Primary percutaneous coronary intervention versus thrombolytic treatment: long term follow up according to infarct location


Objectives: To study the clinical significance of infarct location during long term follow up in a trial comparing thrombolysis with primary angioplasty.

Design: Retrospective longitudinal cohort analysis of prospectively entered data.

Setting: Patients with acute ST elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI).

Patients: In the Zwolle trial 395 patients with acute STEMI were randomly assigned to intravenous streptokinase or PCI.

Main outcome measures: Survival according to infarct location and treatment after 8 (2) years of follow up.

Results: 105 patients died: 63 patients in the streptokinase group and 42 patients in the primary PCI group (relative risk (RR) 1.6, 95% confidence interval (CI) 1.0 to 2.6; p = 0.03). In patients with non-anterior STEMI there was no difference in mortality between streptokinase and PCI treated patients (RR 1.1, 95% CI 0.6 to 2.1; p = 0.68) but the streptokinase group had significantly more major adverse cardiac events (MACE) than the PCI group (RR 2.1, 95% CI 1.2 to 3.6). The number needed to treat to prevent one death was five. Kaplan-Meier analysis confirmed the benefits of primary angioplasty in the first year and showed additional benefit of PCI compared with streptokinase between 1–8 years after the acute event.

Conclusions: Patients with anterior STEMI have better long term survival when treated with PCI than with streptokinase. In patients alive one year after the acute event, PCI confers a significant additional survival benefit, probably due to better preserved residual left ventricular function.
Statistical analysis
The primary end points were death and the combined incidence of death and non-fatal reinfarction (major adverse cardiac events (MACE)). All outcomes were analysed according to the intention to treat principle. Data were statistically analysed with SPSS 10.0 (SPSS Inc, Chicago, Illinois, USA). Differences between group means were tested by two tailed Student’s t test. A χ² statistic was calculated to test differences between proportions, with calculation of relative risks (RRs) and exact 95% confidence intervals (CIs). The Fisher exact test was used when the expected value of cells was smaller than 5. Significance was defined as a value of p < 0.05. Cumulative survival (and mortality) curves were constructed according to the Kaplan-Meier method, and differences between the curves were tested for significance by the log rank statistic. Cox proportional hazards regression models were used to estimate hazard ratios of variables that were significantly different in univariate analysis. Age (>60 years) and left ventricular function (LVEF < 40%) were dichotomised for the multivariate analysis.

RESULTS
Of the 395 patients enrolled, 194 were randomly selected to undergo primary PCI and 201 to receive streptokinase. The groups were similar in age, sex, infarct location, previous myocardial infarction, and history of diabetes mellitus (table 1). The residual LVEF was measured in 189 patients of the PCI group and in 188 patients of the streptokinase group. The mean LVEF was higher in the PCI group than in the streptokinase group (50% vs 45%, p < 0.001). Enzymatic infarct size was measured in 367 patients (93%). Mean (SD) follow up was 8 (2) years. One patient was lost to follow up. At follow up a total of 105 patients had died. In the streptokinase group 63 (31%) patients died compared with 42 (22%) patients in the PCI group (RR 1.65, 95% CI 1.05 to 2.60). Fifty eight patients had a non-fatal recurrent myocardial infarction: 13 (7%) patients in the PCI group and 45 (22%) in the streptokinase group (RR 0.25, 95% CI 0.13 to 0.48). All reinfarctions that occurred within the first 30 days affected the region of the index infarction. Of the 38 reinfarctions after day 30 (15 during the first year of follow up and 23 afterwards), 20 involved the original infarct related artery. The difference in the reinfarction rate was thus entirely due to events in the original infarct related artery. Figure 1 shows Kaplan-Meier curves for overall survival of patient treated with streptokinase or with PCI.

