\textsuperscript{14} Delayed enhancement images covering the whole ventricle were acquired 15–20 min after a double bolus of gadolinium-BOPTA (Gadovist, Schering, Germany), using an inversion recovery gradient echo sequence.\textsuperscript{15} The inversion time was adapted individually to null normal myocardium. All measurements were performed at the MR core laboratory by blinded operators. The mean (±SD) intraobserver and interobserver variabilities for infarct size measurement in this laboratory were 0.8 ± 2.1% and 1.3 ± 1.5%, respectively. Left ventricular ejection fraction, end-diastolic and end-systolic volumes were calculated from the short-axis views. Total left ventricular myocardial mass and infarct size, expressed as percentage of left ventricular mass, were assessed manually as described previously.\textsuperscript{16} Contraindications for MRI included pacemakers, defibrillators, and metallic cerebral clips. Furthermore, those patients who had a recurrent infarction at the same location as the index event, confirmed by an electrocardiogram (ECG), were excluded, as the initial infarct size could not be assessed appropriately.

Endpoints
The primary endpoint was the final infarct size. Secondary study endpoints were infarct size assessed by the area under the curve of the creatine kinase release for measurements obtained every 6 h over 3 days. Furthermore, the ST-segment resolution was assessed as an indirect parameter of myocardial tissue perfusion. The sum of ST-segment elevation was measured by blinded operators 20 s after the end of the QRS complex in the initial and the 90 min ECG, which was obtained after PCI in the facilitated PCI group. ST-segment resolution was expressed as percentage. The clinical secondary endpoint was a composite of death, re-infarction, disabling stroke, and major bleeding within 30 days and 6 months after randomization. Post-hospital follow-up included one outpatient visit at 1 and 6 months to document clinical events. The diagnosis of re-infarction was based on clinical symptoms, new ST-segment changes, and an increase in the creatine kinase and MB level above a reference limit in patients with normalized values after the index event or if there was an increase of at least 50% from the last non-normalized measurement. Disability was defined as a fatal stroke or stroke causing significant mental or physical handicap. Major bleeding was defined as bleeding that requires blood transfusion and/or causes haemodynamic compromise. Outcomes were adjudicated by a clinical events committee unaware of the patient’s assigned treatment.

Statistical analysis
The number of patients included was based on the sample size estimation for the primary study endpoint. On the basis of previous studies, we assumed that the final infarct size would be 6 ± 7% after facilitated PCI and 13 ± 11% after pre-hospital combination-fibrinolysis.\textsuperscript{6,17,18} Choosing a power of 80% and a two-sided α-value of 0.05, we estimated that 60 patients would be required in each group. A total of 164 patients were included to allow for the possibility of missing MRI studies. Pre-defined subgroup analysis was performed for anterior/non-anterior STEMI and different times from symptom onset to reperfusion (<2, 2–4, and >4 h). All
analyses were performed according to the intention-to-treat principle with the exception that patients with non-confirmed STEMI at inclusion were excluded from further analysis. Each categorical variable is expressed as number and percentage of patients. Continuous parameters were estimated as median with interquartile range (IQR). Differences between the treatment groups were assessed by the Fisher’s exact or the $\chi^2$ test for categorical variables and by the Student’s $t$-test for continuous data with normal distribution. Otherwise, the non-parametric Wilcoxon rank sum test was used. For the combined secondary endpoint, the Kaplan–Meier method was applied and differences were assessed by the log-rank test. A two-tailed $P$-value less than 0.05 was considered statistically significant.

Results

Of the 164 patients enrolled, 82 patients were randomly assigned to pre-hospital combination-fibrinolysis and 82 to facilitated PCI (Figure 1). All patients received the assigned pre-hospital combination-fibrinolytic therapy. The baseline characteristics were similar between the groups except a trend towards older age in facilitated PCI (Table 1). In each treatment group, two patients (2%) had to be excluded from further analysis for misdiagnosis of STEMI (pericarditis $n=2$, electrocardiographic misinterpretation $n=1$, and persistent ST-elevation after previous infarction $n=1$). Their clinical course was otherwise uneventful.

