JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 4, NO. 6, 2011

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
DOI: 10.1016/j.jcin.2011.01.013

CVN Interview

Clinical Research

Randomized Comparison of Pre-Hospital–Initiated Facilitated Percutaneous Coronary Intervention Versus Primary Percutaneous Coronary Intervention in Acute Myocardial Infarction Very Early After Symptom Onset

The LIPSIA-STEMI Trial (Leipzig Immediate Prehospital Facilitated Angioplasty in ST-Segment Myocardial Infarction)

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Objectives This multicenter trial sought to assess the merits of facilitated percutaneous coronary intervention (PCI) versus primary PCI in an ST-segment elevation myocardial infarction (STEMI) network with long transfer distances in patients presenting early after symptom onset.

Background Facilitated PCI with fibrinolysis might be beneficial in specific high-risk STEMI situations to prevent myocardial necrosis expansion.

Methods Patients with STEMI (<3 h after symptom onset) were randomized to either pre-hospital–initiated facilitated PCI using tenecteplase (Group A; n = 81) or primary PCI (Group B; n = 81) plus optimal antithrombotic comedication. The primary endpoint was infarct size assessed by delayed-enhancement magnetic resonance imaging. Secondary endpoints were microvascular obstruction and myocardial salvage, early ST-segment resolution, and a composite of death, repeated myocardial infarctions, and congestive heart failure within 30 days.

Results The median time from symptom onset to randomization was 64 min (interquartile range [IQR]: 42 to 103 min) in Group A versus 55 min in Group B (IQR: 27 to 91 min; p = 0.26). Despite better pre-interventional TIMI (Thrombolysis In Myocardial Infarction) flow in Group A (71% vs. 35% TIMI flow grade 2 or 3; p < 0.001), the infarct size tended to be worse in Group A versus Group B (17.9% of left ventricle [IQR: 8.4% to 35.0%] vs. 13.7% [IQR: 7.5% to 24.0%]; p = 0.10). There was also a strong trend toward more early and late microvascular obstruction, (p = 0.06 and 0.09) and no difference in ST-segment resolution (p = 0.26). The combined clinical endpoint showed a trend toward higher event rates in Group A (19.8% vs. 13.6%; p = 0.13, relative risk: 0.52, 95% confidence interval: 0.23 to 1.18).

Conclusions In STEMI patients presenting early after symptom onset with relatively long transfer times, a fibrinolytic-based facilitated PCI approach with optimal antiplatelet comedication does not offer a benefit over primary PCI with respect to infarct size and tissue perfusion. ([LIPSIA-STEMI] The Leipzig Immediate Prehospital Facilitated Angioplasty in ST-Segment Myocardial Infarction; NCT00359918) (J Am Coll Cardiol Intv 2011;4:605–14) © 2011 by the American College of Cardiology Foundation

The greatest benefits of reperfusion in acute ST-segment elevation myocardial infarction (STEMI) can be obtained in the early phase after symptom onset (1,2). In general, primary percutaneous coronary intervention (PCI) performed in a timely manner by experienced operators is superior to in-hospital initiated fibrinolysis for patients presenting to hospitals with and without a cardiac catheterization laboratory (3). However, in the early phase (<2 to 3 h after symptom onset) the relative benefit of primary PCI is not as clear cut (4–7).

See page 615

The reduction of total ischemia time by pre-hospital fibrinolysis might compensate for the inferiority of fibrinolysis in achieving TIMI (Thrombolysis In Myocardial Infarction) flow grade 3 in comparison with primary PCI (8). Current recommendations, therefore, require a first-medical-contact-to-balloon time of <90 min if primary PCI is performed in early presenters (9,10). However, even in an optimized network of community hospitals, tertiary referral centers with 24-h primary PCI availability, and a technically advanced ambulance service, in many patients, these time requirements are not met (11). It is only logical to combine the advantages of pre-hospital fibrinolysis with subsequent PCI to achieve optimal results. However, this facilitated PCI approach failed to show any benefit or even caused harm in comparison with primary PCI (12–14).

Abbreviations and Acronyms

ECG = electrocardiogram
IQR = interquartile range
LV = left ventricle
MRI = magnetic resonance imaging
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction

In contrast, high-risk STEMI subgroups presenting in the early course, those treated in the pre-hospital setting, and those with longer delays from fibrinolysis to PCI might benefit from facilitated rather than primary PCI (15–17). In addition, concomitant antiplatelet therapy was suboptimal in the facilitated PCI arm in some previous trials with late thienopyridine administration and no glycoprotein IIb/IIIa inhibitors (12,13).

The aim of this trial was to assess whether facilitated PCI after pre-hospital fibrinolysis with optimized concomitant antiplatelet therapy leads to smaller infarct size and better reperfusion and clinical outcomes in comparison with primary PCI in STEMI patients presenting very early in a regional network with long transfer distances.

