2

Impact of time-delay on outcome
CHAPTER 2.1

Symptom-onset-to-balloon time and mortality in patients with acute myocardial infarction treated by primary angioplasty

Giuseppe De Luca, Harry Suryapranata, Felix Zijlstra, Arnoud WJ van’t Hof, Jan CA Hoornjte, AT Marcel Gosselink, Jan-Henk Dambrink, and Menko-Jan de Boer, on behalf of the ZWOLLE Myocardial Infarction Study Group

J Am Coll Cardiol 2003; 42: 991-7
Abstract

Objectives. The aim of the study was to evaluate the relationship between symptom-onset-to-balloon time and 1-year mortality in patients with ST-segment elevation myocardial infarction (STEMI) treated by primary angioplasty.

Background. Despite the prognostic implications demonstrated in patients with STEMI treated with thrombolysis, the impact of time-delay on prognosis in patients undergoing primary angioplasty has yet to be established.

Methods. Our study population consisted of 1791 patients with STEMI treated by primary angioplasty from 1994 to 2001. All clinical, angiographic and follow-up data were collected. Subanalyses were conducted according to patient risk profile at presentation and preprocedural TIMI flow.

Results. A total of 103 patients (5.8%) had died at 1 year. Symptom-onset-to-balloon time was significantly associated with the rate of postprocedural TIMI 3 flow (p = 0.012), myocardial blush grade (p = 0.033), 1-year mortality (p = 0.02). A stronger linear association between symptom-onset-to-balloon time and 1-year mortality was observed in non-low-risk patients (p = 0.006) and those with preprocedural TIMI flow 0-1 (p = 0.013). No relationship was found between door-to-balloon time and mortality. At multivariate analysis, a symptom-onset-to-balloon time > 4 hours was identified as an independent predictor of 1-year mortality (p < 0.05).

Conclusions. This study shows that, in patients with STEMI treated by primary angioplasty, symptom-onset-to-balloon time, but not door-to-balloon time, is related to mortality, particularly in non-low-risk patients and in the absence of preprocedural anterograde flow. Furthermore, a
symptom-onset-to-balloon time > 4 hours was identified as independent predictor of 1-year mortality.
The improvement in the management of patients with ST-segment elevation myocardial infarction (STEMI), characterized by early diagnosis and treatment of the acute event, improved management of complications, and general availability of pharmacological and mechanical therapies, has significantly reduced cardiac mortality (1-5).

Although a clear relationship between mortality and time-delay from symptom onset to treatment has been demonstrated in patients with STEMI treated by thrombolysis (6-8), the impact of time delay on prognosis in patients undergoing primary angioplasty still has not been clarified (8-11). The aim of the current study was to evaluate the influence of symptom-onset-to-balloon time and door-to-balloon time on mortality in a large cohort of patients with STEMI treated by primary angioplasty.

**Methods and Materials**

From 1994 to 2001, a total of 1791 patients with (STEMI) fulfilled the criteria for entry into one of the trials (Table 1) at our institution (4, 12-15). Informed consent was obtained from each patient (or from their relatives in case of patient’s inability) before the angiogram. Our study was approved by the Institutional Review Board.

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 re-elevation of ST-segment) were included (4).

All patients received aspirin (500 mg intravenously) and heparin (10000 IU intravenously) before the procedure. Since the benefits of IIb-IIIa inhibitors has only been proved recently (16), most of our trials have been conducted without IIb-IIIa inhibitors, with less than 5% of patients in the current study treated with this additional therapy. All patients were on
aspirin after the procedure. Therapy after stenting has changed across the study period. Patients have been treated with additional 3-month Warfarin therapy before 1996, and additional 1-month antiplatelet therapy with ticlopidine or clopidogrel after 1996.

According to the time from symptom onset to first balloon inflation (symptom-onset-to-balloon time), patients were divided into four groups (< 2 hours, between 2 and 4 hours, between 4 and 6 hours, and > 6 hours). According to the time from hospitalization to first balloon inflation (door-to-balloon time), patients were divided into 4 groups (< 30 minutes, between 31 and 60 minutes, between 61-90 minutes, and > 90 minutes).

The presence of 1 or more TIMI criteria (previous myocardial infarction, anterior infarction, systolic blood pressure < 100 mmHg, sinus tachycardia, atrial flutter or fibrillation, age > 70 years, rales extending upward to cover more than one third of the lung fields, pulmonary edema or cardiogenic shock) was used to stratify patients into “low-risk” and “non-low-risk” patients (17).

Table 1. Characteristics of randomized trials conducted at our Institution in patients with acute myocardial infarction, and the number of patients included from each trial in the current study.

1) Randomized comparison between primary angioplasty or thrombolysis in low-risk patients (45 patients) (12)
2) Randomized comparison between balloon and stenting in primary angioplasty (227 patients) (4)
3) Randomized comparison of intraaortic balloon pump in high-risk patients after primary angioplasty (150 patients) (13)
4) Randomized comparison of high-dose (20000 IU) vs low-dose heparin (5000 IU) in primary angioplasty (584 patients) (14)
5) Randomized comparison between thrombolysis and primary angioplasty in elderly (> 75 ys) (46 patients) (15)
6) Randomized comparison of Glucose-Insulin-Potassium Solution infusion in primary angioplasty (739 patients)*

*Accepted for publication in J Am Coll Cardiol
Angiographic data analysis

All angiograms have been reviewed by two experienced investigators who were blinded to all data apart from the coronary angiogram. TIMI flow grades and myocardial blush grade (MBG) were assessed after the angioplasty procedure, as previously described (18). Residual stenosis was visually assessed. Procedural success was defined as postprocedural TIMI 3 flow and a residual stenosis < 50%.

