Primary Percutaneous Coronary Intervention Compared With Fibrinolysis for Myocardial Infarction in Diabetes Mellitus

Results From the Primary Coronary Angioplasty vs Thrombolysis–2 Trial

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Background: There is growing evidence for a clinical benefit of primary percutaneous coronary intervention (PCI) compared with fibrinolysis; however, whether the treatment effect is consistent among patients with diabetes mellitus is unclear. We compared PCI with fibrinolysis for treatment of ST-segment elevation myocardial infarction in patients with diabetes mellitus.

Methods: A pooled analysis of individual patient data from 19 trials comparing primary PCI with fibrinolysis for treatment of ST-segment elevation myocardial infarction was performed. Trials that enrolled at least 50 patients with ST-segment elevation myocardial infarction and randomized patients to receive either primary PCI or fibrinolysis were considered for inclusion in our study. Clinical end points were total deaths, recurrent infarction, death or nonfatal recurrent infarction, and stroke, measured 30 days after randomization.

Results: Of 6315 patients, 877 (14%) had diabetes. Thirty-day mortality (9.4% vs 5.9%; P = .001) was higher in patients with diabetes. Mortality was lower after primary PCI compared with fibrinolysis in both patients with diabetes (unadjusted odds ratio, 0.49; 95% confidence interval, 0.31-0.79; P = .004) and without diabetes (unadjusted odds ratio, 0.69; 95% confidence interval, 0.54-0.86, P = .001), with no evidence of heterogeneity of treatment effect (P = .24 for interaction). Recurrent infarction and stroke were also reduced after primary PCI in both patient groups. After multivariable analysis, primary PCI was associated with decreased 30-day mortality in patients with and without diabetes, with a point estimate of greater benefit in diabetic patients.

Conclusions: Diabetic patients with ST-segment elevation myocardial infarction treated with reperfusion therapy have increased mortality compared with patients without diabetes. The beneficial effects of primary PCI compared with fibrinolysis in diabetic patients are consistent with effects in nondiabetic patients.

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CME course available at www.archinternmed.com
We compared primary PCI with fibrinolysis in diabetic patients with STEMI based on individual patient data derived from randomized trials.

**METHODS**

**TRIAL SELECTION**

Details of trial selection criteria and primary data analysis have been published previously. If a trial enrolled at least 50 patients with evolving STEMI and randomized patients to either treatment with fibrinolysis (streptokinase or tissue plasminogen activator) or primary PCI (without fibrinolytic therapy; with or without stenting), it was considered for inclusion in our study. To identify eligible trials, a MEDLINE search was performed using a broad range of key terms including “(acute) myocardial infarction,” “fibrinolysis,” “fibrinolytic,” “thrombolysis,” “thrombolytic,” “primary,” “angioplasty,” “stent,” and “percutaneous coronary intervention.” We considered all articles published between January 1990 and December 2002. References from identified articles and abstracts presented at annual international meetings of the American Heart Association (Circulation), American College of Cardiology (Journal of the American College of Cardiology), and European Society of Cardiology (European Heart Journal) were also examined. Each trial identified in this search was then critically evaluated by 3 investigators (E.B., C.M.W., and R.J.S.) for inclusion in the pooled analysis.

A flowsheet of the trial selection process is shown in Figure 1. Nineteen trials were included in the pooled analysis. Design characteristics of included trials are given in Table 1. Each trial was reviewed to determine whether treatment allocation was truly randomized, that there were no exclusions from the analysis, and for the extent to which outcome adjudication was blinded. Any discrepancies between these analyses of data provided and previously published results were queried and resolved. Clinical end points were total deaths, recurrent infarction, death or recurrent infarction, and stroke, measured 30 days after randomization. We compared clinical outcomes between patients with and without diabetes and the interaction of the method of reperfusion therapy and diabetes on outcome.

**STATISTICAL ANALYSIS**

Continuous data were summarized and are given as median values with corresponding interquartile range or as mean values with corresponding SD, whereas dichotomous data are given as counts and percentages. Wilcoxon rank sum, Kruskal-Wallis, or $\chi^2$ tests were used as appropriate. To pool trial- or diabetes-specific outcome data, the Cochran–Mantel-Haenszel method was used, and odds ratios (ORs) and 95% confidence intervals (CIs) for 30-day mortality are given. In addition, the Breslow-Day test was used to assess heterogeneity of treatment effect according to diabetes status or among the trial-specific ORs. Odds ratios were further adjusted for other baseline characteristics, including age, sex, time to randomization, treatment delay, systolic blood pressure, anterior myocardial infarction (MI), previous MI, heart rate, and randomized treatment, using multiple logistic regression. Statistical significance for all analyses was defined as $P < .05$. The number of patients needed to treat was calculated as the inverse of the absolute risk difference in outcome. The 95% CI of the patients needed to treat was estimated using the 95% CI associated with the absolute risk difference.