Time from symptom onset to treatment

The different time steps from symptom onset to reperfusion are shown in Table 2. In 18% of the patients, pre-hospital combination-fibrinolysis could be initiated within 1 h, in 65% within 2 h, and in 79% within 3 h after symptom onset. All patients assigned to facilitated PCI underwent diagnostic angiography, and there were 77 (96%) facilitated PCI procedures (unsuccessful revascularization of occluded vessel $n=1$; no angiographically significant stenosis $n=1$; and coronary artery bypass grafting several days after the index event $n=1$). Immediately prior to PCI, there was TIMI-3 flow in 69% and TIMI-2 flow in 10%. Post-stenting in 93%, the flow in the infarct-related artery was completely restored (TIMI-3). The door-to-balloon time was 63 min (IQR 54–84).

In the pre-hospital combination-fibrinolysis group, 14 patients (18%) showed persistent ischaemia necessitating rescue PCI. Door-to-balloon times in this subgroup were significantly longer (158 min, IQR 89–262, $P=0.003$). An additional 59 patients (73%) underwent elective or urgent PCI 4 days (IQR 1–7) after the index event.

Infarct size

Results of MRI were available in 66 patients (82.5%) of the pre-hospital combination-fibrinolysis and in 68 (85.0%) patients of the facilitated PCI group. Data were missing for the following reasons after pre-hospital combination-fibrinolysis: death $n=6$; neurological deficit, as a result of worsening dementia and after resuscitation $n=3$; re-infarction in the same territory $n=4$; and claustrophobia $n=1$. In the facilitated PCI group, reasons for not performing MRI were death $n=5$; re-infarction $n=3$; lost to follow-up $n=1$; pacemaker $n=1$; refusal $n=1$; and claustrophobia $n=1$. The results are shown in Table 3. The primary endpoint infarct size was lower after facilitated PCI as opposed to pre-hospital combination-fibrinolysis. Despite typical symptoms and typical signs of STEMI in the initial ECG, in eight patients (10.0%) after facilitated PCI.

![Figure 1](https://academic.oup.com/eurheartj/article-abstract/26/19/1956/532092/1956_H_Thiele_et_al)

Randomized ($n=164$)

Pre-hospital combination-fibrinolysis ($n=82$)

- Excluded, no infarction ($n=2$)
- Rescue PCI ($n=14$)
  - Lost to 6-month follow-up ($n=0$)
  - Primary endpoint analysis ($n=66$)
  - Secondary combined endpoint analysis ($n=80$)

Facilitated PCI ($n=82$)

- Excluded, no infarction ($n=2$)
- No stent ($n=3$)
  - Not necessary ($n=2$)
  - Not possible ($n=1$)
- Lost to 6-month follow-up ($n=1$)
- Primary endpoint analysis ($n=68$)
  - Secondary combined endpoint analysis ($n=79$)
## Table 1  Main characteristics of patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pre-hospital combination-fibrinolysis (n = 82)</th>
<th>Facilitated PCI (n = 82)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60 (52–69)</td>
<td>65 (57–72)</td>
<td>0.06</td>
</tr>
<tr>
<td>Male sex [n (%)]</td>
<td>64 (78)</td>
<td>61 (74)</td>
<td>0.71</td>
</tr>
<tr>
<td>Cardiovascular risk factors [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>35 (43)</td>
<td>33 (40)</td>
<td>0.87</td>
</tr>
<tr>
<td>Hypertension</td>
<td>53 (65)</td>
<td>50 (61)</td>
<td>0.75</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>42 (51)</td>
<td>37 (45)</td>
<td>0.53</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (17)</td>
<td>20 (25)</td>
<td>0.34</td>
</tr>
<tr>
<td>Prior myocardial infarction [n (%)]</td>
<td>8 (10)</td>
<td>11 (13)</td>
<td>0.63</td>
</tr>
<tr>
<td>Prior coronary artery bypass grafting</td>
<td>0</td>
<td>1 (1)</td>
<td>1.00</td>
</tr>
<tr>
<td>Anterior myocardial infarction [n (%)]</td>
<td>40 (50)</td>
<td>37 (46)</td>
<td>0.75</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>130 (120–150)</td>
<td>135 (120–150)</td>
<td>0.69</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>80 (74–90)</td>
<td>80 (70–90)</td>
<td>0.37</td>
</tr>
<tr>
<td>Heart rate (b.p.m.)</td>
<td>75 (66–85)</td>
<td>80 (65–92)</td>
<td>0.43</td>
</tr>
<tr>
<td>Killip class on admission [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>72 (88)</td>
<td>67 (82)</td>
<td>0.39</td>
</tr>
<tr>
<td>2</td>
<td>8 (10)</td>
<td>11 (13)</td>
<td>0.63</td>
</tr>
<tr>
<td>3</td>
<td>1 (1)</td>
<td>3 (4)</td>
<td>0.61</td>
</tr>
<tr>
<td>4</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1.00</td>
</tr>
<tr>
<td>Concomitant medications [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>82 (100)</td>
<td>81 (99)</td>
<td>1.00</td>
</tr>
<tr>
<td>ACE&lt;sup&gt;a&lt;/sup&gt;-Inhibitors</td>
<td>82 (100)</td>
<td>81 (99)</td>
<td>1.00</td>
</tr>
<tr>
<td>Aspirin</td>
<td>82 (100)</td>
<td>81 (99)</td>
<td>1.00</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>63 (77)</td>
<td>72 (88)</td>
<td>0.10</td>
</tr>
<tr>
<td>Statins</td>
<td>77 (96)</td>
<td>80 (98)</td>
<td>1.00</td>
</tr>
<tr>
<td>Completion of abciximab infusion</td>
<td>77 (95)</td>
<td>74 (90)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Continuous data are presented as median (interquartile range).

