Door-to-Balloon Time With Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction Impacts Late Cardiac Mortality in High-Risk Patients and Patients Presenting Early After the Onset of Symptoms

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Brodie, B. R., Hansen, C. J., Stuckey, T. D., Richter, S. J., VerSteeg , D. S., Gupta , N., Downey, W. E., Pulsipher, M. (2006). Door-to-Balloon Time with Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction Impacts Late Cardiac Mortality in High-Risk Patients and Patients Presenting Early After the Onset of Symptoms. *Journal of the American College of Cardiology*, 47(2): 289-295.

Made available courtesy of Elsevier: http://dx.doi.org/10.1016/j.jacc.2005.08.065

Abstract:

OBJECTIVES The purpose of this study was to evaluate the impact of door-to-balloon time with primary percutaneous coronary intervention (PCI) on late cardiac mortality.

BACKGROUND The impact of door-to-balloon time on outcomes is controversial, and the impact on late mortality has not been studied.

METHODS Consecutive patients (n _ 2,322) treated with primary PCI from 1984 to 2003 were prospectively identified and followed up for a median of 83 months.

RESULTS Prolonged door-to-balloon times (0 to 1.4 h vs. 1.5 to 1.9 h vs. 2.0 to 2.9 h vs. _3.0 h) were associated with higher in-hospital mortality (4.9% vs. 6.1% vs. 8.0% vs. 12.2%, p _ 0.0001) and late mortality (12.6% vs. 16.4% vs. 20.4% vs. 27.1% at 7 years, p _ 0.0001) and were an independent predictor of late mortality by Cox regression (p _ 0.0004). Prolonged door-to-balloon times (_2 h vs. _2 h) were associated with higher late mortality in high-risk patients (32.5% vs. 21.5%; hazard ratio [HR], 1.53; 95% confidence interval [CI], 1.22 to 1.90; p _ 0.0002) but not in low-risk patients (10.8% vs. 9.2%; HR, 1.13; 95% CI, 0.78 to 1.64; p _ 0.53) and in patients presenting early (_3 h) (24.7% vs. 15.0%; HR, 1.54; 95% CI, 1.24 to 1.90; p _ 0.0001) but not late (_3 h) (21.1% vs. 18.5%; HR, 0.95; 95% CI, 0.62 to 1.45; p _ 0.80).

CONCLUSIONS Delays in door-to-balloon time impact late survival in high-risk but not low risk patients and in patients presenting early but not late after the onset of symptoms. These findings have implications for the triage of patients for primary PCI. (J Am Coll Cardiol 2006;47: 289–95)

Keywords: primary percutaneous coronary intervention (PCI) | door-to-balloon time | late cardiac mortality

Article:

Primary percutaneous coronary intervention (PCI) has been shown to achieve superior outcomes compared with thrombolytic therapy in the treatment of ST-segment elevation acute myocardial infarction (STEMI) (1), and recent guide- lines have recommended primary PCI as the preferred reperfusion strategy when it can be performed by experienced operators in a timely fashion (2). However, primary PCI is often not immediately available, and frequently there are long treatment delays that could potentially impact outcomes. The impact of treatment delays with primary PCI on outcomes has been controversial. Some studies have shown that delays in door-to-balloon time adversely affect outcomes (3,4), whereas other studies have found little correlation between door-to-balloon time and outcomes (5–7). None of these studies have evaluated the effect of door-to-balloon time on late cardiac mortality.

We postulated that the differences in the relationship between door-to-balloon time and mortality may be related to differences in risk profile among studies. Consequently, we examined the relationship between door-to-balloon time and late cardiac mortality in our large database with primary PCI with special attention to subgroup analyses in high- and low-risk patients.

