Long-Term Follow-Up of Early Versus Delayed Invasive Approach After Fibrinolysis in Acute Myocardial Infarction

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Background—Optimal reperfusion strategy in ST-elevation myocardial infarction is controversial. Failure of fibrinolytic therapy is related to limited efficacy, high reocclusion rates, reinfarction, and systemic bleeding complications. Data on the impact of percutaneous coronary intervention (PCI) after fibrinolysis are conflicting. The Southwest German Interventional Study in Acute Myocardial Infarction (SIAM III) evaluated the effects of transfer for early PCI in acute ST-elevation–myocardial infarction compared with a delayed PCI strategy.

Methods and Results—SIAM III was a multicenter, randomized, prospective, controlled trial in patients with ST-elevation–myocardial infarction receiving fibrinolysis ≤12 hours after onset of symptoms. All patients received reteplase, aspirin in combination with ticlopidine, and heparin. Patients of the early PCI group were transferred within 6 hours after fibrinolysis for PCI. The delayed PCI group received elective PCI 2 weeks after fibrinolysis. In total, 197 patients were included; 163 were treated by PCI. The primary end point was the composite of death, reinfarction, target lesion revascularization, and ischemic events. During a mean follow-up time of 7.9±3.4 years (maximum, 11.2 years), early PCI was associated with a significant reduction of the primary end point (hazard ratio, 0.61 [95% confidence interval, 0.42 to 0.88]; P=0.008). Long-term survival was higher in the early PCI group (P=0.057). Ischemic events were significantly reduced after early PCI (P=0.003).

Conclusions—Early PCI after fibrinolysis improves long-term event-free survival compared with a delayed PCI treatment strategy.

Key Words: ST-elevation–myocardial infarction ■ fibrinolysis ■ percutaneous coronary intervention

Fibrinolytic therapy was the first reperfusion treatment for acute ST-elevation–myocardial infarction (STEMI) leading to a significant reduction of mortality rates.1,2 However, fibrinolysis failed in almost 50% of patients because of low patency and high reocclusion rates of the infarct related artery.3–5 Because timely reperfusion with primary percutaneous coronary intervention (PCI) became the method of choice for patients with STEMI,6,7 time delay is the most important limitation impairing a patient’s clinical outcome.6–11 In a high-risk patient population, survival critically depends on door-to-balloon times.12 Furthermore, the benefit of primary angioplasty over thrombolytic therapy was only observed in high-volume centers.13,14

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The combination of fibrinolytic therapy followed by PCI was suggested to be the preferred reperfusion strategy for patients without access to interventional facilities within the guideline-recommended time frame of 90 minutes. However, in the balloon era, coronary angioplasty failed to show a benefit for routine early intervention after fibrinolysis compared with fibrinolytic therapy alone.15–17 It could be assumed that coronary stents and thienopyridine may overcome the limitations of balloon angioplasty after fibrinolysis by preventing early reocclusions. Furthermore, modern antiplatelet and anticoagulant therapy was not given in most of the older facilitated PCI trials. A pharmacoinvasive strategy combining advantages of both fibrinolysis and PCI with stent implantation seems to be a promising but complicated treatment for STEMI.18–24 Optimal strategy and timing of reperfusion are still subject to a sustained debate, and long-term data concerning these questions are lacking.

The Southwest German Interventional Study in Acute Myocardial Infarction (SIAM III) compared the strategy of early PCI after fibrinolysis with a conservative medical treatment strategy and elective PCI 2 weeks after fibrinolysis.18 The presented data show the long-term effects of routine early PCI after fibrinolysis in acute STEMI with a mean follow-up time of 7.9±3.4 years (maximum 11.2 years).

Methods

Study Design

The details of the study design were published previously.18 SIAM III was a prospective, controlled, randomized, multicenter trial...
among patients with acute STEMI enrolled from July 1998 to April 2001 and performed at 5 sites in Germany. The study was approved by the appropriate local ethics committee and was performed according to the Declaration of Helsinki and World Health Organization guidelines. All patients gave written informed consent. Patients were recruited from community hospitals without capability for primary PCI located within a distance to the intervention hospital up to 35 kilometers.

