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Symptom-Onset-to-Balloon Time and Mortality in Patients With Acute Myocardial Infarction Treated by Primary Angioplasty

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OBJECTIVES The aim of the study was to evaluate the relationship between symptom-onset-to-balloon time and one-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 1,791 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 Thrombolysis In Myocardial Infarction (TIMI) flow.

RESULTS A total of 103 patients (5.8%) had died at one year. Symptom-onset-to-balloon time was significantly associated with the rate of postprocedural TIMI 3 flow ($p = 0.012$), myocardial blush grade ($p = 0.033$), and one-year mortality ($p = 0.02$). A stronger linear association between symptom-onset-to-balloon time and one-year mortality was observed in non-low-risk patients ($p = 0.006$) and those with preprocedural TIMI flow 0 to 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 h was identified as an independent predictor of one-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 h was identified as independent predictor of one-year mortality. (J Am Coll Cardiol 2003;42:991–7) © 2003 by the American College of Cardiology Foundation

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 pharmacologic 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

From 1994 to 2001, a total of 1,791 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 h from symptom onset, or between 6 and 24 h 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 (10,000 IU intravenously) before the procedure. Because the benefits of IIb/IIIa inhibitors has only been proved recently (16), most of our trials have been conducted without IIb/IIIa inhibitors, with <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 three-month warfarin therapy before 1996, and additional one-month antiplatelet therapy with ticlopidine 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 h, between 2 and 4 h, between 4 and 6 h, and >6 h). According to the time from

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Abbreviations and Acronyms

LDH_{Q48}	= enzymatic infarct size from serial measurements of lactate dehydrogenase
MBG	= myocardial blush grade
STEMI	= ST-segment elevation myocardial infarction
TIMI	= Thrombolysis In Myocardial Infarction

hospitalization to first balloon inflation (door-to-balloon time), patients were divided into four groups (≤30 min, between 31 and 60 min, between 61 to 90 min, and >90 min).

The presence of one or more Thrombolysis In Myocardial infarction (TIMI) criteria (previous myocardial infarction, anterior infarction, systolic blood pressure <100 mm Hg, 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).

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 h 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.

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 intra-aortic balloon pump in high-risk patients after primary angioplasty (150 patients) (13)
4) Randomized comparison of high-dose (20,000 IU) vs. low-dose heparin (5,000 IU) in primary angioplasty (584 patients) (14)
5) Randomized comparison between thrombolysis and primary angioplasty in elderly (> 75 yrs) (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.

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.

Analysis of variance was used for continuous variables. The chi-square test or the Fisher exact test (in case the expected value of the variable was <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 ± 189 min and 55 ± 36 min. Demographic, clinical, and angiographic characteristics according to symptom-onset-to-balloon time and door-to-balloon time are reported in Tables 2 and 3, respectively. All categorical variables were analyzed using the chi-square test, except for previous angioplasty and previous bypass surgery (Fisher 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 to 3.

A total of 103 patients (5.8%) had died at one-year follow-up. No difference in mortality was observed among patients treated in the first (1994 to 1997) and last four years (1998 to 2001) of the study (5.9% vs. 4.2%, respectively; p = NS). No difference in mortality was observed between patients who were transferred (n = 692) or not transferred (n = 1,099) from other hospitals (6.2% vs. 5.5%, respectively, p = 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).

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 patients and non–low-risk patients. A total of 545 low-risk patients (30.4%) and 1,246 (69.6%) non–low-risk patients were identified (with a one-year mortality of 1.1% vs. 7.8%, respectively; p < 0.0001). As depicted in Fig. 1,

Table 2. Demographic, Clinical, and Angiographic Characteristics According to Symptom-Onset-to-Balloon Time