Table 1: Clinical variables and infarct size in the Zwolle trial patients

<table>
<thead>
<tr>
<th></th>
<th>PCI (n = 194)</th>
<th>SK (n = 201)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;60</td>
<td>94 (48%)</td>
<td>109 (54%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Men</td>
<td>160 (82%)</td>
<td>158 (79%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Hypertension</td>
<td>36 (19%)</td>
<td>40 (20%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Anterior MI</td>
<td>77 (40%)</td>
<td>74 (36%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Previous MI</td>
<td>38 (20%)</td>
<td>31 (15%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16 (8%)</td>
<td>16 (8%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Infarct size (%)</td>
<td>49.8 (10.3)</td>
<td>44.9 (11.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>939 (738)</td>
<td>1289 (1144)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

LDH<sub>20h</sub>, enzymatic infarct size; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; SK, streptokinase.

Patients with non-anterior STEMI in the Zwolle trial
Table 2 shows the baseline characteristics of the Zwolle trial patients according to the infarct location, either anterior or non-anterior. In the group with non-anterior STEMI baseline characteristics did not differ significantly between patients who underwent primary PCI and those who received streptokinase (table 2).

Enzymatic infarct size was larger in patients treated with streptokinase than in patients treated with primary PCI (1099 (1027) vs 822 (566), p = 0.01). Residual LVEF was lower in patients treated with streptokinase than in patients treated with primary PCI (48 (9) vs 52 (9), p = 0.005). At follow up, 23 (20%) patients with non-anterior STEMI died in the group treated with PCI compared with 28 (22%) patients treated with streptokinase (RR 1.1, 95% CI 0.6 to 2.1; p = 0.68). Figure 2 shows Kaplan-Meier curves for overall survival of patients with non-anterior STEMI treated with streptokinase or PCI. The combined end point of MACE was significantly higher in the streptokinase group than in the PCI group: 50 (39%) patients in the streptokinase group and 28 (24%) patients in the PCI group (RR 2.1, 95% CI 1.2 to 3.6). The number needed to treat to prevent one MACE was four.

Patients with anterior STEMI in the Zwolle trial
In the anterior STEMI patient group, the two treatment arms did not differ significantly in terms of sex and history of diabetes mellitus. In the anterior STEMI group, more patients with previous myocardial infarction were treated with PCI (26% vs 12%, p = 0.03). The anterior STEMI patient group...
that received streptokinase was older than the patient group treated with PCI (age > 60 years: 58% vs 40%, p = 0.03). Enzymatic infarct size was larger in patients treated with streptokinase than in patients treated with primary PCI (1592 (1261) vs 1117 (917), p = 0.01). Residual LVEF was lower in patients treated with streptokinase than in patients treated with primary PCI (38 (12) vs 47 (12), p = 0.001). At follow up, in patients with anterior STEMI, 35 (47%) patients in the streptokinase treated group died compared with 19 (25%) in the PCI treated group (RR 2.7, 95% CI 1.4 to 5.5; p = 0.004). The number needed to treat to prevent one death was five.

Figure 3 shows Kaplan-Meier curves for overall survival of patients with anterior STEMI according to treatment with streptokinase or PCI. In univariate analysis of patients with anterior STEMI, some baseline characteristics and residual left ventricular function differed between the PCI group and the streptokinase group. We included these variables (age > 60, previous MI, randomisation, and left ventricular function) in a multivariate model to study their independent value in assessing long term mortality. Multivariate analysis showed that age > 60 and random assignment to PCI treatment were equally strong predictors of long term mortality (table 3).

When LVEF was included in the same model, the only two predictors of long term mortality were age > 60 and LVEF < 40% (table 4).