Study Population

Eligible patients were at least 18 years of age, presented with symptoms of myocardial infarction present for <12 hours, and had, on the basis of 12-lead ECG, ST-segment elevation of ≥1 mm in ≥2 more limb leads, ST-segment elevation of ≥2 mm in the precordial leads, or new left bundle-branch block. They were eligible for fibrinolysis. Angiographic criteria for treatment per protocol included an indication for angioplasty independent of the study with an infarct-related lesion in a native coronary artery of ≥2.5 mm in diameter and a stenosis grade of ≥70% or Thrombolysis In Myocardial Infarction (TIMI) flow less than grade III. Exclusion criteria comprised factors such as chronic renal insufficiency requiring dialysis and a secondary or iatrogenic myocardial infarction. Angiographic criteria for a treatment not per protocol included a coronary anatomy unsuitable for stent placement, an anticipated indication for surgical coronary revascularization within 6 months, a previous myocardial infarction in the area of the infarct-related vessel, or an infarct-related lesion not clearly defined.

Drug Regimens and Interventional Procedure

Reteplase (Rapilysin, Hoffmann-La Roche AG, Grenzach-Wyhlen, Germany) was administered in 2 boluses of 10 MU 30 minutes apart. Patients received 250 mg of aspirin intravenously (Aspisol, Bayer Vital, Germany) and a bolus of 5000 IU heparin. Heparin was continued by an infusion of 1000 IU per hour. The initial rate of heparin infusion was reduced to 800 U per hour for patients weighting ≤80 kg and was adjusted to maintain an activated partial thromboplastin time of 50 to 70 seconds in all patients.

During fibrinolysis in the primary hospital, the patients were randomly assigned to either transfer for early PCI or delayed PCI treatment. Patients of the early PCI group were transferred to the interventional center within 6 hours after fibrinolysis for invasive treatment of the infarct-related artery followed by a second coronary angiography after 2 weeks. Patients in the delayed PCI group underwent elective PCI of the infarct-related artery after 2 weeks or earlier in the case of recurrent ischemia.

Cardiac catheterization was carried out through the right or left femoral artery. Additional heparin was given, depending on the activated clotting time, with a target of 250 seconds. The MultiLink stent (Duet or Tetra; Guidant) was used. Primary interventional success was defined as stent implanted, residual stenosis <15%, and TIMI grade III flow after stent implantation. The index lesion was evaluated with the CAAS II System (Pie Medical, Maastricht, The Netherlands). Biplane left ventricular angiography was used to evaluate measures of left ventricular function. Ejection fraction was calculated by end-diastolic and end-systolic left ventricular area and averaged between frontal and lateral view. The observers were blinded to the treatment. According to the guidelines when conducting the trial, aspirin 100 to 320 mg and ticlopidine 2×250 mg were medicated for 4 weeks followed by aspirin alone.

End Points and Follow-Up

The primary end point was a combined end point consisting of death, reinfarction, target lesion revascularization (TLR), and ischemic events. Reinfarction was defined as 2 or more of the following criteria: chest pain lasting for >15 minutes despite the administration of nitrates, or being accompanied by ECG changes, pulmonary edema, or hypotension.

Left ventricular ejection fraction was evaluated at baseline in the early PCI group and compared between the groups after 2 weeks and 6 months. Major bleeding included need for transfusion; bleeding requiring surgical intervention in a timely connection with the coronary intervention; bleeding documented by computer tomography and/or ultrasound, intracerebral as well as ocular, retroperitoneal, abdominal, intestinal, and urogenital; or a decrease in hemoglobin >4 g% within 72 hours in a timely connection with the coronary intervention.

Patients were interviewed about their medical history and cardiovascular risk factors, and previous patient records were reviewed. Patient records were reviewed in the case of repeated hospitalization. Repeated coronary angiography was scheduled after 6 months.

Statistical Analysis

Comparisons between the 2 treatment groups were performed on an intention-to-treat basis unless otherwise specified. Continuous data are expressed as mean ± SD. Categorical variables were compared using the χ² test, and continuous variables were compared using the Student t test. The effect of randomized treatment on event-free survival was determined by a Kaplan-Meier survival analysis. To obtain a measure of the magnitude of association, we fit Cox proportional hazards regression models and report hazard ratios (HR) with 95% confidence intervals. Statistical analysis was performed with the software package SPSS 15.0 for Windows (SPSS Inc, Chicago, IL).