Enzymatic Infarct Size

Enzymatic infarct size was calculated, as previously described, by cumulative enzyme release (LDH_Q48) from serial measurements up to 48 hours after symptom onset (19).

Clinical outcome

Records of included 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 was used for continuous variables. The chi-square test or the Fisher's exact test (in case the expected value of the variable was less than 5 in at least one group) was used for categorical variables. A p value < 0.05 was considered statistically significant.

The difference in event rates between groups during the follow-up period was assessed by the Kaplan-Meier method using the log-rank test. Multivariate analysis was performed by use of the Cox proportional hazard method. The stepwise selection of variables and estimation of
significant probabilities were computed by means of maximal likelihood ratio test. The chi-square value was calculated from the log of the ratio of maximal partial likelihood functions. The additional value of each category of variables added sequentially was evaluated on the basis of the increases in the overall likelihood statistic ratio.

Results

Symptom-onset-to-balloon time and door-to-balloon time were, respectively, $214 \pm 189$ minutes and $55 \pm 36$ minutes. Demographic, clinical and angiographic characteristics according to symptom-onset-to-balloon time and door-to-balloon time are reported in Table 2 and 3, respectively. All categorical variables were analyzed using the chi-square test, except for previous angioplasty and previous bypass surgery (Fisher’s exact test). An association was found between these two parameters, with age and gender. A higher incidence of anterior infarction, Killip class $> 1$, and larger enzymatic infarct size were observed in patients with short door-to-balloon time. Symptom-onset-to-balloon time but not door-to-balloon time was significantly associated with the rate of postprocedural TIMI 3 flow, procedural success, and MBG 2-3. A total of 103 patients (5.8%) had died at 1-year follow-up. No difference in mortality was observed among patients treated in the first (1994-1997) and last 4 years (1998-2001) of the study (5.9% vs 4.2%, respectively; $p = \text{NS}$). No difference in mortality was observed between patients who were transferred ($n = 692$) or not transferred ($n = 1099$) from other hospitals (6.2% vs 5.5%, respectively, $p = \text{NS}$). As depicted in Figure 1, cardiac mortality was related to symptom-onset-to-balloon time ($p = 0.02$), but not to door-to-balloon time (Fig. 2).
### Table 2. Demographic, clinical and angiographic characteristics according to symptom-onset-to-balloon time.

<table>
<thead>
<tr>
<th>Time</th>
<th>≤ 2 h</th>
<th>2-4 h</th>
<th>4-6 h</th>
<th>&gt; 6h</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>226</td>
<td>1065</td>
<td>427</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>59±11</td>
<td>60±11</td>
<td>61±12</td>
<td>62±13</td>
<td>0.01</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>79.2</td>
<td>81.9</td>
<td>76.3</td>
<td>58.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>8</td>
<td>7.8</td>
<td>9.4</td>
<td>17.8</td>
<td>NS</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>11.1</td>
<td>11.5</td>
<td>12.6</td>
<td>4.1</td>
<td>NS</td>
</tr>
<tr>
<td>Anterior MI or LBBB (%)</td>
<td>51.8</td>
<td>51.5</td>
<td>48</td>
<td>61.6</td>
<td>NS</td>
</tr>
<tr>
<td>Killip class &gt;1 (%)</td>
<td>13.7</td>
<td>11.9</td>
<td>10.5</td>
<td>11.8</td>
<td>NS</td>
</tr>
<tr>
<td>Transferred patients (%)</td>
<td>25.7</td>
<td>41</td>
<td>40</td>
<td>35.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Multivessel disease (%)</td>
<td>44.7</td>
<td>55.1</td>
<td>56.4</td>
<td>46.6</td>
<td>NS</td>
</tr>
<tr>
<td>Pre TIMI 0-1 flow (%)</td>
<td>74.8</td>
<td>72.4</td>
<td>76.3</td>
<td>75.3</td>
<td>NS</td>
</tr>
<tr>
<td>Post TIMI 3 flow (%)</td>
<td>93.4</td>
<td>91.3</td>
<td>86.9</td>
<td>90.4</td>
<td>012</td>
</tr>
<tr>
<td>Procedural success (%)</td>
<td>92.4</td>
<td>89.8</td>
<td>85.9</td>
<td>89.6</td>
<td>0.01</td>
</tr>
<tr>
<td>MBG 2-3 (%)*</td>
<td>80</td>
<td>75.8</td>
<td>70.8</td>
<td>76.8</td>
<td>0.033</td>
</tr>
<tr>
<td>Stent (%)</td>
<td>55.3</td>
<td>47.9</td>
<td>50.3</td>
<td>52.1</td>
<td>NS</td>
</tr>
<tr>
<td>LDH_{Q48} (U/L) †</td>
<td>1632±1712</td>
<td>1858±1552</td>
<td>1834±1510</td>
<td>1815±1557</td>
<td>NS</td>
</tr>
</tbody>
</table>

LBBB = Left anterior bundle branch; LDH_{Q48} = Enzymatic infarct size from serial measurements of lactate dehydrogenase; MBG = Myocardial Blush Grade; MI = Myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction.