Methods

From August 2006 through August 2009, STEMI patients with symptoms <3 h were randomized in the ambulance to pre-hospital fibrinolysis with subsequent direct transfer to an interventional center for facilitated PCI or transfer for primary PCI. The trial was conducted in the region of Leipzig, Germany, covering 19 hospitals without and 3 with interventional cardiology. (See Appendix for a list of participating hospitals and investigators.) The network (Fig. 1) also consists of 24 mobile intensive care units plus 2 helicopters, all of which are physician-staffed and equipped with portable electrocardiogram (ECG) recorders that can transmit the ECG by telemetry. Inclusion criteria were the presence of ischemic symptoms for <3 h plus ST-segment elevation ≥0.1 mV in ≥2 extremity leads or ≥0.2 mV in ≥2 precordial leads. Exclusion criteria were the typical contraindications to fibrinolysis, such as previous stroke, active bleeding, history of major trauma or surgery <30 days, active peptic ulcer, neoplasms, uncontrolled hypertension >200 mm Hg, chronic oral anticoagulation, cardiogenic shock, and pregnancy. Additional exclusion criteria were typical contraindications for magnetic resonance imaging (MRI) at randomization, such as pacemakers, defibrillators, and intracerebral metallic clips.

The study was approved by the local ethics committees, and all patients gave written informed consent.

Study protocol. After diagnosis by the emergency physician, contact was made with the study coordinating center that randomized the patients by drawing sealed envelopes to 1 of the treatment arms: pre-hospital facilitated PCI (Group A) or primary PCI (Group B). All patients received 500 mg of aspirin and heparin (60 U/kg, maximum 5,000 U) intravenously plus 600 mg of clopidogrel orally. In patients assigned to the facilitated PCI arm, this medication was followed by a weight-adjusted dose of intravenous tenecteplase, as described previously (12).

Patients in both groups were transported immediately to 1 of 3 hospitals with catheterization laboratories after telephone announcement, bypassing any emergency department. The aim was to optimize the time-to-first-balloon inflation. The achieved door-to-balloon times for the individual patients were published online on the next day to allow direct feedback between hospital and ambulance staff.

PCI was performed according to local standards in case of a totally occluded infarct-related artery, culprit lesion stenosis of >50%, and/or a reduced TIMI flow grade <3. Stenting of the culprit lesion was recommended unless the vessel had a diameter of <2.0 mm. The use of bare-metal or

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Manuscript received December 23, 2010, accepted January 5, 2011.

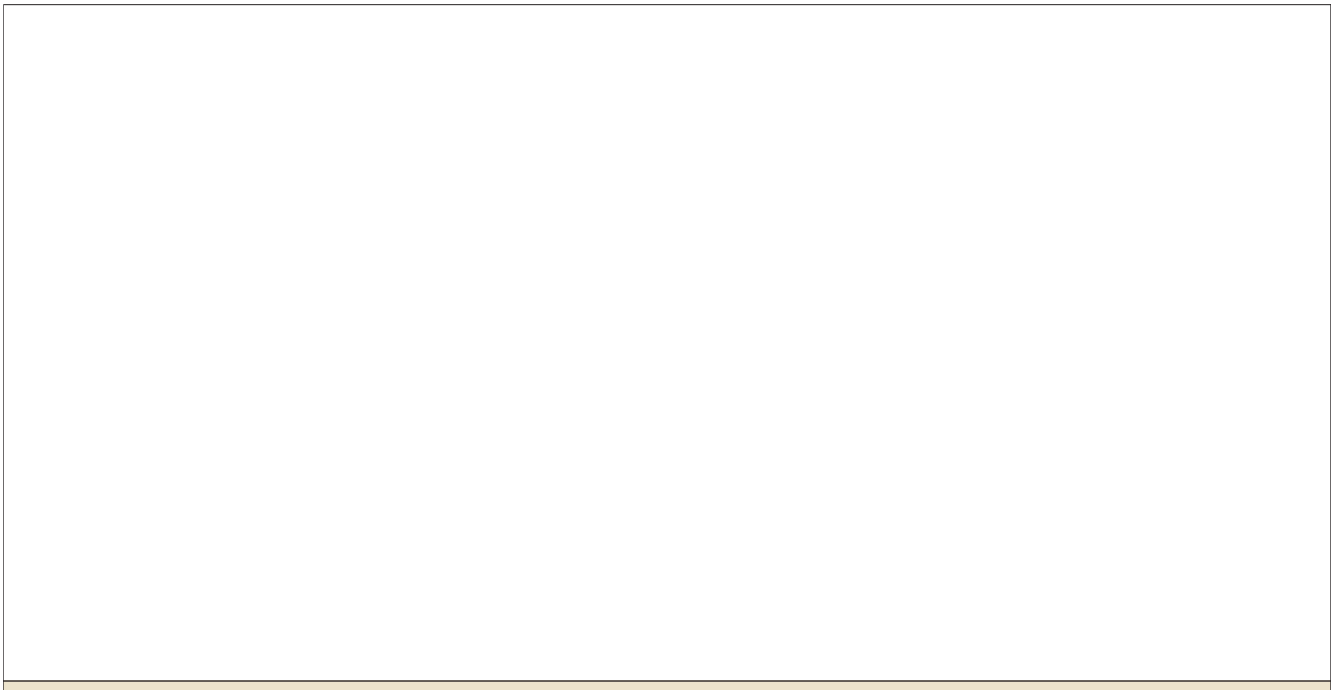

Figure 1. The LIPSIA-STEMI Network

Locations of the 24 mobile intensive care units (most of them with affiliated hospitals) are displayed with **red dots,** location of helicopters with **green dot,** and the 3 catheterization laboratories with **blue crosses.** LIPSIA-STEMI = Leipzig Immediate Prehospital Facilitated Angioplasty in ST-Segment Myocardial Infarction.

drug-eluting stents and thrombectomy was left to the interventionalist's discretion. After PCI, the sheath was removed and the puncture site treated by a closure device or using a compression system until hemostasis.