Significantly more patients in the streptokinase group than in the PCI group reached the combined end point of MACE: 44 (59%) patients in the streptokinase group and 25 (32%) in the PCI group (RR 2.3, 95% CI 1.1 to 5.1). Figure 4 shows significantly better survival for patients with anterior

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**Table 2** Clinical variables and infarct size in the Zwolle trial patients according to infarct location

<table>
<thead>
<tr>
<th>Infarct location</th>
<th>Anterior STEMI (n = 151)</th>
<th>Non-anterior STEMI (n = 244)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCI (n = 77)</td>
<td>SK (n = 74)</td>
</tr>
<tr>
<td>Clinical variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt; 60</td>
<td>31 (40%)</td>
<td>43 (58%)</td>
</tr>
<tr>
<td>Men</td>
<td>61 (79%)</td>
<td>54 (73%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (24%)</td>
<td>16 (22%)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>20 (26%)</td>
<td>9 (12%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6 (8%)</td>
<td>9 (12%)</td>
</tr>
<tr>
<td>Infarct size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>47 (12)</td>
<td>38 (12)</td>
</tr>
<tr>
<td>LDMQ72</td>
<td>1117 (917)</td>
<td>1592 (1261)</td>
</tr>
</tbody>
</table>

STEMI, ST elevation myocardial infarction.

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**Table 3** Predictors of long term mortality in patients with anterior STEMI in the Zwolle trial

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR*</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60 v. 60</td>
<td>2.2</td>
<td>1.2 to 3.8</td>
<td>0.01</td>
</tr>
<tr>
<td>SK v. PCI</td>
<td>2.2</td>
<td>1.2 to 3.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Previous MI</td>
<td>1.3</td>
<td>0.7 to 2.6</td>
<td>0.40</td>
</tr>
</tbody>
</table>

*Cox regression analysis.

CI, confidence interval; OR, odds ratio.

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**Table 4** Predictors of long term mortality in patients with anterior STEMI in the Zwolle trial with LVEF included in the model

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR*</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF &lt;40% v. &gt;40%</td>
<td>3.5</td>
<td>1.8–6.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age &gt; 60 v. 60</td>
<td>2.2</td>
<td>1.2–4.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Previous MI</td>
<td>1.2</td>
<td>0.5–2.4</td>
<td>0.69</td>
</tr>
<tr>
<td>SK v. PCI</td>
<td>1.2</td>
<td>0.6–2.4</td>
<td>0.54</td>
</tr>
</tbody>
</table>

*Cox regression analysis.

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**Figure 2** Kaplan-Meier curves for overall survival after non-anterior ST elevation myocardial infarction (STEMI) in the PCI and streptokinase groups during eight years of follow up.

**Figure 3** Kaplan-Meier curves for overall survival after anterior STEMI in the PCI and streptokinase groups during eight years of follow up.
STEMI treated with PCI than with streptokinase, even when first year deaths are excluded from analysis.

**DISCUSSION**

This study strongly supports our principal goal: that all patients with anterior STEMI should be treated with primary PCI. In the western world where randomised trials have shown PCI to be superior to thrombolysis, some patients are still being treated with thrombolytic regimens for several reasons. Although these reasons may be valid in some cases, it is essential that we treat patients who have proven long term benefit with primary PCI.

**Non-anterior STEMI: primary PCI versus streptokinase**

In our study we did not find that patients treated with PCI had better long term survival than those treated with streptokinase. To show differences in outcome between treatment arms of patients with non-anterior STEMI, large sample sizes, such as those used in thrombolysis studies, are necessary to show benefit of one regimen over another. Although we did not observe better long term survival, patients treated with PCI clearly had a significantly smaller infarct size as measured by residual LVEF (52 (9) v 48 (9), p = 0.005) and by enzymatic infarct size over 72 hours (822 (566) v 1099 (1027), p = 0.01). Residual LVEF is a known important end point of reperfusion and a strong predictor of long term outcome.13 14 Additionally, patients with non-anterior STEMI who were treated with streptokinase had more recurrent myocardial infarctions needing additional admissions and treatment as shown by a significantly higher incidence of MACE in patients treated with streptokinase. Therefore, although long term survival did not differ significantly between treatment modalities, we conclude that for non-anterior STEMI, primary PCI offers clinical benefits over treatment with streptokinase. In addition, patients with uncomplicated non-anterior STEMI can be discharged 2–3 days after primary PCI.15

**Anterior STEMI: primary PCI versus streptokinase**

Our study clearly confirms that primary PCI is the treatment of choice for anterior STEMI. Patients treated with primary PCI had higher residual LVEF (47 (12) v 38 (12), p < 0.001) and smaller enzymatic infarct size (1117 (917) v 1592 (1261), p = 0.01). The absolute difference of residual LVEF was 9% in anterior STEMI when both treatment arms were compared, whereas this absolute difference was only 4% in the patients with non-anterior STEMI in both treatment arms.