METHODS

Study population. Our study population was taken from 2,322 consecutive patients with STEMI treated with primary PCI without previous thrombolytic therapy at our institution from 1984 through 2003. Patients with chest pain of <12 h duration or >12 h for persistent pain or hemodynamic compromise and with electrocardiographic ST-segment elevation >1 mm in >2 contiguous leads or left bundle branch block and without severe co-morbid disease were selected for intervention. After excluding 22 patients with missing door-to-balloon time data, our analyses were performed on a study cohort of 2,300 patients. **Treatment protocol.** Patients were treated with heparin and aspirin in the emergency department and transferred promptly to the catheterization laboratory for mechanical reperfusion. Stents were first used in 1995 and overall were used in 30% of patients. Platelet glycoprotein IIb/IIIa inhibitors were first used in 1996 and overall were used in 29% of patients. Ticlopidine or clopidogrel were used in stent patients and continued for at least one month. Beta- adrenergic blocking agents and nitrates were used at the operator's discretion.

Abbreviations and Acronyms

CADILLAC	= Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications
GUSTO	= Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
NRMI	= National Registry of Myocardial Infarction
PAMI	= Primary Angioplasty in Myocardial Infarction
PCI	= percutaneous coronary intervention
STEMI	= ST-segment elevation myocardial infarction
TIMI	= Thrombolysis In Myocardial Infarction

Clinical and angiographic follow-up. Clinical follow-up was obtained by hospital and office chart review and telephone contact in 97% of hospital survivors at a median follow-up time of 83 months. Follow-up catheterization and angiography were performed routinely during the first three years of the study and during participation in several clinical trials. Otherwise, follow-up catheterization was performed for recurrent ischemic symptoms or after abnormal functional test results. Follow-up catheterization procedures with angiography adequate for measurement of left ventricular ejection fraction were obtained in 40% of hospital survivors at a median follow-up time of 6.4 months. **Definitions and data analysis.** Door-to-balloon time was the time from arrival at the presenting hospital until balloon inflation. Time to presentation was the time from symptom onset until arrival at the presenting hospital. Patients were classified as diabetic if they had been treated with insulin or oral hypoglycemic medication. Coronary flow in the infarct artery was assessed visually by the operator and classified according to the Thrombolysis In Myocardial Infarction (TIMI) grading system on a scale of 0 to 3 (8). Reinfarction was defined as recurrent chest pain associated with any secondary increase in the creatinine kinase level and the MB fraction higher than the nadir, with or without diagnostic electrocardiographic changes. Urgent target vessel revascularization was defined as the need for repeat PCI of the target vessel or bypass surgery for recurrent ischemia or hemodynamic compromise. High-risk patients were defined as patients with Killip class 3 to 4, age >70 years, or anterior infarction. Low-risk patients were all others.

Left ventricular ejection fractions were calculated from tracing the contours of right anterior oblique cine angiograms using the area-length method with correction for the right anterior oblique projection (9).

Statistical analysis. Statistical comparisons of categorical variables were performed using the chi-square test. Continuous variables are presented as mean values (±standard deviation), and

statistical comparisons were performed using analysis of variance. Predictors of in-hospital mortality were evaluated with multiple logistical regression. Differences in late cardiac survival across categories of treatment times were examined with Kaplan-Meier survival curves and their associated Wilcoxon statistics. Predictors of late cardiac mortality were performed using Cox proportional hazards regression models. Variables entered into the models were age, gender, diabetes, prior infarction, prior bypass surgery, anterior infarction, Killip class, hypertension, smoking status, and door-to-balloon time. All analyses were performed with SAS (SAS Institute Inc., Cary, North Carolina) and SPSS (SPSS Inc., Chicago, Illinois) software.