*Data available in 1771 patients; †Data available in 1069 patients.
Table 3. Demographic, clinical and angiographic characteristics according to door-to-balloon time

<table>
<thead>
<tr>
<th>Time</th>
<th>0-30 min</th>
<th>31-60 min</th>
<th>61-90 min</th>
<th>&gt; 90 min</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>409</td>
<td>768</td>
<td>416</td>
<td>198</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>59±11</td>
<td>60±11</td>
<td>61±11</td>
<td>62±13</td>
<td>0.01</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>81.4</td>
<td>79.6</td>
<td>79.6</td>
<td>73.2</td>
<td>0.047</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>7.1</td>
<td>8.5</td>
<td>7.9</td>
<td>13.7</td>
<td>NS</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>10.3</td>
<td>10.8</td>
<td>13.2</td>
<td>12.1</td>
<td>NS</td>
</tr>
<tr>
<td>Anterior MI or LBBB (%)</td>
<td>68.7</td>
<td>49.5</td>
<td>42.3</td>
<td>41.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Killip class &gt;1 (%)</td>
<td>15.4</td>
<td>11.7</td>
<td>8.4</td>
<td>13.6</td>
<td>0.021</td>
</tr>
<tr>
<td>Transferred patients (%)</td>
<td>70.4</td>
<td>37.1</td>
<td>22.1</td>
<td>13.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Multivessel disease (%)</td>
<td>50.4</td>
<td>53.8</td>
<td>56.3</td>
<td>55.6</td>
<td>NS</td>
</tr>
<tr>
<td>Pre TIMI 0-1 flow (%)</td>
<td>72.9</td>
<td>74.3</td>
<td>74</td>
<td>72.7</td>
<td>NS</td>
</tr>
<tr>
<td>Post TIMI 3 flow (%)</td>
<td>90.2</td>
<td>91.7</td>
<td>89.9</td>
<td>87.4</td>
<td>NS</td>
</tr>
<tr>
<td>Procedural success (%)</td>
<td>89.2</td>
<td>90.2</td>
<td>88.8</td>
<td>86.5</td>
<td>NS</td>
</tr>
<tr>
<td>MBG 2-3 (%)*</td>
<td>73.9</td>
<td>76.8</td>
<td>75.8</td>
<td>69.9</td>
<td>NS</td>
</tr>
<tr>
<td>Stent (%)</td>
<td>50.6</td>
<td>49.6</td>
<td>49.5</td>
<td>49.5</td>
<td>NS</td>
</tr>
<tr>
<td>LDH&lt;sub&gt;Q48&lt;/sub&gt; (U/L)†</td>
<td>2082±1836</td>
<td>1821±1576</td>
<td>1696±1382</td>
<td>1606±1382</td>
<td>0.018</td>
</tr>
</tbody>
</table>

LBBB = Left anterior bundle branch; LDH<sub>Q48</sub> = Enzymatic infarct size from serial measurements of lactate dehydrogenase; MBG = Myocardial Blush Grade; MI = Myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction.

*Data available in 1771 patients; †Data available in 1069 patients.

Symptom-onset-to-balloon time, door-to-balloon time, and mortality in low-risk and non-low-risk patients

The relation between symptom-onset-to-balloon time, door-to-balloon time and mortality was also investigated in low-risk and non-low-risk patients. A total of 545 low-risk patients (30.4%) and 1246 (69.6%) non-low-risk patients were identified (with a 1-year mortality of 1.1% vs 7.8%, respectively; p < 0.0001). As depicted in figure 1, mortality increased linearly according to symptom-onset-to-balloon time only in patients with non-low-risk characteristics (p value = 0.006). As shown by Kaplan-Meier survival curves (Fig. 3), the difference in mortality among he 4 groups was already observed at 30 days, and persisted till 1-year
follow-up. No relationship was observed between door-to-balloon time and mortality either in low-risk or non-low-risk patients (Fig. 2).

**Figure 1.** Bar graphs show the relationship between symptom-onset-to-balloon time and 1-year mortality, in all patients, in low and non-low-risk patients (upper graph) and according to preprocedural TIMI flow (lower graph).

**Symptom-onset-to-balloon time, door-to-balloon time, and mortality according to preprocedural TIMI flow**

To investigate the impact of preprocedural TIMI flow on the prognostic role of symptom-onset-to-balloon time and door-to-balloon time, patients were classified according to preprocedural TIMI 0-1 flow (1321 patients (73.8%) and TIMI 2-3 flow (470 patients (26.2%). A linear relationship between symptom-onset-to-balloon time and 1-year mortality
was observed only in patients with preprocedural TIMI 0-1 flow, but not in patients with preprocedural TIMI 2-3 flow (Fig. 1). The relationship between door-to-balloon time and mortality was not affected by preprocedural TIMI flow (Fig. 2).

**Figure 2.** Bar graphs show the relationship between door-to-balloon time and 1-year mortality, in all patients, in low and non-low-risk patients (upper graph) and according to preprocedural TIMI flow (lower graph).

**Multivariate predictors of 1-year mortality**
As shown in table 4, a symptom-onset-to-balloon time > 4 hours (p < 0.05) was an independent predictor of 1-year mortality, together with Killip > 1, age ≥ 70 years, postprocedural TIMI 0-2 flow, anterior MI, and multivessel disease.
**Figure 3.** Kaplan-Meier survival curves according to symptom-onset-to-balloon time in both low-risk (upper graph) and non-low-risk patients (lower graph).