Results

Between July 1998 and April 2001, 197 patients were randomly assigned. Thirty-four patients were not treated according to the study protocol because of an indication for coronary artery bypass grafting (n=17), a nonsignificant infarct-related artery (ie, diameter stenosis of <70% including TIMI 3 flow; n=13), or a not-defined infarct-related artery (n=4). There were no relevant differences in baseline data between the 2 study groups (Table 1). The fraction of high-risk patients was well balanced in both groups. Angiographic data were comparable between the 2 groups (Table 2).

Unplanned premature PCI was performed in 23.5% (n=19) of the delayed PCI group at a median of 3.1±2.4 days after fibrinolysis for recurrent or persistent ECG signs of ischemia (n=9), postinfarction angina pectoris (n=9), or hemodynamic instability (n=1). Three patients in the early PCI group and 1 patient in the delayed PCI group were in cardiogenic shock. The patient in the delayed PCI group presenting with cardiogenic shock was transferred for rescue PCI after the initial treatment. All patients in cardiogenic shock received an intra-aortic balloon pump. Major bleeding complications occurred in 9.8% of patients with early stenting versus 7.4% in the delayed PCI group versus (P=0.374). Five patients of the delayed PCI group died in the first 48 hours after fibrinolysis; all patients of the early PCI group survived the acute phase of the myocardial infarction.

During follow-up, 2 patients with early PCI and 6 patients in the delayed PCI group had a new episode of cardiogenic shock. During a mean follow-up time of 7.9±3.4 years (maximum, 11.2 years), transfer for early PCI was associated
with a significant reduction of the combined primary end point of death, reinfarction, TLR, and ischemic events (HR, 0.61 [95% confidence interval, 0.42 to 0.88]; P=0.008). Long-term survival was higher in the early PCI (P=0.057) (Table 3 and Figure 1). Ischemic events were significantly reduced after early PCI (HR, 0.28 [95% confidence interval, 0.12 to 0.65]; P=0.003). All components of the primary end point were in favor of early PCI (Figure 2 and Figure 3). However, rates of stroke (P=0.585) and reinfarction (P=0.726) were statistically not significant between both groups (Table 3 and Table 4).

**Discussion**

The rationale for timely but not too-early interventional reperfusion is not only to avoid bleeding complications but also from decreasing reocclusion rates. As shown earlier in our study, left ventricular function was significantly improved after early PCI at 2-week and 6-month follow-up, whereas a delayed PCI treatment did not result in a significant improvement of myocardial function. This finding may be attributable to higher patency rates in the early PCI group compared with the delayed PCI group. It is likely that improved left ventricular function escalates the rate of long-term event-free survival, as demonstrated in our long-term follow-up.

Despite the documented superiority of primary PCI over fibrinolysis in patients with STEMI, fibrinolytic therapy remains a frequently used therapeutic option because of constraints in offering primary PCI in a timely manner. To date, it is discussed controversially whether and when combining fibrinolysis with PCI. No long-term follow-up data concerning this question have been presented yet. Earlier trials carried out in the balloon era demonstrated no advantage for early PCI or even higher mortality rates. One reason for this failure of a combined pharmacoinvasive approach was the high early reocclusion rate of the infarct-related artery after successful balloon angioplasty for dissections, rethrombosis, and local intramural bleeding. Furthermore, the benefits of modern antiplatelet therapy were not yet available.
Studies comparing rescue PCI with medical therapy alone presented a reduction in severe heart failure, death, and recurrent ischemia. Trials in the stent era performing facilitated or immediate PCI after fibrinolysis verified higher rates of major and cerebral bleeding or stroke but no benefit compared with a conservative treatment strategy. The use of smaller vascular sheaths, highly fibrin-specific fibrinolytic agents, and lower doses of heparin have contributed to reduced bleeding complications. Additionally, the use of glycoprotein IIb/IIIa antagonists and thienopyridines reduced the incidence of reocclusions after PCI.

In several studies, it has clearly been shown that the time period between fibrinolysis and PCI plays an important role in safety and efficacy of this pharmacoinvasive approach influencing patient outcomes. A period of <3 hours between fibrinolysis and systematic immediate PCI may be harmful, as shown in the facilitated PCI trials. However, a significant proportion of those patients underwent PCI between 2 and 3 hours after fibrinolysis. The lack of clopidogrel preloading and heparin infusion may have contributed to poor outcomes in those trials rather than the early timing of PCI.