	Door-to-Balloon Time (h)				
	0–1.4 (n = 384)	1.5–1.9 (n = 493)	2.0–2.9 (n = 750)	≥3.0 (n = 673)	p Value
Clinical variables					
Age (yrs)	59.0 ± 11.2	58.4 ± 12.4	60.5 ± 12.2	60.4 ± 12.8	0.01
Age >70 yrs (%)	20.1	20.9	24.5	26.3	0.05
Women (%)	25.8	29.8	29.6	34.2	0.03
Diabetes mellitus (%)	11.5	12.8	14.5	18.3	0.009
Previous myocardial infarction (%)	19.5	16.0	18.8	13.5	0.02
Previous bypass surgery (%)	3.9	3.4	5.5	5.6	0.22
Anterior infarction (%)	31.3	40.0	37.6	41.8	0.007
Hypertension (%)	45.4	47.4	47.9	49.2	0.69
Current smoker (%)	49.3	48.2	46.9	45.4	0.63
Killip class 3–4 (%)	12.8	14.4	14.3	23.9	<0.0001
Angiographic variables					
TIMI flow grade 2–3 before PCI (%)	19.8	19.6	21.7	21.4	0.75
TIMI flow grade 3 after PCI (%)	94.3	93.1	94.4	90.9	0.053
Three-vessel coronary artery disease (%)	20.8	22.1	23.5	25.4	0.34
Acute ejection fraction (%)	52.6 ± 12.3	51.4 ± 12.3	50.7 ± 12.9	48.8 ± 13.1	<0.0001

PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

Table 2. Baseline Clinical and Angiographic Variables in High- and Low-Risk Subgroups

	Low Risk (n = 993)	High Risk* (n = 1,307)	p Value
Clinical variables			
Age (yrs)	54.6 ± 8.8	63.7 ± 13.1	<0.0001
Age >70 yrs (%)	0	41.4	<0.0001
Women (%)	23.6	35.5	<0.0001
Diabetes mellitus (%)	12.1	16.8	0.002
Previous myocardial infarction (%)	15.5	17.8	0.15
Previous bypass surgery (%)	4.6	5.0	0.71
Anterior infarction (%)	0	67.3	<0.0001
Hypertension (%)	45.7	49.3	0.09
Current smoker (%)	57.0	39.7	<0.0001
Killip class 3–4 (%)	0	29.7	<0.0001
Angiographic variables			
TIMI flow grade 2–3 before PCI (%)	21.9	20.1	0.30
TIMI flow grade 3 after PCI (%)	95.4	91.4	0.0002
Three-vessel coronary artery disease (%)	19.9	25.9	0.0009
Acute ejection fraction (%)	55.2 ± 10.5	46.9 ± 13.3	<0.0001

*High-risk Killip class 3–4, age >70 years, or anterior infarction.
Abbreviations as in Table 2.

RESULTS

Baseline variables by door-to-balloon time. The median (25th, 75th percentiles) door-to-balloon time was 2.3 h (1.6, 3.2) in all patients, 1.9 h (1.5, 2.5) in patients presenting at the interventional hospital, and 2.9 h (2.3, 3.9) in 871 patients transferred from non-interventional hospitals. Patients with longer door-to-balloon times were older, more often were women, and had a higher frequency of diabetes, anterior infarction, and Killip class 3 to 4, but had a lower frequency of previous infarction (Table 1). Acute ejection fraction was lower in patients with longer door-to-balloon times. A comparison of baseline variables in high- risk versus low-risk patients as previously defined is shown in Table 2.

In-hospital outcomes by door-to-balloon time. In-hospital mortality was significantly higher with longer door-to-balloon times (Table 3). There were no significant correlations between door-to-balloon time and reinfarction or stroke. Peak values of creatinine kinase and the MB fraction were significantly higher in patients with longer door-to-balloon times (Table 3).