**Table 4.** Predictors of 1-year mortality at multivariate analysis.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Relative Risk [95%CI]</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>KILLIP class (&gt; 1)</td>
<td>5.27 [3.4-8.1]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (≥ 70 years)</td>
<td>2.98 [1.9-4.5]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TIMI flow 0-2 post</td>
<td>2.96 [1.84-4.71]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anterior infarction</td>
<td>2.13 [1.34-3.37]</td>
<td>0.001</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>2.34 [1.42-3.8]</td>
<td>0.001</td>
</tr>
<tr>
<td>Symptom-onset-to-balloon (&gt; 4h)</td>
<td>1.55 [1.01-2.4]</td>
<td>0.046</td>
</tr>
<tr>
<td>Procedural success</td>
<td>1.57 [0.72-3.42]</td>
<td>NS</td>
</tr>
<tr>
<td>Preprocedural TIMI 0-1flow</td>
<td>1.32 [0.77-2.26]</td>
<td>NS</td>
</tr>
<tr>
<td>Previous infarction</td>
<td>0.9 [0.51-1.58]</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.97 [0.52-1.8]</td>
<td>NS</td>
</tr>
</tbody>
</table>

TIMI = Thrombolysis in Myocardial Infarction
Discussion

The main finding of the present study is that, among patients with STEMI undergoing mechanical reperfusion, symptom-onset-to-balloon time, but not door-to-balloon time, affects 1-year mortality, particularly in high-risk patients and in the absence of preprocedural TIMI 2-3 flow. In this study, a symptom-onset-to-balloon time > 4 hours has been shown to be an independent predictor of 1-year mortality.

Symptom-onset-to-balloon time and mortality in STEMI

The aim of a successful therapeutic strategy in STEMI is to restore myocardial flow as soon as possible from symptom onset. Despite the demonstrated prognostic role of time to therapy in patients with STEMI treated by thrombolysis (6-8), there is still doubt with regard to its role in patients treated with primary angioplasty (8-11).

Brodie et al (9), observed a better outcome among patients undergoing primary angioplasty within 2 hours from symptom onset, whereas a relatively stable mortality rate was observed between 2 to 12 hours. These data were confirmed by Cannon et al. (11) who, in a cohort of 27080 patients undergoing primary angioplasty, found only door-to-balloon time but not symptom-onset-to-balloon time to be associated with mortality.

In consistence with these data, Zijlstra et al (8), in a recent pooled-analysis of several randomized trials comparing primary angioplasty and thrombolysis, found a direct relationship between time from symptom onset to treatment only in patients treated by thrombolysis, but not by primary angioplasty.

A major limitation of these studies is that they did not stratify patients according to the risk of death. In fact, it seems unlikely to show a prognostic role of time-delay in patients at very low-risk of death.
reperfusion, even when optimal mechanical reperfusion is applied. Supporting the prognostic role of early restoration of antegrade flow in STEMI, Stone and colleagues (24) 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, in comparison with an early reperfusion. This may result in a higher incidence of distal embolization with a lower postprocedural TIMI 3 flow and a poor myocardial perfusion (18, 29). In our study, a delayed reperfusion (> 4 hours) was associated with a lower rate of postprocedural TIMI 3 flow and MBG 2-3.

Some investigators have found a relation between door-to-balloon time and outcome in multicenter studies (10, 11). However, in these settings, door-to-balloon time is probably a surrogate for quality of care. This confounding mechanism does not play a role in single center studies. The absence of any relationship between door-to-balloon time and mortality in our study, is also explained by the fact that this parameter represents only a part of the total ischemia time. Furthermore, we found an higher incidence of anterior infarction, Killip class > 1, and, larger enzymatic infarct size, in patients with a shorter door-to-balloon time (< 30 minutes). This is a consequence of our policy. In fact, quite all patients, according to a regional project, are transferred to our hospital from other hospitals of our region, or directly from home after the in-ambulance diagnosis of a large acute infarction. Thus we try, as previously described, to keep the door-to-balloon time as short as possible, particularly in high-risk patients (30).

Limitations

This is an observational study of patients enrolled in randomized trials at our Institution, thus, potentially, at lower risk in comparison with
patients in the daily clinical practice. Enzymatic infarct size was not available in all patients, with a potential underestimation of the impact of an early treatment on myocardial salvage.

Despite the limited use of stenting (in 50% of patients) and abciximab (in less than 5%) in the present study, currently available data do not show a reduction of mortality by additional use of stenting and abciximab, even with their combination (5).

The lack of an effect of door-to-balloon time may be explained by the shorter door-to-balloon time, when compared with previous reports (11).

Clinical implications

Although primary angioplasty has been demonstrated to be superior to thrombolytic therapy (2, 3), several areas for improvement still remain. Transportation to a tertiary center with angioplasty facilities has been shown to be safe and feasible (31-33). However, the potential time-delay for transportation remains a major drawback to primary angioplasty.

The results of our study suggest that in patients with STEMI undergoing primary angioplasty, all efforts should be made to shorten the time between symptom onset and mechanical reperfusion, particularly in high-risk patients.

Conclusions

This study shows that, in patients with STEMI treated by primary angioplasty, symptom-onset-to-balloon time, but not door-to-balloon time, is related to mortality, particularly in high-risk patients and in the absence of preprocedural anterograde flow. Furthermore, a symptom-
Another limitation of these studies is that all patients were included in the analysis, without any information on preprocedural TIMI flow. Pre-angioplasty TIMI flow may significantly limit the accuracy of time from symptom onset to first balloon inflation as a parameter of total ischemia time. In fact, in those patients, total ischemia time is shorter than that from symptom onset to balloon inflation.