<sup>a</sup>ACE, angiotensin-converting enzyme.

## Table 2  Pre-hospital and inhospital time delays

<table>
<thead>
<tr>
<th>Time interval (min)</th>
<th>Pre-hospital combination-fibrinolysis (n = 82)</th>
<th>Facilitated PCI (n = 82)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom onset—call mobile care unit</td>
<td>54 (25–117)</td>
<td>50 (21–103)</td>
<td>0.92</td>
</tr>
<tr>
<td>Call mobile care unit—arrival at scene</td>
<td>9 (7–12)</td>
<td>9 (7–12)</td>
<td>0.81</td>
</tr>
<tr>
<td>Arrival at scene—first reteplase bolus</td>
<td>30 (21–38)</td>
<td>30 (21–38)</td>
<td>0.80</td>
</tr>
<tr>
<td>Symptom onset—first reteplase bolus</td>
<td>92 (68–179)</td>
<td>90 (60–150)</td>
<td>0.72</td>
</tr>
<tr>
<td>Arrival at scene—start transport to hospital</td>
<td>41 (35–50)</td>
<td>42 (34–52)</td>
<td>0.89</td>
</tr>
<tr>
<td>Start transport—arrival at hospital</td>
<td>10 (7–13)</td>
<td>12 (8–15)</td>
<td>0.06</td>
</tr>
<tr>
<td>Arrival at hospital—first balloon inflation</td>
<td>–</td>
<td>63 (54–84)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range).

## Table 3  Results of MRI

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pre-hospital combination-fibrinolysis (n = 66)</th>
<th>Facilitated PCI (n = 68)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV&lt;sup&gt;a&lt;/sup&gt; ejection fraction (%)</td>
<td>54.0 (42.8–60.6)</td>
<td>55.9 (50.6–60.5)</td>
<td>0.07</td>
</tr>
<tr>
<td>LV&lt;sup&gt;a&lt;/sup&gt; end-diastolic volume (mL)</td>
<td>160.7 (134.5–177.9)</td>
<td>136.0 (116.1–166.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>LV&lt;sup&gt;a&lt;/sup&gt; end-systolic volume (mL)</td>
<td>73.9 (52.4–98.0)</td>
<td>60.9 (45.8–73.5)</td>
<td>0.008</td>
</tr>
<tr>
<td>Infarct size (% of LV&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>10.4 (3.4–16.3)</td>
<td>5.3 (1.3–11.2)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range).

<sup>a</sup>LV, left ventricle.
and in three patients (3.8%) after pre-hospital combination-fibrinolysis, no scar could be detected ($P = 0.22$). Infarct size assessed by the area under the curve of creatine kinase release was higher with 599 $\mu$mol/L/h (IQR 251–1037) in the pre-hospital combination-fibrinolysis group vs. 517 $\mu$mol/L/h (IQR 235–817; $P = 0.04$). The correlation with infarct size assessed by MRI was good ($r = 0.86$).

The primary endpoint was also analysed in several pre-defined subgroups. These results are given in Figure 2 and show the consistency of MRI among the subgroups.