**RESULTS**

Individual patient data were collected for 6763 patients with STEMI enrolled in 22 randomized clinical trials as part of
 ASSOCIATIONS AMONG DIABETIC STATUS, TREATMENT, AND 30-DAY MORTALITY

Of patients without diabetes, 2700 (50%) were randomized to receive primary PCI, compared with 456 (52%) patients with diabetes. Baseline characteristics of patients with diabetes according to the method of reperfusion therapy are summarized in Table 3. There were no significant differences between diabetic patients randomized to receive primary PCI or fibrinolysis. Unadjusted mortality, recurrent MI, and stroke in patients with and without diabetes according to the method of reperfusion therapy are given in Table 4. Primary PCI was associated with a reduction in 30-day mortality in patients with and without diabetes. This reduction was most pronounced in diabetic patients. To save 1 life at 30 days, 48 patients without diabetes (95% CI, 37-60) had to be treated with primary PCI compared with 17 patients with diabetes (95% CI, 11-28). No interaction between type of fibrinolytic agent, mortality, and presence of diabetes was found.

After adjusting for potential confounders, including age, sex, time to randomization, treatment delay, systolic blood pressure, anterior MI, previous MI, heart rate, and randomized treatment, primary PCI was independently associated with improved 30-day survival (OR, 0.64; 95% CI, 0.52-0.79; P < .001), which was evident in patients both with diabetes (OR, 0.50; 95% CI, 0.31-0.80; P = .003) and those without diabetes (OR, 0.68; 95% CI, 0.54-0.86; P = .001; interaction P = .24; Figure 2). This treatment effect was consistent across the pooled trials (Breslow-Day test, P = .52).

This analysis showed no difference in relative mortality reduction after primary PCI in patients with and without diabetes. Because diabetes was associated with in-
increased 30-day mortality, the absolute benefit of primary PCI can be expected to be greater in patients with diabetes.

The negative influence of diabetes on outcome after STEMI has been described previously. In addition to differences in baseline patient characteristics, including age, sex, previous MI, longer ischemic time, or a higher prevalence of multivesSEL disease, prothrombotic derangement and unfavorable lipid metabolism might predispose diabetic patients to future cardiac events.

Because mortality remains particularly high in patients with diabetes after STEMI, it is important to define optimal treatment strategies, including method of reperfusion therapy, in this population.

In a general patient population, primary PCI improves outcome when compared with fibrinolysis. However, effects of reperfusion therapy may be different in patients with diabetes. Percutaneous coronary intervention in patients with diabetes may be more complex, with higher complication rates. Fibrinolysis may also be less effective in diabetic patients. Previous trials comparing primary PCI with fibrinolysis for STEMI in diabetic patients are few and conflicting. Hsu et al found a significant benefit of primary PCI in major cardiac events in 202 diabetic patients in a registry study. A subanalysis of the CAPTIM (Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction) study also revealed a possible beneficial effect of primary PCI in 103 diabetic patients. An analysis of the GUSTO-IIb Angioplasty Substudy (Second Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes), which included only 177 diabetic patients, showed a consistent treatment effect (with wide confidence intervals) of primary PCI in patients with and without diabetes. In our analysis including a large number of patients, it was more clearly demonstrated that primary PCI is associated with improved survival after 30 days in both patients with and without diabetes. The point estimate of the benefit of primary PCI compared with fibrinolysis was greater in diabetic patients, and because the absolute risk is higher in this population, the absolute benefit was greater. This observation may be the result of delay in initiation of therapy and longer ischemic time in diabetic patients, which may be related in part to atypical symptoms. In particular, thrombolytic therapy seems to be negatively influenced by longer time to initiation of therapy. Also, microvascular flow seems to be decreased in dia-

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**Table 2. Baseline Characteristics of Patients With STEMI Without vs With Diabetes**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients Without Diabetes</th>
<th>Patients With Diabetes</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62 ± 12</td>
<td>65 ± 11</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>4043 (74)</td>
<td>560 (64)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>133 ± 24</td>
<td>135 ± 24</td>
<td>.004</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>76 ± 17</td>
<td>79 ± 17</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>79 ± 12</td>
<td>80 ± 12</td>
<td>.001</td>
</tr>
<tr>
<td>Previous MI</td>
<td>701 (13)</td>
<td>143 (16)</td>
<td>.02</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>227 (4)</td>
<td>27 (3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>96 (2)</td>
<td>16 (2)</td>
<td>.56</td>
</tr>
<tr>
<td>Time from symptom onset to randomization, h</td>
<td>137 (90-212)</td>
<td>163 (110-272)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**Table 3. Baseline Characteristics of Patients With Diabetes According to Randomized Method of Reperfusion Therapy: Fibrinolysis vs Primary PCI**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fibrinolysis</th>
<th>Primary PCI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65 ± 11</td>
<td>65 ± 11</td>
<td>.92</td>
</tr>
<tr>
<td>Male sex</td>
<td>268 (64)</td>
<td>292 (64)</td>
<td>.89</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>136 ± 24</td>
<td>134 ± 24</td>
<td>.17</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>80 ± 17</td>
<td>79 ± 17</td>
<td>.26</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>81 ± 12</td>
<td>80 ± 12</td>
<td>.93</td>
</tr>
<tr>
<td>Previous MI</td>
<td>63 (15)</td>
<td>80 (18)</td>
<td>.59</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>13 (3)</td>
<td>14 (3)</td>
<td>.98</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>8 (2)</td>
<td>8 (2)</td>
<td>.97</td>
</tr>
<tr>
<td>Time from symptom onset to randomization, h</td>
<td>160 (105-280)</td>
<td>164 (110-270)</td>
<td>.64</td>
</tr>
</tbody>
</table>

**Abbreviations:** CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention.

*Data are given as mean ± SD or number (percentage) unless otherwise indicated.