In contrast with previous studies, we analyzed the prognostic role of symptom-onset-to-balloon time according to patient risk profile. Using TIMI criteria (17), we identified a non-low-risk population, and we found a significant relationship between symptom-onset-to-balloon time and mortality in these patients but not in low-risk patients.

We also analyzed the impact of preprocedural flow on the prognostic role of time-delay, and we found a significant relationship between symptom-onset-to-balloon time and mortality in patients with preprocedural TIMI flow 0-1. No relationship was found between door-to-balloon time and mortality, even if the analysis was conducted according to the patient risk profile and preprocedural TIMI flow.

In our study, a symptom-onset-to-balloon time > 4 hours was, together with Killip class (20), postprocedural TIMI flow (21), age (22, 23), multivessel disease (24), and anterior infarction (24), an independent predictor of 1-year mortality.

In consistence with our data, Antoniucci et al (25) found, in a population of 1332 patients undergoing primary angioplasty, a relationship between time-delay and mortality in high-risk patients.

Several explanations may account for our findings. As demonstrated in animal models (26-28), the duration of coronary occlusion is a main determinant of infarct size. Therefore, late reperfusion is expected to result in less myocardial salvage and, conceivably, in a higher mortality rate, in comparison with early
onset-to-balloon time > 4 hours was identified as an independent predictor of 1-year mortality.
REFERENCES


Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO IIb) trial. Circulation 1999; 100: 14-20.


33. Moon JC, Kalra PR, Coats AJ. DANAMI-2: is primary angioplasty superior to thrombolysis in acute MI when the patient has to be transferred to an invasive centre? Int J Cardiol 2002; 85: 199-201.
CHAPTER 2.2

Time-delay to Treatment and Mortality in Primary Angioplasty for Acute Myocardial Infarction: Every minute of delay counts

Giuseppe De Luca, Harry Suryapranata, Jan Paul Ottervanger, and Elliott M Antman*

Department of Cardiology, ISALA Klinieken, Zwolle, The Netherlands, *Cardiovascular Division, Brigham and Women’s Hospital, Boston, USA

Abstract

Introduction. 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 continuous function, and to estimate the risk of mortality for each 30-minute delay.

Methods. Our study population consisted of 1791 patients with STEMI treated by primary angioplasty. The relationship between ischemic time and 1-year mortality was assessed as continuous function, and plotted using a quadratic regression model. The Cox proportional-hazards regression model was used to calculate relative risks (for each 30-minute), adjusted for baseline characteristics related to ischemic time.

Results. Variables related to time-to-treatment were age > 70 (p<0.0001), female (p=0.004), diabetes (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-minute delay was associated with a relative risk [95% CI] for 1-year mortality of 1.075 [1.008-1.15] (p = 0.041).

Conclusions. These results suggest that every minute of delay in primary angioplasty for STEMI affects one-year mortality, even after adjusting for baseline characteristics. Therefore, all efforts should be attempted to shorten the total ischemic time, not only for thrombolytic therapy, but also for primary 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 (3-6). In a recent study (7), we have shown that symptom-onset-to-balloon time, 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 continuous function, and to estimate the risk of mortality for each 30-minute delay in treatment.

**Methods and Materials**

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 re-elevation of ST-segment) were included (7). All patients received aspirin (500 mg) and heparin (10000 IU) intravenously, before the procedure. Therapy after stenting has changed across the study period. All patients were on aspirin, and were treated with additional 3-month Warfarin (before 1996), or 1-month ticlopidine or clopidogrel (after 1996). Time-to-treatment was calculated from symptom-onset to first balloon inflation (true ischemic time).

**Angiographic data analysis**

All angiograms were analyzed by independent corelab (Diagram, Zwolle, The Netherlands), blinded to all data apart from the coronary
angiogram. TIMI flow and myocardial blush grade (MBG) were assessed after the angioplasty procedure, as previously described (18). Residual stenosis was visually assessed. Successful reperfusion was defined as post-procedural TIMI 3 flow, residual stenosis < 50%, and MBG 2-3.

**Ejection fraction**

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

**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. The analysis of variance and chi-square test were appropriately used 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 continuous function, and plotted using a quadratic regression model. The Cox proportional-hazards regression model was used to calculate relative risks (for each 30-minute), adjusted for baseline characteristics related to ischemic time.

**Results**

Time–to-treatment according to patients’ demographic, clinical and angiographic characteristics is reported in table 1. Variables significantly
related to time-to-treatment were age > 70 years (237±149 vs 208±139 minutes, p <0.0001), female gender (233±137 vs 208±139 minutes, p = 0.004), diabetes (248±195 vs 211±135 minutes, p = 0.002) and previous revascularization (217±146 vs 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 continuous variables), gender, diabetes, and previous revascularization, each 30-minute delay was associated with an odds ratio [95% CI] of predischarge ejection fraction < 30% of 1.087 [1.023-1.15] (p = 0.005). Patients with successful reperfusion had a significantly shorter ischemic time (208±120 vs 229±188 minutes, p = 0.006).

Table 1. Patients' characteristics and ischemic time

<table>
<thead>
<tr>
<th>Variable</th>
<th>Yes</th>
<th>No</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 70 years</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>
</tr>
<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 pre</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 = Coronary artery bypass graft; PCI = Percutaneous coronary intervention;
*Defined as postprocedural TIMI 3 flow, residual restenosis < 50% and myocardial blush grade 2-3; EF = Ejection fraction at discharge (available in 1143 patients)
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 Figure 1. After adjustment for age (as continuous variables), gender, diabetes, and previous revascularization, each 30-minute delay was associated with a relative risk [95% CI] of 1-year mortality of 1.075 [1.008-1.15] (p = 0.041).

