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Original Contribution

# Thrombolytic therapy vs primary percutaneous intervention after ventricular fibrillation cardiac arrest due to acute ST-segment elevation myocardial infarction and its effect on outcome

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**Abstract** The aim of this study was to evaluate the effect of thrombolytic therapy on neurologic outcome and mortality in patients after cardiac arrest due to acute ST-elevation myocardial infarction and to compare this with those in patients treated with primary percutaneous coronary intervention (PCI).

We retrospectively examined patients after they had ventricular fibrillation cardiac arrests. To assess the effect of thrombolysis and PCI on outcome, we used odds ratios and their 95% confidence intervals and logistic regression modeling.

Thrombolysis was applied in 101 patients (69%) and PCI in 46 patients (31%). More patients who received thrombolysis had favorable functional neurologic recovery (cerebral performance category 1 and 2) and survived to 6 months compared with patients with primary PCI ($P = .38$ and $P = .13$, respectively).

In patients with cardiac arrest due to ST-elevation myocardial infarction, it may be acceptable to use thrombolysis as a reperfusion strategy. This applies especially in hospitals where immediate PCI is not available.



## 1. Introduction

An estimated 17 million people die from cardiovascular diseases, particularly myocardial infarctions (MIs) and strokes, every year. Coronary heart disease is responsible for 7% of disability-adjusted life years lost in men worldwide [1]. In up to 5% of cases, an MI leads to cardiac arrest. This serious complication increases the risk of death of these patients approximately 15-fold [2].

Reperfusion therapy in acute MI attempts to reduce mortality and morbidity. Therefore, it is necessary to obtain complete and sustained patency of the infarct-related coronary artery as early as possible [3]. Because primary angioplasty results in higher patency rates, this technique is increasingly advocated as the preferred approach for treating acute ST-segment elevation myocardial infarction (STEMI)

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[4,5]. On the other hand, because of logistic reasons, the use of primary angioplasty as the preferred reperfusion strategy could lead to delays that could abolish its benefit [6]. Furthermore, primary angioplasty is not available around the clock in many centers.

The Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) trial suggested that early fibrinolysis could lead to comparable results such as those of primary angioplasty [7]. Patients with cardiac arrest due to MI are seen very early after the onset of ischemia because most of the time the collapse is only preceded by a short duration of symptoms. A further advantage of thrombolysis in these patients could be a positive effect on the microcirculatory reperfusion of the brain [8].

In an anteceding study, we showed that thrombolysis after cardiac arrest could improve neurologic outcome [9]. The shortcoming of this study was that patients in the control group were not thrombolysed. Because revascularization after acute MI per se improves mortality, this could have introduced an unjustified bias.

We therefore compared in this follow-up study the effect of thrombolytic therapy on mortality and neurologic outcome with those of primary percutaneous coronary intervention (PCI) in patients after cardiac arrest due to acute STEMI.

## 2. Materials and methods

### 2.1. Patients

We retrospectively examined patients after cardiac arrest who were admitted to the ED of a tertiary university hospital between July 1991 and December 2003. Data were obtained from 2 registry databases of cardiac arrest and acute MI at our institution. The MI database records all patients with acute MI and evaluates risk factors for coronary artery disease, blood pressure and heart rate on admission, time delays from symptom onset to start of revascularization strategies (door-to-needle and door-to-balloon times), method of intervention, infarct location, ST-segment changes, release of creatine kinase and creatine kinase–MB, medical treatment, and bleeding complications. The cardiac arrest database contains the data of all patients who were treated at the department of emergency medicine after cardiac arrest and holds times and details on cardiac arrest. Data of cardiopulmonary resuscitation were recorded according to the Utstein style [10]. Evaluated data included no-flow and low-flow times, time until restoration of spontaneous circulation, witnessed arrest, primary rhythm, epinephrine dose, location of cardiac arrest, and number of defibrillations.

We included all adult patients with witnessed cardiac arrest due to acute STEMI according to the American College of Cardiology criteria [11], ventricular fibrillation as the first documented rhythm and successful restoration of spontaneous circulation, who received either thrombolysis or primary PCI. Patients were excluded if they had a history of cerebrovascular disease or if they underwent bypass grafting within the first 7 days after admission.

The study procedures were in accordance with the ethical standards of the responsible committee of human experimentation and with the Helsinki Declaration of 1975 as revised in 1983.

### 2.2. General patient care

Cardiopulmonary resuscitation and inhospital intensive care were performed according to international resuscitation guidelines and local treatment recommendations [12,13].