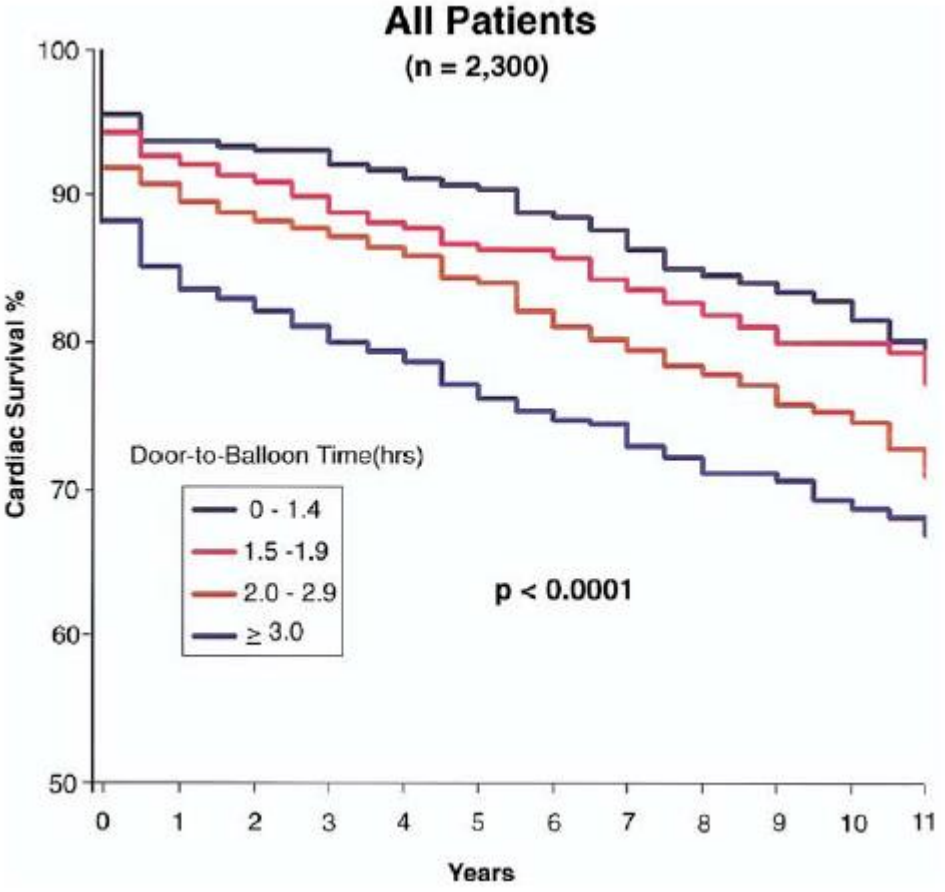
After adjusting for differences in baseline variables, door- to-balloon time was a significant independent predictor of in-hospital mortality when expressed as a continuous variable (odds ratio [OR] = 1.06; 95% confidence interval [CI], 1.01 to 1.11; p=0.02) (OR expressed per 0.1 h) and as a categorical variable (compared with 0 to 1.4 h: 1.5 to 1.9 h, OR = 1.34, 95% CI, 0.67 to 2.67; p = 0.41; 2.0 to 2.9 h: OR = 1.99; 95% CI, 1.07 to 3.69; p = 0.03; >3.0 h: OR = 2.38; 95% CI, 1.30 to 4.37; p = 0.005).

Late cardiac mortality by door-to-balloon time. Prolonged door-to-balloon times (0 to 1.4 h vs. 1.5 to 1.9 h vs. 2.0 to 2.9 h vs. >3.0 h) were associated with higher late mortality (12.6% vs. 16.4% vs. 20.4% vs. 27.1% at 7 years, p < 0.0001) with survival curves that diverged over time (Fig. 1). After adjusting for differences in baseline variables with Cox regression, door-to-balloon time was a significant independent predictor of late cardiac mortality (Table 4). Door-to-balloon time expressed as a continuous variable was also a significant independent predictor of late cardiac mortality (hazard ration [HR] = 1.04; 95% CI, 1.01 to 1.07; p = 0.003) (HR expressed per 0.1 h).