![Figure 1](image)

**Figure 1.** The relationship between time-to-treatment and 1-year mortality, as continuous function, was assessed using a quadratic regression model. The dotted lines represent 95% confidence intervals of the predicted mortality.

**Discussion**

The major finding of the present study is that every minute delay in treatment of 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, comparing thrombolysis and primary angioplasty, Zijlstra et al. (3) 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, but not symptom-onset-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 strongly been supported by recent reports (6, 7). A major limitation of the study by Cannon et al (4) 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 (true ischemic time), but not door-to-balloon time, was 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 in a higher mortality rate, in comparison with early reperfusion, even when optimal mechanical reperfusion is applied. Supporting these data, Stone et al. (12) found pre-procedural
TIMI-3 flow to be an independent predictor of mortality. Furthermore, a delay in reperfusion may be associated with an older, organized intracoronary thrombus, in comparison with an early reperfusion. This may result in a higher incidence of distal embolization with a lower postprocedural TIMI-3 flow and a poor myocardial perfusion (8). In fact, we found that patients with successful reperfusion (postprocedural TIMI-3 flow with residual stenosis < 50%, and optimal myocardial perfusion - MBG 2-3) had a significantly shorter ischemic time.

Because of the time-dependence of thrombolytic therapy in obtaining an optimal restoration of epicardial flow, time-delay to treatment would be expected to increase the relative risk of mortality more remarkably when trombolysis is administrated, in comparison with mechanical reperfusion. Although primary angioplasty, in comparison with thrombolysis, may guarantee a higher rate of reperfusion in patients presented late, it cannot prevent myocardial necrosis, which is related to the duration of occlusion, particularly in higher risk patients (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 attempted to shorten the total ischemic time, not only for thrombolytic therapy, but also for primary angioplasty.
REFERENCES


12. Stone GW, Cox D, Garcia E, et al. Normal flow (TIMI-3) before mechanical reperfusion therapy is an independent determinant of
CHAPTER 2.3

Time-to-treatment significantly affects the extent of ST-segment resolution and myocardial blush in patients with acute myocardial infarction treated by primary angioplasty

Giuseppe De Luca, Arnoud WJ van’t Hof, Menko-Jan de Boer, Jan Paul Ottervanger, Jan CA Hoornmte, AT Marcel Gosselink, Jan-Henk Dambrink, Felix Zijlstra and Harry Suryapranata

Eur Heart J (in press)
Abstract

Aims. The prognostic role of time-to-treatment in primary angioplasty is still a matter of debate. The aim of our study was to evaluate the relationship between time-to-treatment and myocardial perfusion in patients with ST-segment elevation myocardial infarction (STEMI) treated by primary angioplasty.

Methods and results. Our study population consisted of 1072 patients with STEMI treated by primary angioplasty from 1997 to 2001. Myocardial perfusion was evaluated using ST-segment resolution and myocardial blush grade. Time-to-treatment was defined as the time between symptom-onset to the first balloon inflation. Time-to-treatment was significantly associated with the extent of ST-segment resolution, myocardial blush grade, enzymatic infarct size and 1-year mortality. After adjustment for baseline confounding factors, time-to-treatment was still associated with impaired ST-segment resolution (adjusted OR [95% CI] = 1.01[1.01-1.02], p < 0.001) and myocardial blush (adjusted OR [95% CI] = 1.01 [1.01-1.02], p < 0.0001).

Conclusions. This study shows that, in patients with STEMI treated by primary angioplasty, prolonged ischemic time is associated with impaired myocardial perfusion, larger infarct size and higher 1-year mortality. Therefore, all efforts should be attempted to shorten as much as possible ischemic time, in order to achieve better myocardial perfusion and myocardial salvage in primary angioplasty for STEMI.
Although a clear relationship between mortality and time-delay from symptom onset to treatment has been demonstrated in patients with 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 (3-8). In the current study, we investigated the impact of time-to-treatment on myocardial perfusion after primary angioplasty for STEMI.

Methods

From April 1997 to October 2001, a total of 1548 patients with STEMI have been treated with primary angioplasty. All patients were admitted within the first 6 hours, or between 6 and 24 hours, if they had persistent symptoms with evidence of ongoing ischemia, were included in the current study. Our study was approved by the Institutional Review Board. Analysis were performed by an independent core laboratory (Diagram, Zwolle, the Netherlands) blinded to all clinical data and outcome. Time-to-treatment was defined as the time from symptom-onset to the first balloon inflation.

Myocardial blush grade (MBG) was assessed after primary angioplasty, as previously described (9): Grade 0, no myocardial blush; Grade 1, minimal myocardial blush or contrast density; Grade 2, moderate myocardial blush or contrast density but less than that obtained during angiography of a contra or ipsilateral non-infarct related coronary artery; Grade 3, normal myocardial blush or contrast density, comparable with that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery. When myocardial blush persisted (“staining”), this phenomenon suggested leakage of contrast medium into the extravascular space and was graded 0.
Analysis of ST-segment resolution was performed by comparison between baseline and 3 hours 12-lead electrocardiograms (ECGs), as previously described (10). ST-segment resolution was defined according to a threshold of 50%.

Enzymatic infarct size and predischarge ejection fraction were measured as previously described (9), and categorised according to the 50th percentile.