*Calculated at each hospital site.

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betic patients after fibrinolysis. Possibly, this is associated with increased platelet aggregation and reduced ability to induce endothelium-mediated vasodilation. In addition to the superiority of primary PCI compared with fibrinolysis in restoring optimal epicardial flow, percutaneous intervention is associated with improved microvascular flow.

It is not known whether the clinical benefit of primary PCI compared with fibrinolysis is sustained with time because no long-term follow-up data are yet available. No data on the type of treatment of diabetes (insulin or no insulin) were present. Furthermore, the effect of long-term glycometabolic control in diabetic patients according to method of reperfusion therapy could not be assessed because glycosylated hemoglobin levels were unavailable. Most patients in the fibrinolysis group in the current analysis were not treated with prehospital fibrinolysis. Selection is a potential limitation of randomized controlled trials. Indeed, the prevalence of diabetes in the present patients is somewhat lower when compared with registries. Also, the relatively young age of our patient group may suggest some bias resulting from the inclusion process. However, the demonstration of a clear benefit of primary PCI compared with fibrinolysis in these patients only strengthens our conclusions.

**CONCLUSIONS**

Diabetic patients with STEMI treated with reperfusion therapy have higher mortality compared with nondiabetic patients. The beneficial effect of primary PCI compared with fibrinolysis is consistent in patients with and without diabetes. Wider application of timely primary PCI could be an important strategy to improve outcomes in the high-risk population of diabetic patients.

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**Table 4. Thirty-Day Clinical End Points in Patients According to Diabetes Status and Randomized Method of Reperfusion Therapy**

<table>
<thead>
<tr>
<th>End Point</th>
<th>PCI</th>
<th>Fibrinolysis</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without diabetes</td>
<td>130 (4.8)</td>
<td>189 (6.9)</td>
<td>0.69 (0.54-0.86)</td>
<td>.001</td>
</tr>
<tr>
<td>With diabetes</td>
<td>30 (6.6)</td>
<td>52 (12.4)</td>
<td>0.49 (0.31-0.79)</td>
<td>.004</td>
</tr>
<tr>
<td>Recurrent MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without diabetes</td>
<td>62 (2.3)</td>
<td>182 (6.7)</td>
<td>0.33 (0.25-0.44)</td>
<td>.001</td>
</tr>
<tr>
<td>With diabetes</td>
<td>15 (3.4)</td>
<td>23 (5.5)</td>
<td>0.60 (0.30-1.16)</td>
<td>.12</td>
</tr>
<tr>
<td>Death or recurrent MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without diabetes</td>
<td>182 (6.7)</td>
<td>343 (12.5)</td>
<td>0.51 (0.42-0.61)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>With diabetes</td>
<td>44 (9.6)</td>
<td>72 (17.1)</td>
<td>0.52 (0.35-0.77)</td>
<td>.001</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without diabetes</td>
<td>38 (1.5)</td>
<td>66 (2.5)</td>
<td>0.58 (0.39-0.86)</td>
<td>.007</td>
</tr>
<tr>
<td>With diabetes</td>
<td>7 (1.5)</td>
<td>16 (3.7)</td>
<td>0.40 (0.16-0.99)</td>
<td>.04</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention.

*Data are given as number (percentage) unless otherwise indicated.*

**Figure 2. Adjusted odds ratios and 95% confidence intervals for the risk of 30-day mortality according to the method of reperfusion therapy in patients with and without diabetes. DM indicates diabetes mellitus; PCI, percutaneous coronary intervention.**
Italy; and Eulogia Garcia, MD, University Hospital Gregorio Maranon, Madrid, Spain. Limburg Myocardial Infarction Trial: Fritz Bar, MD, PhD, University of Maastricht, Maastricht, the Netherlands. STAT (Stenting vs Thrombolysis in Acute Myocardial Infarction Trial): Michel R. LeMay, MD, Ottawa Heart Institute, Ottawa, Ontario. STOPAMI (Stent vs Thrombolyis for Occluded Coronary Arteries in Patients With Acute Myocardial Infarction) studies: Adnan Kastrati, MD, and Albert Schömig, MD, Deutsches Herzzentrum Munchen, Munich, Germany. C-PORT (Cardiovascular Patient Outcome Research Team) Trial: Thomas Aversano, MD, The Johns Hopkins School of Medicine, Baltimore, Maryland. DANAMI-2 (Second Danish Trial of Acute Myocardial Infarction): Henning Rud Andersen, MD, and Torsten T. Nielsen, MD, Aarhus University Hospital, Aarhus, Denmark.

REFERENCES