### ST-segment resolution

The median time between ECG I and ECG II was similar between both treatment groups (pre-hospital combination-fibrinolysis: 127 min, IQR 111–150 and facilitated PCI: 143 min, IQR 122–162; $P = 0.12$). The percentage of patients with complete ST-elevation recovery (>70%) after 90 min was higher in patients undergoing facilitated PCI in comparison with pre-hospital combination-fibrinolysis (80.0 vs. 51.9%, $P < 0.001$). Intermediate (70–30%) and no ST-elevation recoveries (<30%) were 15.0 vs. 26.6% and 5.0 vs. 21.5% (<0.001).

### Clinical outcome

At 30-day follow-up, four patients (5.0%) died in the pre-hospital combination-fibrinolysis and two died (2.5%) in the facilitated PCI group. Non-fatal re-infarctions occurred in seven patients (8.8%) after pre-hospital combination-fibrinolysis and in three patients (3.8%) after facilitated PCI. In addition, there was one disabling stroke among patients after pre-hospital combination-fibrinolysis. The incidence of major bleedings was not different (five patients after combination-fibrinolysis and four patients after facilitated PCI). Thus, the composite endpoint of death, re-infarction, stroke, and major bleeding was reached in 17 patients (20.5%) after pre-hospital combination-fibrinolysis and in nine patients (11.3%) after facilitated PCI (relative risk 0.52, 95% CI 0.23–1.18, $P = 0.13$).

By 6 months, the incidence of the combined endpoint was 25.3% after pre-hospital combination-fibrinolysis and 15.0% after facilitated PCI (relative risk 0.57, 95% CI 0.28–1.13, $P = 0.10$) (Figure 3). The cumulative incidence of death during this period was similar to 7.5 vs. 6.3% (relative risk 0.83, 95% CI 0.22–2.99, $P = 0.68$).

### Discussion

In variance with previously published studies, our results shed a different light on certain important issues in the management of acute STEMI in a metropolitan area: (i) the time delay to reperfusion was extremely short, as pre-hospital fibrinolysis allows to treat the majority of patients within the first 2 h after symptom onset; (ii) at the time of angiography, the infarcted vessel had been re-opened completely by combination-fibrinolysis alone in 69%, supporting that very early treatment has the highest success rates; (iii) combining pharmacological with mechanical reperfusion resulted in improved tissue perfusion with a smaller final infarct size when compared with pre-hospital combination-fibrinolysis alone.

In acute STEMI, it is generally accepted that 'time is muscle'. This has been convincingly shown for fibrinolysis, where early treatment results in improved survival.1,19 This timely relationship appears to be less obvious with angioplasty. However, increased times to reperfusion also correlate with increased mortality.2,20 One reason why time to treatment may be less important for PCI is that reperfusion can be achieved irrespective of the time of thrombus formation, whereas in fibrinolysis, this is

![Figure 2](https://academic.oup.com/eurheartj/article-abstract/26/19/1956/532092) Differences in the infarct size (median and IQR) and the relative risk of death, re-infarction, stroke, or major bleeding in the pre-hospital combination-fibrinolysis and facilitated PCI group according to various characteristics. Horizontal bars indicate the 95% CI for the relative risk of the combined clinical endpoints and the IQR for the median infarct size.
time-dependent. The highest TIMI-3 flow (>70%) can be achieved by treatment within the first 2 h after symptom onset. A short-time window, where the majority of patients (43–80%) can only be treated by pre-hospital fibrinolysis, as supported by our trial. In contrast, the percentage of patients treated very early by intrahospital fibrinolysis or PCI is much lower ranging from 12 to 28%. Therefore, for optimal early reperfusion, the pharmacological and mechanical combination is only logical. A recently published trial failed to show any benefit by this combined approach with respect to infarct size. This difference, in comparison with our trial, might be explained by the much longer ischaemia times, as treatment started intrahospital. Furthermore, patients were included with symptoms up to 12 h.

A typical criticism of pre-hospital fibrinolysis is the additional time delay required for the administration of the lytic agent rather than starting immediate hospital transfer. However, trials have shown that by pre-hospital fibrinolysis approximately 7–15 additional minutes are required, which still result in a time gain in comparison with primary PCI or intrahospital fibrinolysis of >1 h. This is similar to the time difference of the first lytic bolus in comparison with balloon inflation in the facilitated PCI group in the current trial, and in comparison with the real world data, the current door-to-balloon times were excellent. Nevertheless, door-to-balloon times might further be shortened by optimization of the pre-hospital and intrahospital triage to ~30 min, particularly when patients are pre-announced by the ambulance service.