Late cardiac mortality by door-to-balloon patient subgroups. The effects of door-to-balloon times on late cardiac mortality in patient subgroups (with HRs adjusting for differences in baseline variables) are shown in Table 5. Delays in door-to-balloon time (>2 vs. <2 h) had a greater impact on late mortality in women versus men, anterior versus non-anterior infarction, Killip class 3 to 4 versus Killip class 1 to 2, early (<3 h) versus late (>3 h) presentation, and high- versus low-risk patients. High-risk patients were defined as patients with Killip class 3 to 4, age >70 years, or anterior infarction. There were trends or significant interactions between door-to-balloon time and each of the following variables: gender (p = 0.06), infarct location (p = 0.13), Killip class (p = 0.03), time to presentation (p = 0.16), and high- versus low-risk patients (p = 0.02).

Table 3. In-Hospital Outcomes by Door-to-Balloon Time

	Door-to-Balloon Time (h)				
	0–1.4 (n = 384)	1.5–1.9 (n = 493)	2.0–2.9 (n = 750)	≥3.0 (n = 673)	p Value
In-hospital outcomes					
Mortality (%)	4.9	6.1	8.0	12.2	<0.0001
Reinfarction (%)	2.9	2.4	2.9	2.2	0.84
Stroke (%)	0.8	1.0	1.1	1.9	0.31
Cardiac enzymes and ejection fraction					
Peak creatinine kinase (U/l)	2,067 ± 1,882	2,436 ± 2,605	2,486 ± 2,517	2,569 ± 2,878	0.02
Peak MB fraction (ng/ml)	170 ± 170	187 ± 164	201 ± 173	213 ± 202	0.002
Follow-up ejection fraction (%)	55.3 ± 12.8	55.5 ± 12.3	53.0 ± 13.2	53.8 ± 14.9	0.13



Kaplan-Meier unadjusted estimates of late cardiac survival show that prolonged door-to-balloon times (>2 vs. <2 h) were associated with higher late mortality in high-risk patients (32.5% vs. 21.5% at seven years; HR, 1.53; 95% CI, 1.22 to 1.90; p = 0.0002) but not in low-risk patients (10.8% vs. 9.2%; HR, 1.13; 95% CI, 0.78 to 1.64; p = 0.53) (Table 5, Fig. 2). Survival curves also showed that prolonged door-to-balloon times (>2 vs. <2 h) were associated with higher late mortality in patients presenting early after the onset of symptoms (<3 h) (24.7% vs. 15.0% at seven years; HR, 1.54; 95% CI, 1.24 to 1.90; p = 0.0001) but not late after the onset of symptoms (>3 h) (21.1% vs. 18.5%; HR, 0.95; 95% CI, 0.62 to 1.45; p = 0.80) (Table 5, Fig. 3).

DISCUSSION

The major findings of this study are that delays in door-to- balloon time with primary PCI for STEMI have a major impact on late cardiac mortality, and this impact is seen primarily in high-risk patients and patients who present early after the onset of symptoms.

Previous studies. Previous studies have shown conflicting results regarding the importance of door-to-balloon time on mortality (3–7). Door-to-balloon time was significantly correlated with in-hospital mortality in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO)-IIb trial (3) and the National Registry of

Myocardial Infarction (NRMI) (4). The NRMI Investigators found that door-to-balloon times >2 h were associated with significantly increased mortality.

Conversely, data from the Stent Primary Angioplasty in Myocardial Infarction (PAMI) trial (5), the Zwolle Group (6), and the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial (7) found no significant correlation between door-to- balloon time and mortality (although the latter two trials did show a significant correlation between overall time to reperfusion and mortality). There may be several reasons for these differences. As documented in our study, delays in door-to-balloon time impact mortality primarily in high- risk patients. Study cohorts with large numbers of low-risk patients may not show a significant correlation between door-to-balloon time and mortality because of dilution of the study cohort with low-risk patients. Secondly, sicker patients may require additional procedures and additional evaluation (such as cardiopulmonary resuscitation, temporary pacemakers, intra-aortic balloon pumps, computed tomography scans, etc.), which create additional time delays before reperfusion. This potential bias for longer door-to- balloon times in sicker patients would be more pronounced in "real-world registries," such as NRMI and our database, than in randomized trials. This is exemplified in our study, in which patients with the longest door-to-balloon times were older and had a much higher frequency of anterior infarction, diabetes, shock, and congestive heart failure. Thirdly, in large multicenter registries, door-to balloon time may be a surrogate for quality of care. Finally, studies that look at short-term mortality would not appreciate the effect of treatment delays on long-term mortality.