### 2.3. Revascularization therapy

Patients were eligible for revascularization strategies if there was more than 0.1 mV ST-segment elevation in at least 2 limb leads or more than 0.2 mV ST-segment elevation in 2 or more continuous precordial leads within 6 hours of the suspected onset of MI. The decision whether thrombolysis or PCI was to be performed was dependent on the attending physician and the availability of the catheterization laboratory. Active bleeding or hemorrhagic diathesis, known history of cerebrovascular accident or structural central nervous system disease, severe hypertension (systolic blood pressure of >180 mm Hg, diastolic blood pressure of >110 mm Hg), and major surgery within 3 weeks were contraindications for thrombolysis [14]. Thrombolytic therapy was applied either with 100 mg reteplase in a front-loaded regimen [15] or with tenekteplase in a weight-adjusted manner immediately after admission to the ED and diagnosis of acute MI.

Primary PCI was performed if skilled personnel were immediately available (door-to-balloon interval of within 90 minutes).

All patients received additional intravenous treatment of 250 mg aspirin, a bolus of 4000IE to 5000IE heparin, followed by a continuous infusion of heparin starting with 1000IE/h for at least 24 hours and adjusted every 6 hours according to a target-activated partial thromboplastin time between 50 and 70 seconds. $\beta$-Blocking agents, nitrates, and angiotensin-converting enzyme inhibitors were given as deemed clinically appropriate at the discretion of the attending physician.

### 2.4. Definition of end points

We recorded the best-achieved functional neurologic recovery within 6 months after cardiac arrest as the primary outcome parameter. Secondary outcome parameter was mortality at 6 months. Neurologic recovery was assessed with the cerebral performance category (CPC) score (CPC 1, conscious and alert with normal function or only slight disability; CPC 2, conscious and alert with moderate

disability; CPC 3, conscious with severe disability; CPC 4, comatose or in a persistent vegetative state; CPC 5, brain death) [16]. CPC 1 and CPC 2 were defined as a favorable neurologic recovery, whereas CPC 3 to 5 as unfavorable neurologic recovery.

### 2.5. Statistical analysis

Data are presented as median and as range between the 25th and 75th quartile; binary data are expressed as number and percentage. Demographic and baseline data were compared using the Mann-Whitney $U$ test for continuous data and the $\chi^2$ test or Fisher exact test, as appropriate, for categorical data.

To assess the effect of thrombolysis and PCI on outcome, we calculated odds ratios and their 95% confidence intervals (CIs). We used logistic regression modeling to assess whether the effect was affected by potential confounders. Dependent variable was one of the outcome variables in each analysis (good CPC, yes/no; survival, yes/no). We entered thrombolysis (yes/no) and potential confounders that were considerably different in the univariate analysis as covariates. The Hosmer-Lemeshow test was used to assess the model's goodness of fit.

We used the Kaplan-Meier method to plot survival over time for exposed and unexposed patients. The log-rank test was used to compare both groups with regard to their observation time–related data. We used SPSS (SPSS Inc, Chicago Ill) for Windows 10.0.7 and Excel 2002 (Microsoft, Redmond, Wash) for data management and analysis. A 2-sided $P$ value of less than .05 was considered statistically significant.

**Table 1** Patients receiving either thrombolytic therapy or primary PCI

| | Thrombolysis (n = 101) | Primary PCI (n = 46) | $P$ |
|---|---|---|---|
| Age (y) | 53 (46-62) | 57 (49-63) | .20 |
| Male | 82 (81) | 35 (76) | .51 |
| History of MI | 12 (12) | 5 (11) | 1.00 |
| History of peripheral or cerebral vascular disease | 2 (2) | 3 (7) | .17 |
| History of PCI | 1 (1) | 3 (7) | .09 |
| History of coronary artery bypass graft | 3 (2) | 3 (3) | .55 |
| History of diabetes | 7 (7) | 5 (11) | .52 |
| Family history of coronary heart disease | 4 (4) | 2 (4) | 1.00 |
| History of hyperlipidemia | 10 (10) | 4 (9) | 1.00 |
| History of hypertension | 21 (21) | 6 (13) | .36 |
| History of smoking | 43 (43) | 17 (38) | .72 |

Data are expressed as median (interquartile range) or as number (percentage).