The use of glycoprotein IIb/IIIa inhibitors was recommended at standard dose for 12 h in both groups, in particular, in patients with high thrombus burden and reduced TIMI flow grade after PCI. During PCI, additional heparin doses were given adjusted to the activated clotting time (target: 200 to 250 s).

In both study groups, there was no continuous heparin infusion after hospital arrival. Clopidogrel at 75 mg/day was recommended for 12 months.

The following times were recorded: initial onset of angina, arrival on scene of the emergency physician, first 12-lead ECG, injection of the tenecteplase bolus, hospital arrival, first balloon inflation, and post-PCI ECG.

Angiographic analysis. The initial and final TIMI flow grades of the culprit vessel were assessed offline in the angiographic core laboratory by 2 blinded observers with averaging of the TIMI flow grades in cases of disagreement.

ST-segment resolution. For ECG interpretation, blinded observers measured the sum of ST-segment elevation 20 ms after the end of the QRS complex in the initial pre-hospital ECG and that obtained early after PCI directly after transfer to the intensive care unit. By protocol, no additional ECG was obtained immediately before cardiac catheterization to optimize door-to-balloon times. ST-segment resolution was calculated as the sum of ST-segment elevation before minus the sum of ST-segment elevation after PCI divided by the sum of ST-segment elevation before PCI. ST-segment resolution was expressed as a percentage, as described previously (18).

Magnetic resonance imaging. Myocardial infarct size, microvascular obstruction, and myocardial salvage were acquired on clinical 1.5-T scanners from different vendors (Philips, Best, the Netherlands; and Siemens, Erlangen, Germany) using the same acquisition protocol as described previously (18). Left ventricular (LV) function was assessed by a steady-state free precession technique. For area-at-risk determination, short-axis slices covering the whole ventricle using a T_2-weighted turbo spin-echo sequence were obtained. Early and delayed enhancement images covering the whole ventricle were acquired approximately 1 and 15 min after intravenous administration of 0.2 mmol/kg body weight of gadolinium chelate. Total LV mass, early and late microvascular obstruction, area at risk, and infarct size were assessed manually from these images by fully blinded operators at the MRI core laboratory (18). The following parameters were calculated: 1) area at risk = volume edema/volume LV mass × 100; 2) percent infarct size = volume infarct/volume LV mass × 100; 3) percentage of microvascular obstruction = volume microvascular obstruction/volume LV mass × 100; 4) myocardial salvage = area

at risk-infarct size; and 5) myocardial salvage index = (area at risk-infarct size)/area at risk.

The MRI core laboratory has excellent reproducibility and interobserver and intraobserver variability for infarct size measurement (19).

Infarct size measured by enzyme release. Infarct size was also assessed indirectly by the area under the curve of creatine kinase-myocardial band release derived from measurements every 6 h over 48 h.

Clinical endpoints. Clinical endpoints were a composite of death, reinfarction, and the occurrence of new congestive heart failure <30 days after randomization. For post-hospital follow-up each patient had a 30-day outpatient visit. The diagnosis of reinfarction was based on previous definitions (18). New heart failure was defined as any congestive heart failure (rales, dyspnea, New York Heart Association functional class III to IV) occurring >24 h after the index event. Outcomes were adjudicated by a clinical events committee blinded to the patients' assigned treatments.

Safety. Major safety endpoints were severe or life-threatening, moderate, or minor bleeding as assessed by the GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) trial (20) and the occurrence of any ischemic stroke.

Statistical analysis. The number of patients included was based on the sample size estimation for the primary study endpoint, infarct size. Based on a previous study comparing pre-hospital initiated facilitated PCI versus pre-hospital fibrinolysis with standard care and previous primary PCI trials (21–23), we assumed that the final infarct size would be 7 ± 6% after facilitated PCI and 12 ± 10% after primary PCI. With a power of 80% and a 2-sided alpha value of 0.05, we estimated that 64 patients would be required in each group. Based on previous trials, we expected that not all patients would undergo MRI for primary endpoint assessment and, therefore, included 162 patients. A predefined subgroup analysis was performed for anterior/nonanterior STEMI, and different times from symptom onset to randomization (<1 h, 1 to 2 h, and >2 h). With the exception that patients with nonconfirmed STEMI at inclusion were excluded, all analyses were performed according to the intention-to-treat principle.

Categorical data are presented as counts or proportions with the corresponding percentages. Most continuous variables had non-normal distribution (as evaluated by Kolmogorov-Smirnov test). For reasons of uniformity, summary statistics for all continuous variables are therefore presented as medians with interquartile range (IQR).