	≤2 h	2–4 h	4–6 h	>6 h	p Value
Number of patients	226	1,065	427	73	
Age (yrs)	59 ± 11	60 ± 11	61 ± 12	62 ± 13	0.01
Male gender (%)	79.2	81.9	76.3	58.9	< 0.001
Diabetes (%)	8	7.8	9.4	17.8	NS
Previous MI (%)	11.1	11.5	12.6	4.1	NS
Anterior MI or LBBB (%)	51.8	51.5	48	61.6	NS
Killip class >1 (%)	13.7	11.9	10.5	11.8	NS
Transferred patients (%)	25.7	41	40	35.6	< 0.0001
Multivessel disease (%)	44.7	55.1	56.4	46.6	NS
Pre-TIMI 0–1 flow (%)	74.8	72.4	76.3	75.3	NS
Post-TIMI 3 flow (%)	93.4	91.3	86.9	90.4	0.012
Procedural success (%)	92.4	89.8	85.9	89.6	0.01
MBG 2–3 (%)*	80	75.8	70.8	76.8	0.033
Stent (%)	55.3	47.9	50.3	52.1	NS
LDH_{Q48} (U/l)†	1,632 ± 1,712	1,858 ± 1,552	1,834 ± 1,510	1,815 ± 1,557	NS

*Data available in 1,771 patients; †data available in 1,069 patients.
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.

mortality increased linearly according to symptom-onset-to-balloon time only in patients with non-low-risk characteristics (p = 0.006). As shown by Kaplan-Meier survival curves (Fig. 3), the difference in mortality among the four groups was already observed at 30 days, and persisted until one-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).

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 to 1 flow (1,321 patients [73.8%]) and TIMI 2 to 3 flow (470 patients [26.2%]). A linear relationship between symptom-onset-to-balloon time and one-year mortality was observed only in patients with preprocedural TIMI 0 to 1 flow, but not in patients with preprocedural TIMI 2 to 3 flow (Fig. 1). The relationship between door-to-balloon time and mortality was not affected by preprocedural TIMI flow (Fig. 2).

Multivariate predictors of one-year mortality. As shown in Table 4, a symptom-onset-to-balloon time >4 h (p < 0.05) was an independent predictor of one-year mortality, together with Killip >1, age ≥70 years, postprocedural TIMI 0 to 2 flow, anterior MI, and multivessel disease.

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

Table 3. Demographic, Clinical, and Angiographic Characteristics According to Door-to-Balloon Time

	≤30 min	31–60 min	61–90 min	>90 min	p Value
Number of patients	409	768	416	198	
Age (yrs)	59 ± 11	60 ± 11	61 ± 11	62 ± 13	0.01
Male gender (%)	81.4	79.6	79.6	73.2	0.047
Diabetes (%)	7.1	8.5	7.9	13.7	NS
Previous MI (%)	10.3	10.8	13.2	12.1	NS
Anterior MI or LBBB (%)	68.7	49.5	42.3	41.9	< 0.001
Killip class > 1 (%)	15.4	11.7	8.4	12.1	0.021
Transferred patients (%)	70.4	37.1	22.1	13.6	< 0.0001
Multivessel disease (%)	50.4	53.8	56.3	55.6	NS
Pre-TIMI 0–1 flow (%)	72.9	74.3	74	72.7	NS
Post-TIMI 3 flow (%)	90.2	91.7	89.9	87.4	NS
Procedural success (%)	89.2	90.2	88.8	86.5	NS
MBG 2–3 (%)*	73.9	76.8	75.8	69.9	NS
Stent (%)	50.6	49.6	49.5	49.5	NS
LDH_{Q48} (U/l)†	2,082 ± 1,836	1,821 ± 1,576	1,696 ± 1,382	1,606 ± 1,382	0.018

*Data available in 1,771 patients; †data available in 1,069 patients.
Abbreviations as in Table 1.