**Table 2** Patients receiving either thrombolytic therapy or primary PCI—cardiopulmonary resuscitation–specific data

| | Thrombolysis (n = 101) | Primary PCI (n = 46) | $P$ |
|---|---|---|---|
| Witnessed CA | 101 (100) | 45 (98) | .31 |
| Bystander CPR | 37 (37) | 23 (49) | .20 |
| Out-of-hospital CA | 94 (93%) | 45 (98%) | .44 |
| No-flow (min) | 2 (0-7) | 1 (0-5) | .45 |
| Low-flow (min) | 17 (10-28) | 17 (11-27) | .65 |
| Epinephrine (mg) | 3 (0-6) | 3 (1-4) | .56 |
| No. of defibrillations | 3 (0-6) | 4 (2-6) | .06 |

Data are expressed as median (interquartile range) or as number (percentage). No-flow refers to time from the beginning of cardiac arrest until the onset of basic life support; low-flow, time from the beginning of basic life support until restoration of spontaneous circulation; epinephrine, cumulative dose of epinephrine; CA, cardiac arrest; CPR, cardiopulmonary resuscitation.

## 3. Results

### 3.1. Patients

Between July 1991 and December 2003, 147 patients fulfilled the selection criteria and were included in the study. Thrombolysis was applied in 101 patients (69%) and PCI in 46 patients (31%). Demographic data are presented in Table 1, cardiac arrest–specific data in Table 2, and hemodynamic- and intervention-related data are presented in Table 3. Patients in the thrombolysis group differed significantly in some baseline variables

**Table 3** Patients receiving either thrombolytic therapy or primary PCI—data of hospital admission

| | Thrombolysis (n = 101) | Primary PCI (n = 46) | $P$ |
|---|---|---|---|
| HR (beats/min) | 110 (90-120) | 110 (90-120) | .58 |
| RR syst (mm Hg) | 110 (90-130) | 120 (100-140) | .04 |
| Lactat (mmol/L) | 11.5 (8.5-14.5) | 8 (6-10) | .10 |
| Potassium | 3.2 (2.3-3.7) | 3.6 (3.1-4) | .004 |
| Infarct site (anterior) | 61 (60%) | 32 (70%) | .36 |
| Door-to-needle time (min) | 39 (25-90) | | |
| Door-to-balloon time (min) | | 119 (104-205) | |
| Cooling | 20 (20%) | 17 (37%) | .04 |

Data are expressed as median (interquartile range) or as number (percentage). Cooling refers to mild artificial hypothermia (33°C) during 24 hours after admission; HR, heart rate; RR syst, systolic blood pressure; RR diast, diastolic blood pressure.

**Table 4** Effect of thrombolysis on outcome

| Outcome | Thrombolysis (n = 101) | primary PCI (n = 46) | Odds ratio (95% CI) | *P* |
|---|---|---|---|---|
| Univariate analysis | | | | |
| CPC 1 or 2 | 57 (56) | 22 (48) | 1.41 (0.70-2.84) | 0.38 |
| Survival at 6 mo | 69 (68) | 24 (55) | 1.79 (0.87-3.70) | 0.13 |
| Adjusted analysis[a] | | | | |
| CPC 1 or 2 | | | 1.24 (0.58-2.62) | 0.58 |
| Survival at 6 mo | | | 1.74 (0.80-3.80) | 0.17 |

Data are expressed as number (percentage). CPC refers to best-achieved cerebral performance category score within 6 months.

[a] Adjusted for cardiac arrest in public place, cooling, sex, and age using logistic regression analysis.

from the patients who underwent PCI: they had lower potassium serum levels, fewer patients were treated with therapeutic hypothermia after cardiac arrest, and they had lower blood pressure.

## 3.2. Outcome

### 3.2.1. Neurologic outcome and survival

Regardless of treatment, 93 (63%) of 147 patients survived for 6 months, and 79 (53%) of 147 patients survived for 6 months and had favorable neurologic recovery (CPC 1 or 2).

More patients who received thrombolysis had favorable functional neurologic recovery (CPC 1 and 2) and survived to 6 months compared with patients with primary PCI, although the difference was not statistically significant. This effect did not change considerably when we adjusted for potential confounders (Table 4).

In the Kaplan-Meier plot (Fig. 1), the mean survival time was 135 days (95% CI, 121-149 days) in patients who received thrombolysis and 116 days (95% CI, 93-140 days) in patients with primary PCI (log-rank test, $P = .17$).

## 4. Discussion

We found no significant difference in neurologic recovery and mortality when we compared thrombolytic therapy to PCI as a revascularization strategy after ventricular fibrillation cardiac arrest due to STEMI.

There are 2 targets to follow to improve outcome after acute MI. One is the reestablishment of coronary flow, and the second is the speed with which this is accomplished. The earlier patency of the infarct-related artery is achieved, the lower is the mortality irrespective of the revascularization method used [17-19]. Thrombolysis can be applied very early, although the patency rate is lower than primary PCI. This may be the reason why thrombolysis seems to be equally effective compared with primary PCI in the early phase of acute MI, as shown recently by the CAPTIM study group [7,20]. In our data, the beneficial time course of thrombolysis is demonstrated by the shorter door-to-needle time of 39 minutes compared with a door-to-balloon time of 119 minutes.

