Time Delay to Treatment and Mortality in Primary Angioplasty for Acute Myocardial Infarction
Every Minute of Delay Counts

Giuseppe De Luca, MD; Harry Suryapranata, MD, PhD; Jan Paul Ottervanger, MD, PhD; Elliott M. Antman, MD

Background—Although the relationship between mortality and time delay to treatment has been demonstrated in patients with acute ST-segment elevation myocardial infarction (STEMI) treated by thrombolysis, the impact of time delay on prognosis in patients undergoing primary angioplasty has yet to be clarified. The aim of this report was to address the relationship between time to treatment and mortality as a continuous function and to estimate the risk of mortality for each 30-minute delay.

Methods and Results—The study population consisted of 1791 patients with STEMI treated by primary angioplasty. The relationship between ischemic time and 1-year mortality was assessed as a continuous function and plotted with a quadratic regression model. The Cox proportional hazards regression model was used to calculate relative risks (for each 30 minutes of delay), adjusted for baseline characteristics related to ischemic time. Variables related to time to treatment were age ≥70 years (P<0.0001), female gender (P=0.004), presence of diabetes mellitus (P=0.002), and previous revascularization (P=0.035). Patients with successful reperfusion had a significantly shorter ischemic time (P=0.006). A total of 103 patients (5.8%) had died at 1-year follow-up. After adjustment for age, gender, diabetes, and previous revascularization, each 30 minutes of delay was associated with a relative risk for 1-year mortality of 1.075 (95% CI 1.008 to 1.15; P=0.041).

Conclusions—These results suggest that every minute of delay in primary angioplasty for STEMI affects 1-year mortality, even after adjustment for baseline characteristics. Therefore, all efforts should be made to shorten the total ischemic time, not only for thrombolytic therapy but also for primary angioplasty. (Circulation. 2004;109:1223-1225.)

Key Words: myocardial infarction ■ prognosis ■ mortality ■ angioplasty

Although the relationship between mortality and time delay to treatment has been demonstrated in patients with acute ST-segment elevation myocardial infarction (STEMI) treated by thrombolysis,1-3 the impact of time delay on prognosis in patients undergoing primary angioplasty has yet to be clarified.4-6 In a recent study,7 we have shown that time from symptom onset to balloon inflation, but not door-to-balloon time, is strongly related to 1-year mortality in patients treated by primary angioplasty. The aim of this report was to address the relationship between time to treatment and mortality as a continuous function and to estimate the risk of mortality for each 30-minute delay in treatment.

Methods
From 1994 to 2001, a total of 1791 patients with STEMI underwent primary angioplasty.7 Informed consent was obtained from each patient (or from their relatives in case of patient’s inability) before the angiogram. All patients presenting within 6 hours from symptom onset or between 6 and 24 hours if they had continuous symptoms and signs of ischemia (persistent or recurrent chest pain and/or persistent elevation or reelevation of ST segment) were included.7 All patients received aspirin (500 mg) and heparin (10 000 IU) intravenously before the procedure. Therapy after stenting changed during the study period. All patients were taking aspirin and were treated with an additional 3 months of warfarin (before 1996) or 1 month of ticlopidine or clopidogrel (since January 1996). Time to treatment was calculated from symptom onset to first balloon inflation (true ischemic time).

Angiographic Data Analysis
All angiograms were analyzed by an independent core laboratory (Diagram, Zwolle, The Netherlands) blinded to all data apart from the angiogram. TIMI (Thrombolysis In Myocardial Infarction) flow and myocardial blush grade were assessed after the angioplasty procedure, as described previously.8 Residual stenosis was assessed visually. Successful reperfusion was defined as postprocedural TIMI 3 flow, residual stenosis <50%, and myocardial blush grade 2 to 3.

Ejection Fraction
Left ventricular ejection fraction was measured by radionuclide ventriculography at discharge, as described previously.8

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Patient Characteristics and Ischemic Time

<table>
<thead>
<tr>
<th>Variable</th>
<th>Yes</th>
<th>No</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;70 y</td>
<td>237±149</td>
<td>208±139</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female gender</td>
<td>233±137</td>
<td>208±139</td>
<td>0.004</td>
</tr>
<tr>
<td>Diabetes</td>
<td>248±195</td>
<td>211±135</td>
<td>0.002</td>
</tr>
<tr>
<td>Previous CABG/PCI</td>
<td>217±146</td>
<td>190±68</td>
<td>0.035</td>
</tr>
<tr>
<td>Previous infarction</td>
<td>202±76</td>
<td>216±148</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>203±70</td>
<td>218±156</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>205±121</td>
<td>217±146</td>
<td>NS</td>
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<tr>
<td>Smoking</td>
<td>212±124</td>
<td>217±155</td>
<td>NS</td>
</tr>
<tr>
<td>Killip class &gt;1</td>
<td>214±123</td>
<td>214±144</td>
<td>NS</td>
</tr>
<tr>
<td>Anterior infarction</td>
<td>215±148</td>
<td>213±135</td>
<td>NS</td>
</tr>
<tr>
<td>TIMI flow 0–1 preprocedure</td>
<td>214±128</td>
<td>215±174</td>
<td>NS</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>213±112</td>
<td>215±169</td>
<td>NS</td>
</tr>
<tr>
<td>Successful reperfusion*</td>
<td>208±120</td>
<td>229±188</td>
<td>0.006</td>
</tr>
<tr>
<td>Stent</td>
<td>211±119</td>
<td>217±161</td>
<td>NS</td>
</tr>
<tr>
<td>EF &lt;30%†</td>
<td>237±138</td>
<td>214±140</td>
<td>0.04</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass graft; PCI, percutaneous coronary intervention; EF, ejection fraction at discharge.
*Defined as postprocedural TIMI flow 3, residual restenosis <50%, and myocardial blush grade 2 to 3.
†Ejection fraction at discharge was available in 1143 patients.