Differences between the treatment groups were assessed by Fisher exact or the chi-square tests for categorical variables and by the Student *t* test for continuous data with normal distribution. Otherwise, the nonparametric Wilcoxon rank sum test was used. For the combined secondary clinical endpoint, the Kaplan-Meier method was applied, and differences were assessed by the log-rank test.

A multivariable linear-regression model including age, sex, diabetes, hypertension, symptom duration-randomization, infarct location, pre- and post-interventional TIMI flow grade, and glycoprotein IIb/IIIa inhibitor use was applied to assess confounders for infarct size. All statistical tests were performed with SPSS software (version 17.0, IBM, Armonk, New York). A 2-tailed p value <0.05 was considered statistically significant.

Results

Of the 162 patients enrolled, 81 were randomly assigned to pre-hospital facilitated PCI and 81 to primary PCI (Fig. 2). All patients received the assigned pre-hospital therapy. Most patients were included in the rural setting (72.3%), and the median transport distance for all patients was 42 km (IQR: 21 to 53 km). Baseline characteristics were similar between the 2 treatment groups (Table 1). Altogether, 4 patients (2.5%) had to be excluded from further analysis for misdiagnosis of STEMI (pericarditis, n = 1; ECG misinterpretation, n = 2; apical ballooning syndrome, n = 1). Their clinical course was otherwise uneventful.

Reperfusion. The different time-steps from symptom onset to reperfusion are shown in Figure 3. Due to slightly longer symptom arrival times of the mobile intensive care unit and due to longer treatment and transportation times in the facilitated PCI group, the overall symptom-onset-to-first-balloon-inflation times were longer (158 min, IQR: 119 to 222 vs. 131 min, IQR: 106 to 175 min; p = 0.01), although the door-to-balloon times were extremely short in both groups with 23 min (IQR: 20 to 31 min) versus 25 min (IQR: 18 to 34 min; p = 0.75).

All patients assigned to facilitated PCI underwent diagnostic angiography, and there were 74 (92.5%) facilitated PCI procedures (death before PCI, n = 1; no angiographically significant stenosis, n = 3; coronary artery bypass grafting several days after the index event, n = 1; small peripheral vessel, n = 1). In the primary PCI group, all patients underwent diagnostic angiography, and PCI was not performed in 2 patients (coronary artery bypass grafting, n = 1; no relevant stenosis after spontaneous lysis, n = 1). Immediately before PCI, there were TIMI flow grades 2 and 3 in 26.6% and 44.3% of the facilitated PCI group and 10.3% and 24.4% of the primary PCI group (p < 0.001). Post-stenting, TIMI flow grade 3 in the infarct-related artery was present in 83.2% versus 88.5% (p = 0.44).

Magnetic resonance imaging. Complete MRI results were available in 69 patients (86.3%) of the pre-hospital facilitated PCI group and in 71 (91.0%) of the primary PCI group (Table 2). Reasons for missing data are shown in Figure 2. MRI was performed at day 3 (IQR: 2 to 4 days) in both groups (p = 0.44). Patients in both groups had

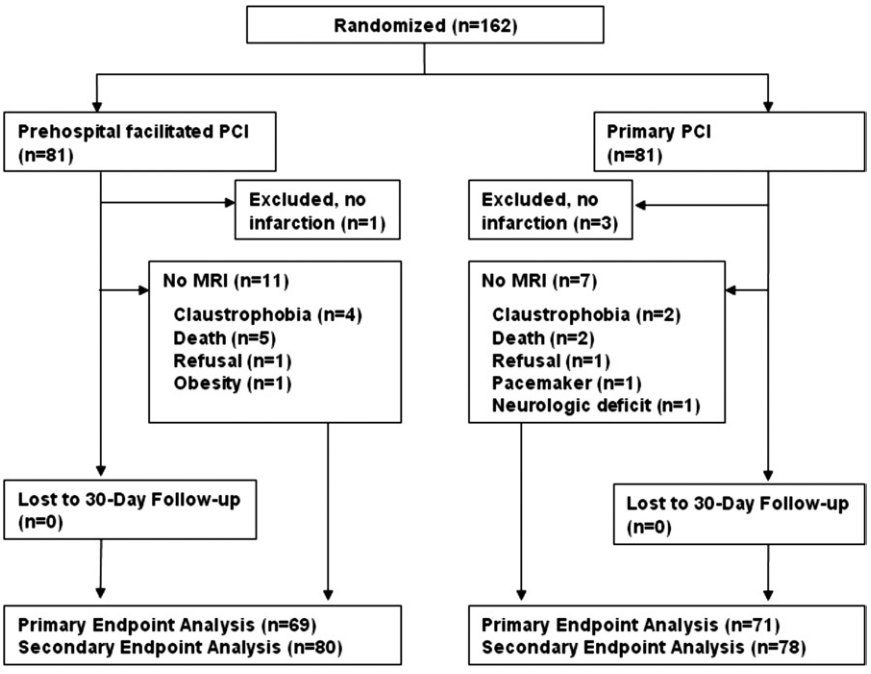

Figure 2. Trial Profile

Trial profile showing the number of patients screened, excluded, and evaluated for the primary endpoint and for the clinical endpoint with follow-up. The reasons for exclusion are shown. MRI = magnetic resonance imaging; PCI = percutaneous coronary intervention.

similar areas at risk. The primary endpoint, infarct size, tended to be higher in the facilitated PCI group ($p = 0.10$), and there was also a strong trend toward a greater extent of early and late microvascular obstruction in the facilitated PCI group ($p = 0.06$ and 0.09, respectively).