Impact of treatment delays on mortality in subgroups. Our study found that delays in door-to-balloon time had a major impact on late cardiac mortality in high-risk patients but had little effect in low-risk patients. Previous studies had not evaluated the relationship between door-to-balloon time and mortality in high- and low-risk patients, but several studies had found that total time to reperfusion (time from symptom onset to balloon inflation) correlated with mortality in high-risk patients but not in low-risk patients (6,7,10,11).

We found that delays in door-to-balloon time had a greater impact on late mortality in patients with Killip class 3 to 4 versus 1 to 2, in anterior versus non-anterior infarction, in women versus men, and in diabetic versus non-diabetic patients. We also found that delays in door- to-balloon time were associated with increased late mortality in patients presenting early (<3 h) but had little effect on mortality in patients presenting late after the onset of symptoms (>3 h). The CADILLAC investigators reported similar findings and found that delays in door-to-balloon time were associated with increased one-year mortality in patients presenting early (<2 h) but not in patients presenting late (>2 h) (7).

Table 4. Multivariable Predictors of Late Cardiac Mortality by Cox Regression

	Hazard Ratio (95% Confidence Interval)	p Value
Killip class 3–4	3.03 (2.48–3.69)	<0.0001
Previous bypass surgery	2.15 (1.54–3.01)	<0.0001
Age >70 yrs	1.93 (1.57–2.37)	<0.0001
Diabetes	1.75 (1.41–2.18)	<0.0001
Anterior infarction	1.49 (1.24–1.78)	<0.0001
Door-to-balloon time (h)		
1.5–1.9	1.17 (0.84–1.62)	0.36
2.0–2.9	1.46 (1.09–1.96)	0.01
≥3.0	1.71 (1.27–2.29)	0.0004
Previous infarction	1.23 (0.99–1.54)	0.06
Female	1.19 (0.98–1.45)	0.08

Paradigm for the mechanism of benefit of reperfusion therapy. Our data suggesting that delays in door-to- balloon time impact mortality in patients presenting early but not late after the onset of symptoms are consistent with an expanded paradigm for the mechanism of mortality benefit with reperfusion therapy (12). In patients who undergo reperfusion therapy early, the mortality benefit may be related primarily to myocardial salvage, and this is very time dependent. In patients who undergo reperfusion later, the mortality benefit may be related to the effect of an open infarct artery in preventing left ventricular remodeling and in promoting electrical stability, and this is not very time dependent. Previous and recent studies have documented that to achieve significant myocardial salvage, reperfusion usually must be established at <2 to 3 h (13,14).