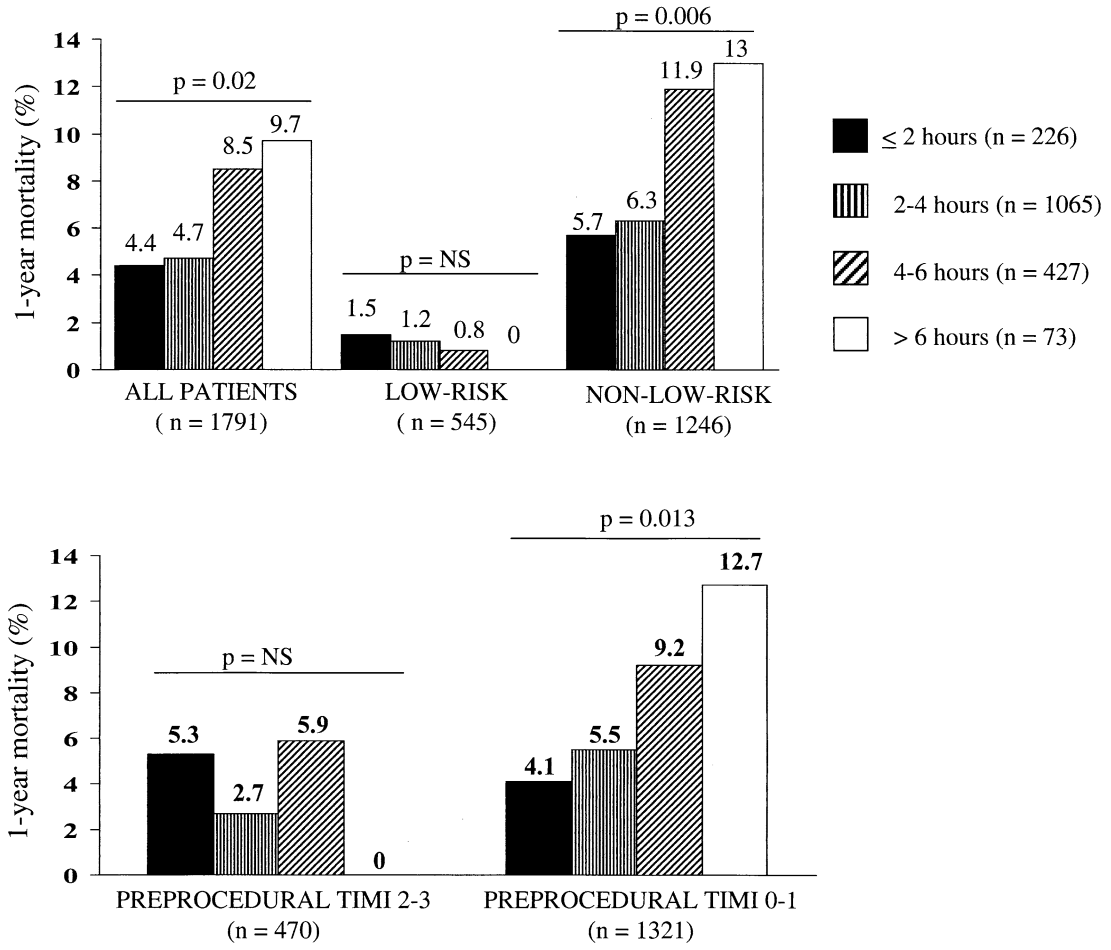

Figure 1. Bar graphs show the relationship between symptom-onset-to-balloon time and one-year mortality, in all patients, in low- and non–low-risk patients **(upper graph)**, and according to preprocedural Thrombolysis In Myocardial Infarction (TIMI) flow **(lower graph)**.

time, affects one-year mortality, particularly in high-risk patients and in the absence of preprocedural TIMI 2 to 3 flow. In this study, a symptom-onset-to-balloon time >4 h has been shown to be an independent predictor of one-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 h from symptom onset, whereas a relatively stable mortality rate was observed between 2 to 12 h. These data were confirmed by Cannon et al. (11) who, in a cohort of 27,080 patients undergoing primary angioplasty, found only door-to-balloon time, but not symptom-onset-to-balloon time, to be associated with mortality.

Consistent 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.