There were no significant differences in the corresponding myocardial salvage, myocardial salvage index, or LV function and volumes.

The primary endpoint was also analyzed in several predefined subgroups. These results show the consistency of MRI among the subgroups (Figs. 4A and 4B).

In a multivariable linear regression model, the strongest predictors for increasing infarct size were post-PCI TIMI flow grade, symptom duration, and anterior infarct location ($p < 0.01$ for all). The reperfusion type and glycoprotein IIb/IIIa inhibitor use had no effect on infarct size ($p = 0.21$ and 0.34). There was also no difference in the primary endpoint with respect to transportation distances and pre-PCI TIMI flow grade.

Infarct size measured by enzyme release. The infarct size assessed by the area under the curve of creatine kinase-myocardial band release was higher in the facilitated PCI in comparison with the primary PCI group (67.9 μmol/l/h, IQR: 44.0 to 94.8 μmol/l/h vs. 48.5 μmol/l/h, IQR: 26.8 to 83.7 μmol/l/h; $p = 0.02$).

ST-segment resolution. The number of leads with ST-segment elevation in the pre-hospital setting was 5.0 (IQR: 4.0 to 6.0) in the facilitated PCI and 5.0 (IQR: 4.0 to 5.5) in the primary PCI group ($p = 0.27$). Similarly, the absolute ST-segment elevation was 1.2 mV (IQR: 0.8 to 1.9 mV) versus 1.1 mV (IQR: 0.7 to 1.7 mV; $p = 0.20$). The median time between the pre-hospital ECG and the post-PCI ECG was similar between both treatment groups (pre-hospital facilitated PCI: 120 min, IQR: 99 to 143 min; primary PCI: 113 min, IQR: 93 to 136 min; $p = 0.14$). ST-segment resolution as a continuous variable was similar in the facilitated PCI in comparison with the primary PCI group (66.7, IQR: 44.5 to 92.9 vs. 75.0, IQR: 50.0 to 100.0; $p = 0.26$). Accordingly, the percentage of patients with complete (42.9% vs. 57.7%), intermediate (40.2% vs. 29.5%), and no ST-segment recovery (16.9% vs. 12.8%) was similar in both groups ($p = 0.18$).

Clinical endpoints. At 30-day follow-up, 5 patients (6.1%) died in the pre-hospital facilitated PCI and 4 (4.9%) in the primary PCI group. Nonfatal reinfarctions occurred in 5 patients (6.1%) after pre-hospital facilitated PCI and in 4 (4.9%) after primary PCI. Additionally, there were 6 (7.4%) versus 3 (3.7%) patients with new congestive heart failure. The composite secondary endpoint of death, reinfarction, and new congestive heart failure was reached in 16 patients (19.8%) after pre-hospital facilitated PCI and in 11 (13.6%) after primary PCI (relative risk: 0.52, 95% confidence interval: 0.23 to 1.18, $p = 0.13$).

Table 1. Main Patient Characteristics

Variable	Pre-Hospital Facilitated PCI (n = 80)	Primary PCI (n = 78)	p Value
Age, yrs	63 (54–73)	61 (53–72)	0.57
Male	61 (76)	64 (82)	0.48
Cardiovascular risk factors			
Current smoking	33 (41)	38 (48)	0.43
Hypertension	53 (66)	50 (64)	0.91
Hypercholesterolemia	32 (40)	21 (26)	0.12
Diabetes mellitus	29 (36)	19 (24)	0.15
Prior myocardial infarction	2 (3)	4 (5)	0.65
Prior coronary artery bypass grafting	0	1 (1)	0.99
Anterior myocardial infarction	34 (43)	38 (51)	0.39
Systolic blood pressure, mm Hg	130 (112–143)	133 (114–146)	0.51
Diastolic blood pressure, mm Hg	80 (70–86)	79 (67–87)	0.93
Heart rate, beats/min	83 (69–93)	77 (70–85)	0.18
Killip class on admission			0.36
1	57 (71)	58 (74)	
2	11 (14)	14 (18)	
3	5 (6)	4 (5)	
4	7 (9)	2 (3)	
Concomitant medications			
Beta-blockers	77 (96)	77 (99)	0.63
ACE inhibitors/AT1 antagonists	78 (98)	76 (97)	0.63
Aspirin	79 (99)	78 (100)	0.99
Clopidogrel	80 (100)	78 (100)	1.00
Statins	78 (98)	76 (97)	0.63
Aldosterone antagonists	5 (6)	3 (4)	0.74
Glycoprotein IIb/IIIa inhibitors	23 (29)	71 (88)	<0.001

Values are median (interquartile range) or n (%).
ACE = angiotensin-converting enzyme; AT1 = angiotensin 1; PCI = percutaneous coronary intervention.