Table 5. Late Cardiac Mortality by Door-to-Balloon Time in Patient Subsets

	Late Cardiac Mortality*				
	Door-to-Balloon Time <2 h (%)	Door-to-Balloon Time ≥2 h (%)	Hazard Ratio	95% Confidence Interval	p Value
Age ≥ 70 yrs (n = 541)	28.4	41.7	1.44	1.05–1.98	0.02
Age <70 yrs (n = 1,759)	12.4	17.9	1.37	1.08–1.73	0.01
Female (n = 698)	18.0	29.8	1.79	1.29–2.49	0.0005
Male (n = 1,602)	14.6	20.9	1.23	0.97–1.56	0.09
Diabetes (n = 339)	24.0	40.7	1.72	1.12–2.62	0.01
No diabetes (n = 1,961)	14.3	20.5	1.33	1.08–1.65	0.008
Anterior infarction (n = 880)	19.2	31.0	1.62	1.23–2.12	0.0005
Non-anterior infarction (n = 1,420)	13.4	19.1	1.18	0.91–1.54	0.22
Killip class 3–4 (n = 388)	35.9	58.3	1.78	1.25–2.53	0.001
Killip class 1–2 (n = 1,912)	12.4	15.7	1.22	0.97–1.54	0.09
Early presentation (≤3 h) (n = 1,767)	15.0	24.7	1.54	1.24–1.90	0.0001
Late presentation (>3 h) (n = 533)	18.5	21.1	0.95	0.62–1.45	0.80
High risk (n = 1,307)†	21.5	32.5	1.53	1.22–1.90	0.0002
Low risk (n = 993)	9.2	10.8	1.13	0.78–1.64	0.53

*Kaplan-Meier estimates at 7 years (median follow-up time). †Killip class 3–4, age >70 years, or anterior infarction.

Clinical implications. Our study has implications regarding the triage of patients with STEMI presenting at non-interventional hospitals. The results from recent randomized trials have found that outcomes are better when patients with STEMI who present at non-interventional hospitals are transferred to an interventional facility for primary PCI compared with being given fibrinolytic therapy at the local hospital (15–17). The additional treatment delays of primary PCI compared with fibrinolytic therapy in these trials ranged from 55 to 104 min. The optimum reperfusion strategy when delays to primary PCI are longer than this has not been evaluated.

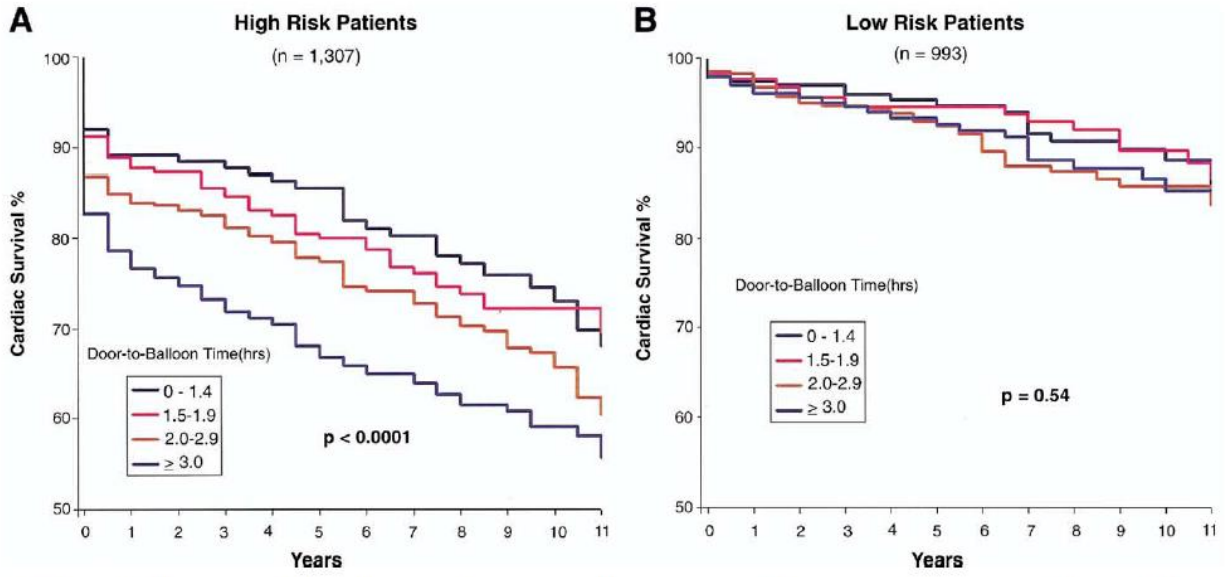


Figure 2. Kaplan-Meier estimates of late cardiac survival in patients treated with primary percutaneous coronary intervention for ST-segment elevation myocardial infarction according to door-to-balloon times. **(A)** High-risk patients (Killip class 3 to 4, age >70 years, or anterior infarction). **(B)** Low-risk patients.