In contrast, early PCI in a time interval between 3 and 24 hours after fibrinolysis improved event-free survival compared with conservative treatment. On the basis of these findings, to define and establish an optimal time frame from fibrinolytic therapy to PCI seems to be important more than ever.

Figure 1. Kaplan-Meier analysis of survival. Intention-to-treat analysis. PCI indicates percutaneous coronary intervention.

Figure 2. Kaplan-Meier analysis of event-free survival (freedom from death, reinfarction, TLR, or stroke). Intention-to-treat analysis. PCI indicates percutaneous coronary intervention; TLR, target lesion revascularization.
A meta-analysis of randomized trials that enrolled patients with STEMI to evaluate advantages of PCI after fibrinolysis defined various time-related strategies: rescue PCI in the case of fibrinolysis failure, systematic early PCI, and delayed, ischemia-guided PCI, respectively, and elective PCI after fibrinolysis. This meta-analysis suggests that fibrinolysis cannot be recommended as a facilitating strategy for PCI. In contrast, rescue and systematic early PCI after fibrinolysis showed beneficial effects on survival or reinfarction. A recent meta-analysis reported that early routine PCI after fibrinolysis in STEMI significantly reduced reinfarction and recurrent ischemia at 1 month, with no significant increase in adverse bleeding events compared with standard therapy. Benefits of early PCI persisted at 6 to 12 months of follow-up.

Corresponding to the SIAM III trial and in accordance with recent published studies, the new timely modus should establish PCI not as facilitated modus immediately after fibrinolysis but between 3 and 6 hours after fibrinolysis to avoid bleeding complications of persisting fibrinolytic activity and thrombotic complications caused by overshooting platelet activation.

Although our trial was not powered to detect differences in mortality rates, a significant reduction of the mortality rate to 20% in the early PCI group compared with 34% in the delayed PCI group was detected (P < 0.038). These results are in accordance with recent studies demonstrating a trend for a reduction in mortality rate after early PCI during short-term follow-up.

In the SIAM III study, PCI within 6 hours after fibrinolytic therapy was performed. This concept shows a significant improvement in event-free survival and about 42% reduction of mortality rates during long-term follow-up. However, the benefit in event-free survival was achieved during the first 1 to 3 years. Later on, there were no signs of a late catch-up. The strategy of delayed PCI after recovery and stabilization for 2 weeks was inferior to systematic, early PCI, even when fibrinolysis was successful. Patients with failed reperfusion after fibrinolysis underwent rescue PCI and showed an outcome similar to successful fibrinolytic therapy. Early PCI compared with delayed intervention significantly improved left ventricular function, which increased during the initial 6-month follow-up.

SIAM III was the first of 6 trials comparing a pharmacoinvasive strategy with a delayed PCI strategy after fibrinolytic therapy. The present study represents the first long-term follow-up report. However, the study is limited by its small sample size. The differences observed in this well-controlled study population may be greater than would be expected in a larger study. Furthermore this long-term follow-up was not part of the initial study protocol.

In conclusion, the present long-term follow-up data in patients with STEMI demonstrate that early PCI was associated with a significant reduction of the combined clinical end point, a composite of death, reinfarction, TLR, and ischemic events. Long-term survival was higher with early PCI. Timely but not too-early, interventional reperfusion after fibrinolysis leads to a significantly improved event-free survival compared with a delayed PCI strategy after fibrinolysis.
Disclosures

None.

References


**CLINICAL PERSPECTIVE**

Optimal reperfusion strategy in ST-elevation–myocardial infarction is controversial. Failure of fibrinolytic therapy is related to limited efficacy, high reocclusion rates, reinfarction, and systemic bleeding complications. Data on the impact of percutaneous coronary intervention (PCI) after fibrinolysis are conflicting. The Southwest German Interventional Study in Acute Myocardial Infarction (SIAM III) evaluated the effects of transfer for early PCI in acute ST-elevation–myocardial infarction compared with a conservative delayed PCI treatment strategy in patients receiving fibrinolysis <12 hours after onset of symptoms. During a mean follow-up time of 7.9±3.4 years (maximum, 11.2 years), early PCI was associated with a significant reduction of the primary end point consisting of death, reinfarction, target lesion revascularization, and ischemic events. Early PCI after fibrinolysis improves long-term event-free survival compared with a conservative delayed PCI treatment strategy. Therefore, patients undergoing fibrinolysis in ST-elevation–myocardial infarction should be transferred for early PCI.
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