Safety. There were no differences in bleeding according to the GUSTO severity criteria in the 2 treatment groups (severe/life-threatening: 2.5% vs. 2.5%, moderate: 2.5% vs. 3.7%, mild: 4.9% vs. 7.4%; p = NS for all). In addition, there was 1 ischemic stroke in each group.

Discussion

In line with previous studies comparing facilitated PCI versus primary PCI, there was no benefit of facilitated PCI over primary PCI even in patients presenting very early after symptom onset in the pre-hospital setting with relatively long transfer distances to a cardiac catheterization laboratory.

The trend toward greater infarct sizes on MRI in the facilitated PCI group (significant with enzyme measurements) seems paradoxical at first glance. Patients in the facilitated PCI group in the current trial displayed higher TIMI flow grade 3 before PCI, indicating earlier reperfusion in comparison with primary PCI patients. From a conventional point of view, this should result in smaller infarct size and greater myocardial salvage in the facilitated PCI group. In fact, a previous large trial using PCI facilitation with half-dose reteplase and abciximab showed improved TIMI flow grades before facilitated PCI with subsequent decrease in the area under the curve for creatine kinase compared with primary PCI, implying greater myocardial salvage (13). In the current study, however, a trend in the opposite direction was seen. Several hypotheses might explain these findings. First, a typical criticism of pre-hospital fibrinolysis is the additional time delay required for administration of the lytic agent rather than starting immediate hospital transfer. Previous trials have shown that pre-hospital fibrinolysis requires approximately 7 to 15 additional minutes before the start of transport to the hospital, eventually resulting in longer symptom-onset-to-balloon times as compared to patients undergoing primary PCI (5,24). In the current trial, the difference in symptom-onset-to-balloon times between groups was >20 min in median, presumably caused by the preparation and application of the fibrinolytic bolus. This delay might be especially relevant in patients not achieving adequate TIMI flow grade by fibrinolysis alone. The benefit of a higher infarct artery patency rate upon initial angiography in the facilitated PCI group might have been offset by the delay in mechanical

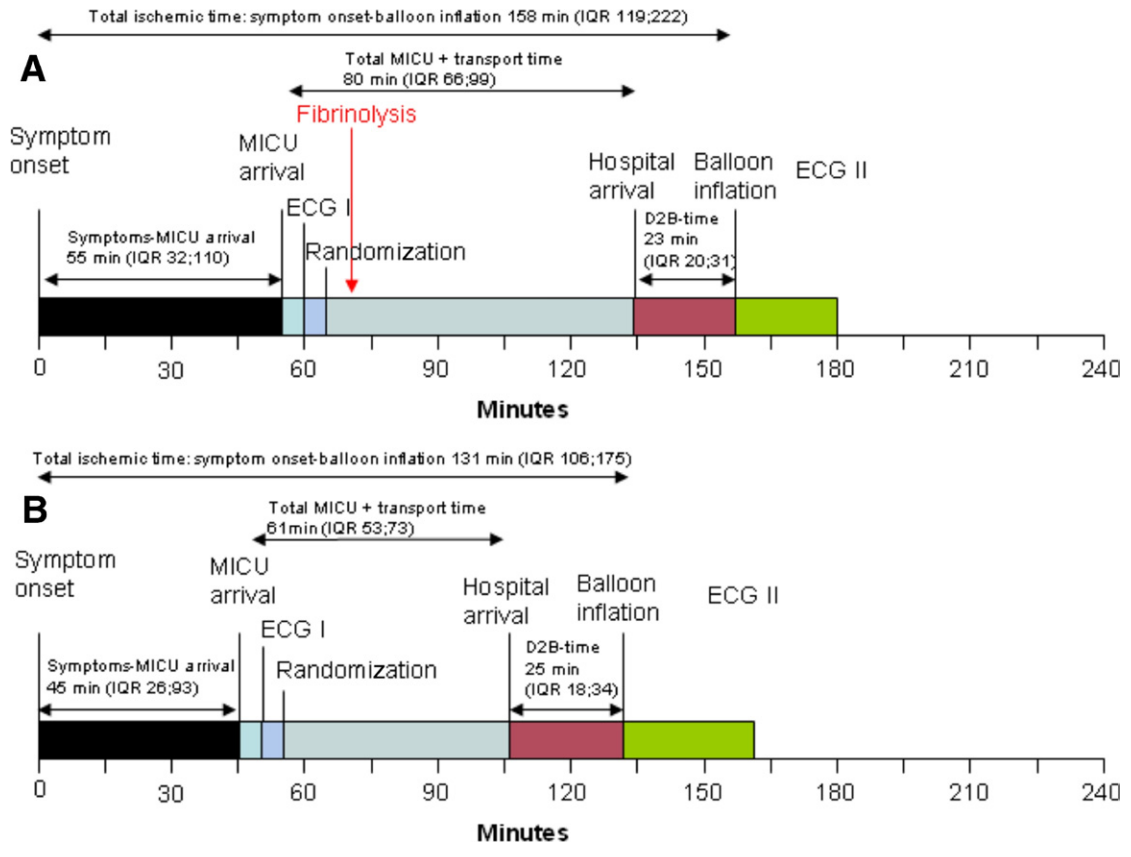

Figure 3. Key Median Treatment Intervals

The key median treatment intervals for facilitated PCI **(A)** and primary PCI **(B).** D2B = door-to-balloon time; ECG = electrocardiogram; IQR = interquartile range; MICU = mobile intensive care unit.