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

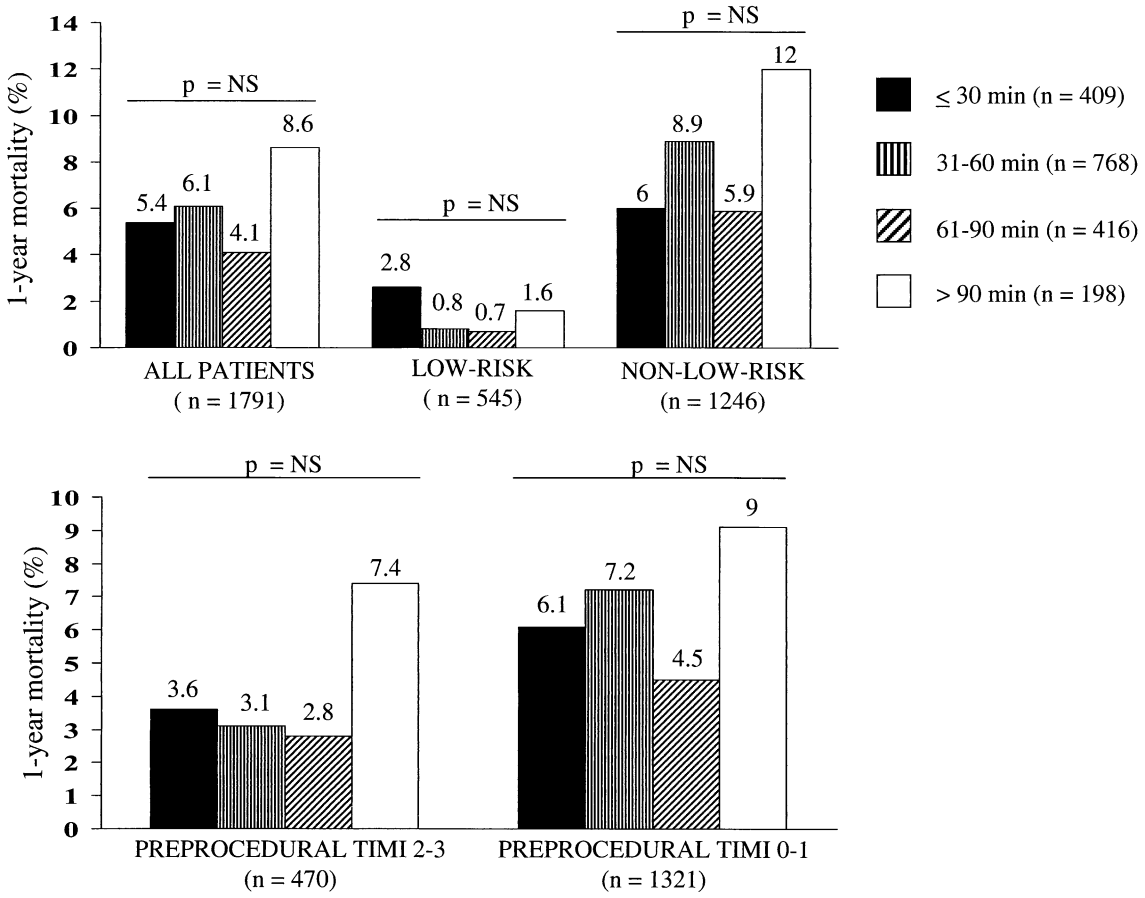

Figure 2. Bar graphs show the relationship between door-to-balloon time and one-year mortality, in all patients, in low- and non–low-risk patients **(upper graph)**, and according to preprocedural Thrombolysis In Myocardial Infarction (TIMI) flow **(lower graph)**.

mortality in patients with preprocedural TIMI flow 0 to 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 h was, together with Killip class (20), postprocedural TIMI flow (21), age (22,23), multivessel disease (24), and anterior infarction, (24) an independent predictor of one-year mortality.

Consistent with our data, Antoniucci et al. (25) found, in a population of 1,332 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 reperfusion, even when optimal mechanical reperfusion is applied. Supporting the prognostic role of early restoration of antegrade flow in STEMI, Stone et al. (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 h) was associated with a lower rate of postprocedural TIMI 3 flow and MBG 2 to 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 a higher incidence of anterior infarction, Killip class >1, and larger enzymatic infarct size in patients with a shorter door-to-balloon time (<30 min). 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).

Study limitations. This is an observational study of patients enrolled in randomized trials at our Institution, thus,