All patients were reviewed at outpatient clinic. 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 and standard deviation and categorical data as percentage. The one-way analysis of variance and the chi-square test were used for continuous and categorical variables, respectively (two-sided tests). A trend analysis was done as described by Schlesselman (11). A p value < 0.05 was considered statistically significant.

Logistic regression analysis was performed to calculate the risk of impaired myocardial perfusion related to time-to-treatment adjusted for baseline confounding characteristics. All variables were entered in block. The significance testing, the odds ratios and the confidence intervals were calculated by the Wald statistics. To assess the linearity assumption we included new variables (representing the highest 3 quartiles vs the lowest quartile of time-to-treatment) in the regression model and plotted the estimated logistic regression coefficients versus the quartile midpoints of time-to-treatment.
Results

ST-segment resolution analysis was available in 1072 patients, who represent our study population. A part of this population (73%) has previously been described (8). The reasons for missing ST-segment resolution analysis were: poor ECG quality (2.7%), intraventricular conduction delay (16.4%) and missing paired ECG (80.8%).

Patients characteristics according to time-to-treatment are reported in Table 1. Patients with longer ischemic time were older, more often women, with diabetes, higher procedural success and had less often preprocedural recanalisation.

Table 1. Demographic, clinical and angiographic characteristics according to symptom-onset-to-balloon time.

<table>
<thead>
<tr>
<th>Ischemic time (hours)</th>
<th>&lt; 2</th>
<th>2-4</th>
<th>4-6</th>
<th>&gt; 6</th>
<th>p (trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>114</td>
<td>555</td>
<td>227</td>
<td>176</td>
<td></td>
</tr>
<tr>
<td>Age (&gt; 70)</td>
<td>15.7</td>
<td>22.0</td>
<td>25.1</td>
<td>28.0</td>
<td>0.011</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>80.4</td>
<td>80.1</td>
<td>77.3</td>
<td>65.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>8.9</td>
<td>8.0</td>
<td>10.7</td>
<td>19.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>12.5</td>
<td>9.9</td>
<td>11.6</td>
<td>6.3</td>
<td>0.18</td>
</tr>
<tr>
<td>Anterior MI or LBBB (%)</td>
<td>45.5</td>
<td>47.2</td>
<td>42.7</td>
<td>50.6</td>
<td>0.75</td>
</tr>
<tr>
<td>Killip class &gt;1 (%)</td>
<td>10.7</td>
<td>6.1</td>
<td>4.9</td>
<td>8.0</td>
<td>0.58</td>
</tr>
<tr>
<td>Multivessel disease (%)</td>
<td>45.5</td>
<td>53.0</td>
<td>56.9</td>
<td>51.7</td>
<td>0.33</td>
</tr>
<tr>
<td>Pre TIMI 0-1 flow (%)</td>
<td>68.2</td>
<td>67.8</td>
<td>75.2</td>
<td>77.9</td>
<td>0.046</td>
</tr>
<tr>
<td>Post TIMI 3 flow (%)</td>
<td>94.6</td>
<td>92.4</td>
<td>87.6</td>
<td>84.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angio success (%)</td>
<td>94.6</td>
<td>91.5</td>
<td>86.2</td>
<td>83.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Collaterals (%)</td>
<td>7.1</td>
<td>9.0</td>
<td>13.8</td>
<td>10.9</td>
<td>0.087</td>
</tr>
<tr>
<td>Stent (%)</td>
<td>56.3</td>
<td>58.4</td>
<td>60.0</td>
<td>55.2</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Medical therapy at discharge

<table>
<thead>
<tr>
<th></th>
<th>Statins (%)</th>
<th>Beta-blockers (%)</th>
<th>Ace-inhibitors (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins (%)</td>
<td>59.8</td>
<td>62.4</td>
<td>64.9</td>
</tr>
<tr>
<td>Beta-blockers (%)</td>
<td>86.6</td>
<td>88.1</td>
<td>88.4</td>
</tr>
<tr>
<td>Ace-inhibitors (%)</td>
<td>51.8</td>
<td>51.2</td>
<td>47.1</td>
</tr>
</tbody>
</table>

LBBB = Left anterior bundle branch; MI = Myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction.
As shown in Figure 1, time-to-treatment was significantly associated with the extent of ST-segment resolution, myocardial blush grade, and enzymatic infarct size. The impact of time-to-treatment of myocardial perfusion was also confirmed in the analysis restricted to patients with postprocedural TIMI 3 flow.

After adjustment for baseline confounding factors (age, diabetes, gender and preprocedural TIMI flow), time-to-treatment (as continuous variables) was still associated with impaired ST-segment resolution (adjusted OR [95% CI] = 1.001 [1.001-1.002], p < 0.001) and myocardial blush (adjusted OR [95% CI] = 1.001 [1.001-1.002], p < 0.001). The linearity assumption was confirmed by plotting estimated logistic regression coefficients vs quartile midpoints of time-to-treatment (Figure 2).

Figure 1. Bar graphs show the relationship between time-to-treatment, ST-segment resolution, myocardial blush grade, predischarge ejection fraction and enzymatic infarct size (*according to the 50th percentile), in all population and in patients with postprocedural TIMI 3 flow.
Figure 2. The linearity assumption was visually analysed by plotting the estimated logistic regression coefficients of the highest 3 quartiles and the mid point quartiles of time-to-treatment for both poor myocardial perfusion (upper graph) and ST-segment resolution (lower graph).

These data explained the observed significant impact of time-to-treatment on 1-year mortality (Figure 3).