treatment of the infarct-related artery. This might be especially relevant in STEMI patients presenting very early after symptom onset, as supported by recent MRI data demonstrating a progressive decrease of the salvaged area at risk (while infarct size and microvascular obstruction increase) when reperfusion occurs >90 min of coronary occlusion (1). There seems to be a "golden window" during which even small delays in reperfusion time are highly clinically relevant. Second, the trend toward greater infarct size and microvascular obstruction in the facilitated PCI group might also be attributed to paradoxical fibrinolytic-induced platelet aggregation and thrombin-induced platelet

Table 2. MRI Results

Variable	Pre-Hospital Facilitated PCI (n = 69)	Primary PCI (n = 70)	p Value
LV ejection fraction, %	57.4 (49.7–66.9)	60.3 (51.5–67.0)	0.72
LV end-diastolic volume, ml	125.1 (100.9–153.9)	115.4 (104.2–140.0)	0.31
LV end-systolic volume, ml	55.5 (33.8–72.3)	47.3 (35.4–63.8)	0.47
Area at risk	33.1 (24.4–48.7)	32.2 (19.9–41.1)	0.34
Infarct size, % LV	17.9 (8.4–35.0)	13.7 (7.5–24.0)	0.10
Early MO, % LV	3.4 (1.0–7.9)	1.9 (0.0–5.9)	0.06
Late MO, % LV	1.3 (0.5–6.1)	0.9 (0.0–3.9)	0.09
Myocardial salvage, % LV	13.5 (5.1–23.7)	15.3 (9.1–21.6)	0.35
Myocardial salvage index	42.9 (27.0–66.9)	48.9 (33.7–68.5)	0.11

Values are median (interquartile range).
LV = left ventricle; MO = microvascular obstruction; PCI = percutaneous coronary intervention.

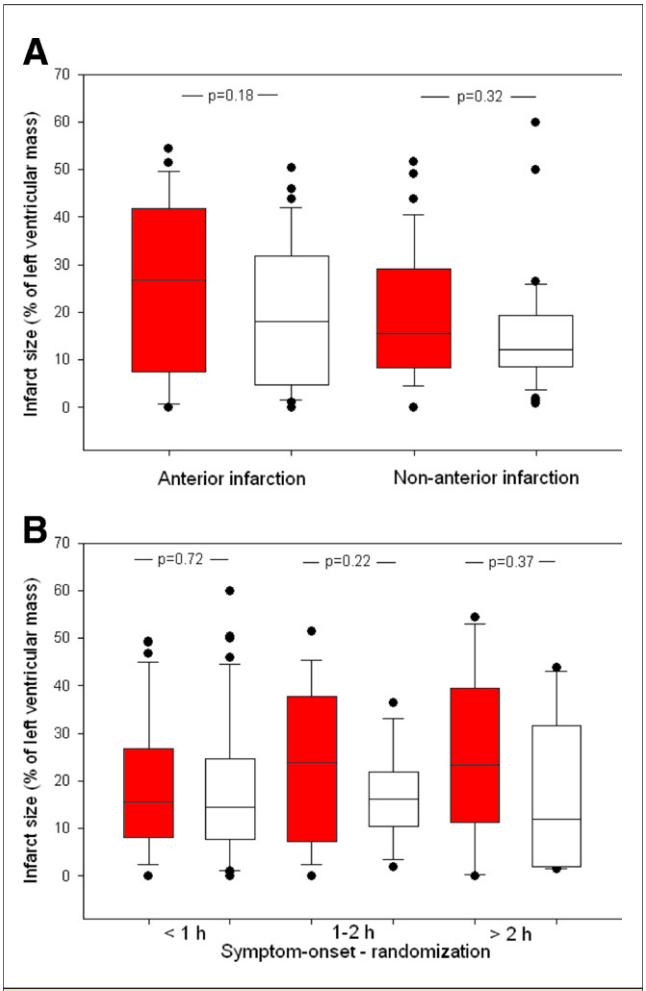

Figure 4. Subgroup Analysis

Subgroup analysis for the comparison of facilitated percutaneous coronary intervention (PCI) **(red boxes)** versus primary PCI **(white boxes)** for anterior and nonanterior infarction **(A)** and different times from symptom onset to randomization **(B). Boxes** indicate 25th percentile, median, and 75th percentile; **whiskers** indicate the 10th and 90th percentiles. **Dots** indicate outliers.