Clinical Outcome

Records of all patients who visited our outpatient clinic were reviewed. For all other patients, information was obtained from the patient’s general physician or by direct telephone interview with the patient. For patients who died during follow-up, hospital records and necropsy data were reviewed. No patient was lost to follow-up.

Statistical Analysis

Statistical analysis was performed with the SPSS 10.0 statistical package. Continuous data were expressed as mean±SD and categorical data as percentage. ANOVA and χ² test were used appropriately for continuous and categorical variables, respectively. A logistic regression analysis was used to evaluate the relationship between time to treatment and predischarge ejection fraction, after adjustment for baseline characteristics related to ischemic time. The relationship between ischemic time and 1-year mortality was assessed as a continuous function and plotted with a quadratic regression model. Cox proportional hazards regression model was used to calculate relative risks (for each 30-minute delay), adjusted for baseline characteristics related to ischemic time.

Results

Time to treatment according to patients’ demographic, clinical, and angiographic characteristics is reported in the Table. Variables significantly related to time to treatment were age >70 years (237±149 versus 208±139 minutes, P<0.0001), female gender (233±137 versus 208±139 minutes, P=0.004), diabetes (248±195 versus 211±135 minutes, P=0.002), and previous revascularization (217±146 versus 190±68 minutes, P=0.035). When analyzed as a continuous variable, age was linearly related to ischemic time (r=0.096, P<0.0001). Ischemic time was inversely associated with predischarge ejection fraction (r=-0.068, P=0.022). After adjustment for age (as a continuous variable), gender, diabetes, and previous revascularization, each 30-minute delay was associated with an OR of predischarge ejection fraction <30% of 1.087 (95% CI 1.023 to 1.15; P=0.005). Patients with successful reperfusion had a significantly shorter ischemic time (208±120 versus 229±188 minutes, P=0.006).

A total of 103 patients (5.8%) had died at 1-year follow-up. The relationship between time to treatment and mortality is depicted in the Figure. After adjustment for age (as a continuous variable), gender, diabetes, and previous revascularization, each 30-minute delay was associated with a relative risk of 1-year mortality of 1.075 (95% CI 1.008 to 1.15; P=0.041).

Discussion

The major finding of the present study is that every minute in delay of treatment in patients with STEMI does affect 1-year mortality, not only in thrombolytic therapy but also in primary angioplasty. In fact, the risk of 1-year mortality is increased by 7.5% for each 30-minute delay.

Despite the demonstrated prognostic role of time delay to treatment in patients with STEMI treated by thrombolysis,1–3 its role in patients treated with primary angioplasty remains controversial.3,7 In a pooled analysis of all randomized trials that compared thrombolysis and primary angioplasty, Zijlstra et al8 found that mortality linearly increased with time delay only in patients treated by thrombolysis, whereas it was relatively stable in patients treated by primary angioplasty. Cannon et al,4 in a cohort of 27 080 patients undergoing primary angioplasty, found that only door-to-balloon time and not symptom on–to–balloon time was associated with mortality. The absence of any relationship between ischemic time and mortality in primary angioplasty may be related to the potential low-risk profile of patients enrolled in randomized trials.3 In fact, as reported by Antoniucci et al,5 symptom onset–to–balloon time was associated with higher mortality, particularly in high-risk patients. These data have been strongly supported by recent reports.6,7 A major limitation of the study by Cannon et al8 is that very long door-to-balloon time (>2 hours) was observed in up to 50% of patients, which may affect the relationship between time delay and mortality. This confounding mechanism does not play a major role in single-center studies. In our previous report,7 symptom onset–to–balloon time (true ischemic time) and not door-to-balloon time was a predictor of 1-year mortality.

A major explanation for our findings is that as demonstrated in animal models,9–11 infarct size is significantly affected by the duration of coronary occlusion. Therefore,
late reperfusion is expected to result in less myocardial salvage and a higher mortality rate than found with early reperfusion, even when optimal mechanical reperfusion is applied. In support of these data, Stone et al\textsuperscript{12} found preprocedural TIMI-3 flow to be an independent predictor of mortality. Furthermore, a delay in reperfusion may be associated with an older, organized intracoronary thrombus compared with an early reperfusion. This may result in a higher incidence of distal embolization with lower postprocedural TIMI-3 flow and poor myocardial perfusion.\textsuperscript{8} In fact, we found that patients with successful reperfusion (postprocedural TIMI-3 flow with residual stenosis <50\% and optimal myocardial perfusion [myocardial blush grade 2 to 3]) had a significantly shorter ischemic time.

Because of the time dependence of thrombolytic therapy in obtaining optimal restoration of epicardial flow, time delay to treatment would be expected to increase the relative risk of mortality more remarkably when thrombolysis is administered than when mechanical reperfusion is used. Although primary angioplasty, in comparison with thrombolysis, may guarantee a higher rate of reperfusion in patients presenting late, it cannot prevent myocardial necrosis, which is related to the duration of occlusion, particularly in higher-risk patients.\textsuperscript{5–7}

Conclusions
The results of this study strongly support the prognostic implication of time delay in patients with STEMI undergoing primary angioplasty. Therefore, all efforts should be made to shorten total ischemic time, not only for thrombolytic therapy but also for primary angioplasty.

References