These differences have been described before, but their importance becomes clear in the long term outcome.12 Furthermore, residual LVEF after primary PCI improves over time, especially in patients with anterior STEMI. Therefore, not only is residual LVEF better immediately after the index acute STEMI, but also long term recovery after STEMI, when treated with PCI, may contribute importantly to better survival.12 13

Patients with anterior STEMI had a much better survival when treated with primary PCI than when treated with streptokinase. Long term mortality was 25% in the PCI group and 47% in the streptokinase group. Therefore, there was a 22% absolute risk reduction for long term mortality; the number needed to treat to save one life is only five patients. Since some baseline characteristics differed between patients treated with primary PCI and with streptokinase, we studied the independent predictors of long term mortality with multivariate regression analysis. This analysis showed that age (>60 years) and random assignment to PCI were the two predictors for long term survival among patients with anterior STEMI. However, when residual LVEF (<40%) was included in this model, the two predictors for long term survival among patients with anterior STEMI were age (>60 years) and residual LVEF (<40%). This analysis shows that the long term improved survival of patients with anterior STEMI treated with PCI results from better preserved LVEF than when treated with streptokinase. Treatment with thrombolysis, as in our study with streptokinase, results in more recurrent myocardial infarction than after primary PCI. It is therefore conceivable that the better survival of patients treated with primary PCI would in part be due to the recurrent (fatal) reinfarctions that occur mainly within one year after the acute event. We therefore analysed long term mortality after excluding all deaths in the first year after the index acute STEMI. Figure 4 clearly shows the difference in mortality of patients with anterior STEMI when the two treatment modalities are compared.

**Limitations**

While multicentre thrombolysis trials have enrolled many thousands of patients with acute myocardial infarction undergoing reperfusion, we studied only 395 patients from a single centre. During the study period intracoronary stenting and glycoprotein IIb/IIIa receptor antagonists were not used. These two new treatments may well have a profound effect on clinical outcome.22-24

**Conclusion**

In all patients with acute STEMI, left ventricular function is better preserved by primary PCI than by treatment with streptokinase. In patients with acute anterior STEMI treated with primary PCI, the additional mortality benefit during long term follow is probably due to better preserved residual left ventricular function. The number needed to treat to prevent one death is five and the number needed to treat to prevent one MACE is four. In patients with non-anterior STEMI treated with primary PCI, the principle benefit is the reduction in MACE. Independent predictors of long term mortality after acute anterior STEMI are age and residual left ventricular function.

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No conflicts of interest
treatment for 45 days, the patient was hospitalized, and after antibiotic therapy for mitral valve replacement and no evidence of Willis.

Mycotic aneurysms commonly involve intracranial arteries and are located distally over the cerebral cortex. We report a case of a 21 year old man admitted to our hospital because of fever of one week's duration, signs of meningitis, and heart murmur. Cerebrospinal fluid and blood cultures were both negative. An echocardiogram showed a vegetation in the mitral valve 19 mm in length. Empiric antibiotic treatment was started with good response. Routine cerebral magnetic resonance angiography showed a total occlusion of the left internal carotid artery caused by heterogeneous material (probable embolism) and an aneurysm at the origin of the artery compatible with a mycotic aneurysm of 11 × 25 mm in diameter (panels A and B). Left hemisphere circulation was preserved through the circle of Willis.

The patient successfully underwent surgery for mitral valve replacement and no focal neurological deficit appeared. At hospital discharge, and after antibiotic treatment for 45 days, the patient was asymptomatic. Doppler echocardiography performed before the patient was discharged showed that the left internal carotid artery was still occluded and the mycotic aneurysm had not changed in size.

REFERENCES