Safety is a key issue in facilitated PCI. Combination-fibrinolysis, a non-inferior regimen in comparison with standard fibrinolysis, might be the optimal pre-treatment as it allows the reduction of the lytic agent and as it has favourable effects on tissue perfusion. In the current trial, major bleeding was low and non-fatal, although a slightly higher maximal heparin bolus dose was used as recommended in current guidelines. The rates were equal to those reported after PCI, thus supporting that there is no additional risk for facilitated PCI using state-of-the-art fibrinolysis, anticoagulation, and interventional techniques. However, other small trials reported recently an excess of complications with facilitated PCI, and so far no clear safety conclusions can be drawn as a result of limited data.

Infarct size as an endpoint in reperfusion trials has been advocated because of its potential prognostic value. We used a sensitive and reliable method. In comparison with scintigraphic studies, MRI has the advantage of higher spatial resolution with the ability to detect even small sub-endocardial infarcts. Furthermore, its higher accuracy allows a subsequent sample size reduction. Although different techniques and imaging timepoints limit a direct comparison of final infarct size, the median infarct size of 5.3% after facilitated PCI is the lowest ever reported. After primary or facilitated PCI, median infarct sizes ranged from 8 to 14%. Furthermore, the infarct size of 10.4% after pre-hospital combination-fibrinolysis is lower than that reported after intrahospital fibrinolysis. The lower infarct size in facilitated PCI influenced...
the end-diastolic and end-systolic volumes favourably, parameters with prognostic impact. Transferring our findings of infarct size into clinical outcome might explain the observed identical clinical outcome for pre-hospital fibrinolysis and primary angioplasty and may account for a further improvement with facilitated PCI after pre-hospital fibrinolysis.

Mortality at 30 days for the pre-hospital combination-fibrinolysis group was in the lower range when compared with that reported for pre-hospital fibrinolysis. This might have been influenced by the high proportion of patients with rescue PCI or early elective PCI. Such a liberal PCI use after fibrinolysis is likely to have favourably affected the results in this group with respect to re-infarctions, infarct size, and improved long-term outcome. Post hoc analysis revealed that by consequent adherence to ST-segment resolution definition, the rescue-PCI rate would have been even higher, as an additional six patients showed ST-segment resolution as a consequence of complete symptom relieve. Nevertheless, additional benefit was gained, without an excess in bleeding complications, from facilitated PCI with respect to myocardial tissue perfusion and infarct size. Therefore, early reperfusion by combination-fibrinolysis in combination with facilitated PCI might be the optimal reperfusion strategy for STEMI, if confirmed by larger trials.

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Appendix

The following investigators participated in the Leipzig Pre-hospital Fibrinolysis Study: Steering committee, G. Schuler (chairman), L. Engelmann (co-chairman), and H. Thiele; Study coordinating center, L. Engelmann; Data coordinating center, H. Thiele; K. Elsner, K. Rahimi, E. Boudriot, and M.J. Kappl; Magnetic resonance core laboratory, S. Powalla, A. Wurzbacher, M.J. Kappl, and H. Thiele; Angiographic core laboratory, C. Dönath, K. Elsner, and K. Luderer; ECG core laboratory, M.J. Kappl and H. Thiele; and Clinical follow-up center, H. Thiele, K. Elsner, and M.J. Kappl. Participating hospitals and principal investigators (the number in parentheses is the number of patients treated): Ev-Luth. Diakonissen-Krankenhaus, T. Möller and M. Burkhardt (7); Kath. Krankenhaus St Elisabeth, D. Schneider and I. Hartung (3); Park-Krankenhaus Leipzig Südost GmbH, I. Weise (5); Städt. Klinikum St Georg Stadtkrankenhaus, H. J. Heberling and G. Holle (19); Städt. Klinikum St Georg and AIK, A. Hartmann, M. Ludewig, G. D. Kneissl, and W. Rothe (26); Universität Leipzig, Zentrum für Innere Medizin, L. Engelmann and D. Pfeiffer (27); and Universität Leipzig – Herzzentrum GmbH, G. Schuler and H. Thiele (77).

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