Figure 3. Kaplan-Meier survival curves according to time-to-treatment.
Discussion

The main finding of the present study is that, among patients with STEMI undergoing mechanical reperfusion, impaired myocardial perfusion and larger infarct size explain the higher mortality rate observed in patients with prolonged time-delay.

Time-to-treatment, myocardial perfusion, and mortality after primary angioplasty for STEMI

Despite several studies have shown the relevant impact of time-to-treatment on myocardial perfusion (12), myocardial salvage (13), and mortality (1-3) in patients with STEMI treated by thrombolysis, the prognostic role of ischemic time in patients with STEMI treated by primary angioplasty is still a matter of debate (3-7). Brodie et al (4), observed a better outcome among patients undergoing primary angioplasty within 2 hours from symptom onset, whereas a relatively stable mortality rate was observed between 2 to 12 hours. These data were confirmed by Cannon et al. (6) who, in a cohort of 27,080 patients undergoing primary angioplasty, found only door-to-balloon time, but not time-to-treatment, to be associated with mortality. Similar findings were reported by Zijlstra et al (3), in a pooled-analysis of several randomised trials, comparing primary angioplasty and thrombolysis. They found a direct relationship between time-to-treatment and mortality only in patients treated by thrombolysis, but not by primary angioplasty.

Confirming these data, Schomig et al. (13) found a significant relationship between time-to-treatment and myocardial salvage only in patients treated by thrombolysis but not in those treated by primary angioplasty.

In our previous report (8), we found time-to-treatment to be an independent predictor of mortality in patients with STEMI treated with angioplasty, particularly in those at high-risk. These data have been
confirmed by Antoniucci et al. (7) in a population of 1332 patients undergoing primary angioplasty. Supporting the prognostic role of early restoration of antegrade flow in patients undergoing primary angioplasty, Stone and colleagues (14) found preprocedural TIMI 3 flow to be an independent predictor of mortality. In the current study, we found impaired myocardial perfusion and larger infarct size as potential explanations for the higher mortality observed in patients with prolonged time-delay to first balloon inflation. In fact, as demonstrated in animal models (15-17), the duration of coronary occlusion is a main determinant of infarct size. Therefore, late reperfusion is expected to result in poor perfusion, less myocardial salvage and, thus, in a higher mortality rate, in comparison with early reperfusion, even after optimal mechanical reperfusion. These results were also confirmed in the analysis restricted to patients with postprocedural TIMI 3 flow.

Several factors may explain the time dependent mechanism of impaired myocardial perfusion despite optimal epicardial flow. Experimental studies have shown that long balloon inflations may induce morphological alterations (swelling of endothelial and cardiac cells, with occlusion or compression of microcirculation) in the cardiac capillaries and arterioles (12). Furthermore, recent studies have focused on the role of microembolisation of atherosclerotic debris, blood clots, and platelet plugs in the microcirculation (15-16). A delay in reperfusion may be associated with an older, organised intracoronary thrombus, in comparison with an early reperfusion. This may result in a higher incidence of distal microembolisation and poor myocardial perfusion (10, 18), despite optimal epicardial flow.

Further studies should investigate the additional role of pharmacological therapy (19-22) and mechanical devices (23) in patients with longer time-delay to treatment in order to improve myocardial
Time-delay and myocardial perfusion

perfusion and to reduce ischemic-reperfusion damages and infarct size, beyond epicardial reperfusion.

Limitations

A major limitation of the current study is that up to 30% of the total population has been excluded due to missing or inadequate baseline and/or 3-hour ECGs. The evaluation of myocardial perfusion has been performed by using myocardial blush and ST-segment resolution. Despite the non-uniformity of methods used among trials (11, 22, 24-26), they still represent a cheap, simple and validated method to evaluate myocardial reperfusion. Differently from our previous report (11), ST-segment resolution was analysed at 3 hours, as it is our policy since 1997. In fact, the analysis at 3 hours would improve the sensitivity in the identification of patients with complete resolution. Because the aim of the study was not a prognostic risk stratification along the different degrees of ST-segment resolution, we have used a ST-segment resolution cut-off of 50% as surrogate of effective reperfusion (22). However, myocardial reperfusion is a dynamic process during which alternating episodes of ST-segment resolution may occur (27). Thus continuous ST-segment monitoring would have improved the evaluation of myocardial reperfusion (27-28). Consistent with our first report on myocardial blush grade (9), we have defined optimal myocardial perfusion as myocardial blush grade 2 to 3.

Enzymatic infarct size and ejection fraction were not available in all patients. Since their benefits have only been recently proven (22), additional administration of IIb-IIIa inhibitors have been applied to less than 5% of our population. Furthermore no distal protection devices have been used in this series of patients.
Clinical implications

Although primary angioplasty has been demonstrated to be superior to thrombolytic therapy, several areas for improvement still remain. The results of our study suggest that all efforts should be aimed at shortening the total ischemic time. This can be obtained by pre-hospital triage at home or in the ambulance for early identification of STEMI, direct transportation and early pretreatment with pharmacological agents to obtain optimal reperfusion before primary angioplasty, particularly in high-risk patients and when long-distance transportation to a tertiary center with angioplasty facilities is required.

Conclusions

This study shows that, in patients with STEMI treated by primary angioplasty, prolonged ischemic time is associated with higher mortality, mainly due to impaired myocardial perfusion and larger infarct size. Therefore, all efforts should be attempted to shorten the time-delay to reperfusion in order to achieve better myocardial perfusion.
REFERENCES


Time-delay and myocardial perfusion