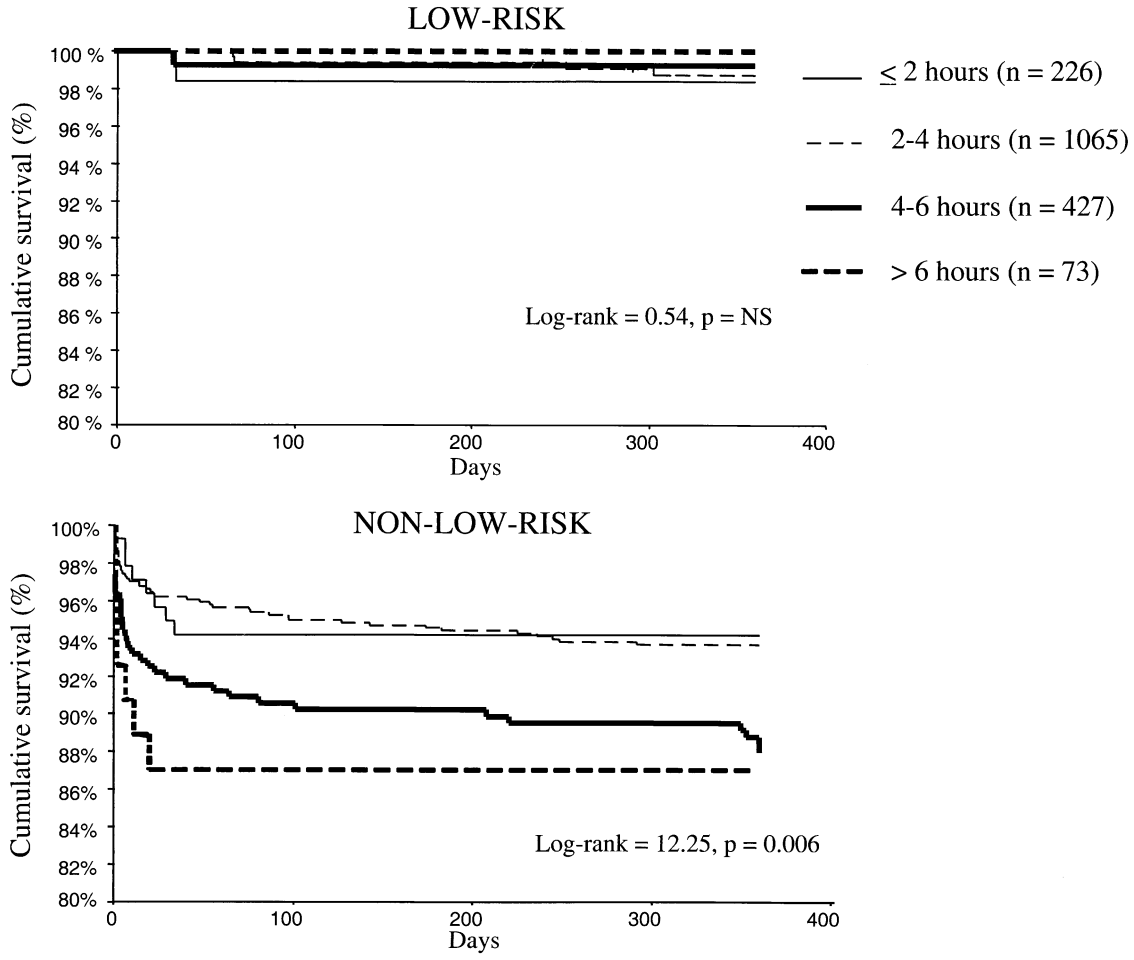

Figure 3. Kaplan-Meier survival curves according to symptom-onset-to-balloon time in both low-risk **(upper graph)** and non–low-risk patients **(lower graph)**.

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 <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

Table 4. Predictors of One-Year Mortality at Multivariate Analysis

	Odds Ratio (95% CI)	p Value
Killip class (>1)	5.27 (3.4–8.1)	< 0.0001
Age (≥70 yrs)	2.98 (1.9–4.5)	< 0.0001
TIMI flow 0–2 post	2.96 (1.84–4.71)	< 0.0001
Anterior infarction	2.13 (1.34–3.37)	0.001
Multivessel disease	2.34 (1.42–3.8)	0.001
Symptom-onset-to-balloon (>4 h)	1.55 (1.01–2.4)	0.046
Procedural success	1.57 (0.72–3.42)	NS
Preprocedural TIMI 0–1 flow	1.32 (0.77–2.26)	NS
Previous infarction	0.9 (0.51–1.58)	NS
Diabetes	0.97 (0.52–1.8)	NS

CI = confidence interval; TIMI = Thrombolysis In Myocardial Infarction.

absence of preprocedural anterograde flow. Furthermore, a symptom-onset-to-balloon time >4 h was identified as an independent predictor of one-year mortality.

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