In addition, thrombolysis seems to have a positive effect in the early period after cardiopulmonary resuscitation when the no-reflow phenomenon of the brain occurs and blood coagulation is activated [9,21,22]. In the 1950s, it had already been described by Crowell et al [23,24] that the resolution of microthrombi by thrombolytic therapy during or immediately after restoration of spontaneous circulation led to an improved reperfusion of the brain and consequently shortened the duration of brain ischemia with the result of better neurologic outcome. Very similar results were found by Fischer et al [8] who showed that thrombolytic therapy improved microcirculatory reperfusion of a normothermic cat brain.

The clinical studies of thrombolysis after cardiac arrest had a disadvantage in that no reperfusion therapy was initiated in the control group, which could lead to an overestimation of the treatment effect because revascularization itself has a positive effect on outcome [9,25-27]. In the anteceding study to this trial, we showed the beneficial effect of thrombolysis on functional neurologic outcome compared to a control group with no thrombolysis [9]. In this study, we compared 2 different reperfusion strategies in patients with cardiac arrest due to MI. There was a higher rate of good neurologic recovery and lower mortality in

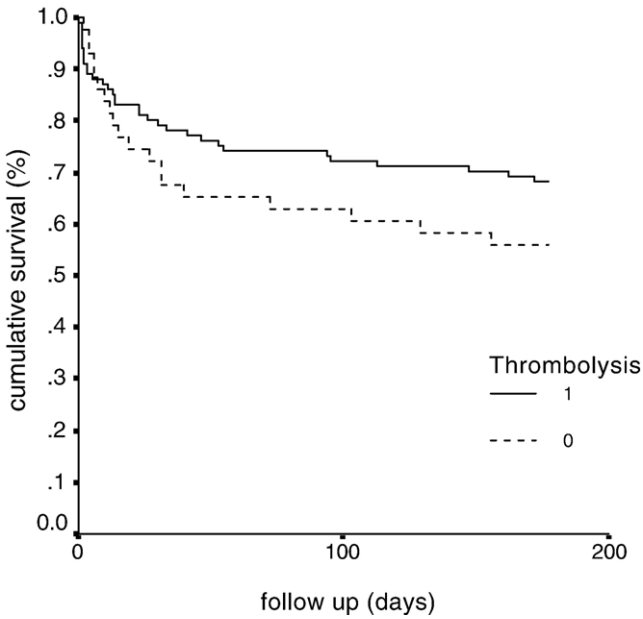


**Fig. 1** Kaplan-Meier plot. Cumulative survival in the thrombolysis and primary PCI groups. Straight line represents thrombolysis group; dashed line, primary PCI group.

patients treated with thrombolysis, but this was not significantly different. On the other hand, this implies that primary PCI was also not better than thrombolysis. These findings question the concept of subjecting every patient after cardiac arrest due to STEMI to urgent primary PCI. Because primary PCI is available 24 hours a day in few centers only, it may be admissible to use thrombolysis as reperfusion strategy in such patients. The bleeding complication rate in resuscitated patients who underwent thrombolysis, although the duration of cardiac arrest was longer than 10 minutes, was comparable with that of patients who were not thrombolysed. This is in accordance with other reports on bleeding complications in thrombolysed patients after cardiac arrest [27-29]. Therefore, resuscitation from cardiac arrest should no longer be considered as a contraindication for the use of thrombolytic therapy.

There are several limitations to mention. The number of individuals analyzed was small. The study was retrospective, but the data were prospectively recorded in 2 databases by using internationally recognized protocols immediately after admission of patients [10,11]. Furthermore, selection bias might have been a problem. The decision to use either thrombolytic therapy or primary PCI was done by the attending physician and was based on clinical judgment and the capacity of the catheterization laboratory. We tried to minimize this by adjusting for possible confounders in a logistic regression analysis. In addition, the study was underpowered. We found a trend toward improvement of neurologic outcome with thrombolytic therapy. However, the powers to detect a difference for neurologic recovery and survival were 11% and 27%, respectively.

## 5. Conclusion

In patients with cardiac arrest due to acute STEMI, we found no evidence that PCI offers an important advantage compared with thrombolysis. Although the study was retrospective and too small to draw a definitive conclusion, it may be an acceptable option to use thrombolysis as a reperfusion strategy in such patients. This applies especially in hospitals where immediate PCI is not available.

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