activation, despite the early and concomitant use of clopidogrel (25). A different pharmacological regimen such as half-dose fibrinolytics in conjunction with glycoprotein IIb/IIIa inhibitors might be more beneficial in this situation's results (16). Third, early reperfusion of the infarct-related artery may not reflect tissue-level myocardial reperfusion and TIMI flow grade 3, therefore, does not guarantee effective myocardial perfusion (26). Fourth, another significant difference between study groups was the lower use of glycoprotein IIb/IIIa inhibitors in the facilitated PCI group, which was likely influenced by investigator decisions and the fear of bleeding complications with a combined full-dose fibrinolytic drug. Of note, its use was significantly higher in comparison with a previous trial because glycoprotein IIb/IIIa inhibitors were not restricted to bailout indications (12). Despite the concomitant antiplatelet therapy, no higher bleeding complications or stroke were noted. Fifth, the actual delays from medical contact to balloon inflation were still quite short because of the optimized network. It may be that facilitated PCI has advantages over primary PCI only in patients with much longer delays to PCI. Finally, despite having included a relative high-risk population characterized by the relatively high event rates in both groups and the number of affected leads in the ECG, only extreme high-risk patients might benefit from facilitated PCI.

Infarct size as an endpoint in reperfusion trials has been advocated because of its prognostic value (23). MRI is considered the reference method, and it has also the advantage to allow the assessment of microvascular obstruction with its additional independent prognostic impact (27,28). Moreover, we also used state-of-the-art techniques to assess the area at risk and also the salvaged myocardium, excluding any baseline differences between the treatment groups (1,18).

The current study is in line with several large-scale trials showing that a facilitated approach as compared to primary PCI causes harm or is neutral at best (12–14). However, this is in contrast to trials comparing facilitated PCI versus fibrinolysis only (29). Given the current evidence, more efforts should be directed to establish well-functioning networks with short door-to-balloon times to deliver primary PCI to most patients (23). Although nearly 80% of the adult population lives within a 1-h drive of a PCI center in the United States and also in many European countries (30), the full benefits of primary PCI still cannot be offered to most of these patients (11). The door-to-balloon times in the current trial were much shorter than those reported from other studies and registries with door-to-balloon times of 87 to 108 min (31). This clearly demonstrates the ability to meet current first-medical-contact-to-balloon time requirements even for patients in rural settings (10). To achieve these extremely short first-medical-contact and also door-to-balloon times, a dedicated network of mobile intensive care units and helicopters with direct access to a catheterization laboratory as well as pre-announcement by the ambulance service are required.

Study limitations. The most important limitation is the open-label design that led to a lower use of glycoprotein IIb/IIIa inhibitors in the facilitated PCI group. However, multivariable adjustment did not show an influence of glycoprotein IIb/IIIa inhibitor use. MRI, angiographic, laboratory, and ECG results were assessed by blinded observers, and stringent definitions for reporting were provided, limiting the influence of the open-label design. Another limitation is that this trial had sufficient statistical power only to assess final infarct size—this precludes meaningful interpretation of the combined clinical endpoint—and some patients were not assessed for the primary study endpoint due to contraindications. The exclusion of patients from MRI is

inherent to this imaging method. However, the percentage of patients excluded from MRI was similar to previous trials, and this was taken into account by the a priori sample size calculation (21,23). Moreover, these patients were included in the enzymatic infarct size, ST-segment resolution, and clinical adverse events analysis.

Conclusions

In an optimized STEMI network, pre-hospital initiated facilitated PCI does not add a benefit over primary PCI with respect to infarct size in STEMI patients presenting very early after symptom onset despite an earlier angiographic reperfusion and optimal antithrombotic comedication. These results based on a surrogate endpoint do not support proceeding to a large-scale clinical trial of facilitated PCI in this selected patient group. However, facilitated PCI could still prove beneficial in patients with longer delays to PCI.

Acknowledgments
The authors are indebted to the participating emergency physicians, the medical and technical staff in the coronary care units, and the catheterization laboratories of the participating institutions.

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Key Words: acute myocardial infarction ■ angioplasty ■ fibrinolysis ■ percutaneous coronary intervention ■ prehospital treatment.

Appendix

The following investigators participated in the LIPSIA-STEMI trial: *Steering committee* – H. Thiele (chairman), G. Schuler (co-chairman); *Study coordinating center* — H. Thiele; *Data coordinating centers* — H. Thiele, I. Eitel, A. Leuschner; *Magnetic resonance core laboratory* – C. Meinberg, I. Eitel; *Angiographic core laboratory* – G. Fuernau, S. Desch, H. Thiele; *ECG core laboratory* – I. Eitel, A. Leuschner; *Clinical follow-up center* – H. Thiele, I. Eitel, A. Leuschner, J. Zachrau, S. Desch. Participating hospitals and principal investigators: *Städtisches Klinikum St. Georg*: A. Hartmann, F. Mickley, O. Gunkel; *University of Leipzig, Klinik für Kardiologie und Angiologie*: D. Pfeiffer, N. Klein, A. Hagendorff; *Krankenhaus, Naumburg*: U. Lotze, *Krankenhaus, Altenburg*: W. Strauβ; *University of Leipzig – Herzzentrum*: H. Thiele, G. Schuler.