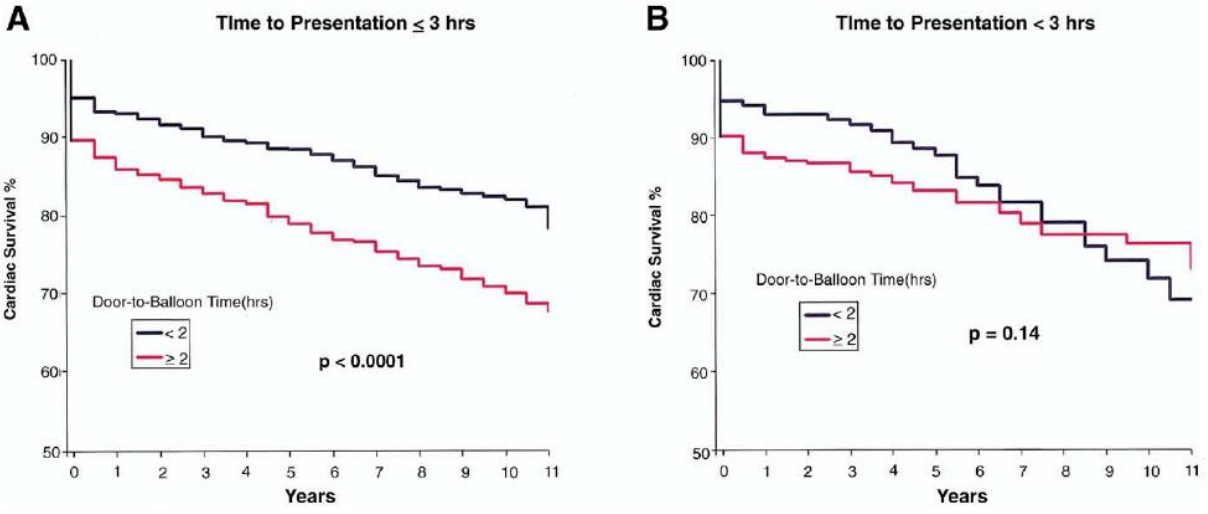


Figure 3. Kaplan-Meier estimates of late cardiac survival after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction according to door-to-balloon times. **(A)** Patients presenting early after the onset of symptoms (≤3 h). **(B)** Patients presenting late after the onset of symptoms (>3 h).

Our data indicate that in patients who present early after the onset of symptoms, delays in door-to-balloon times with primary PCI seem to have a significant impact on late mortality. If these

delays are long enough, primary PCI may lose its mortality advantage over fibrinolytic therapy. (The advantage of primary PCI over fibrinolytic therapy in reducing reinfarction with fewer complications of intracranial hemorrhage and stroke may be less time dependent.) The optimum reperfusion strategy in these patients may include alternative reperfusion strategies such as local fibrinolytic therapy or combined pharmacologic therapy and PCI (facilitated PCI). In contrast, in patients who present later, treatment delays have much less effect on mortality, and transfer for primary PCI may be the best reperfusion option, even with longer delays. The results of large ongoing randomized trials of facilitated PCI in patients with STEMI presenting to non-interventional hospitals should help define the optimum reperfusion strategies in subgroups of patients who have long treatment delays to primary PCI.

Door-to-balloon times in this study are quite long, especially for patients transferred from community hospitals to our institution. Similarly long door-to-balloon times have been recently reported from the NRMI (18). Although door-to-balloon times have improved some at our institution in recent years, the prolonged delays in this study and the NRMI emphasize the need in this country to develop better protocols for the triage and transfer of patients from community hospitals to interventional facilities.

Study limitations. This is a single-center observational study, and there may be differences in baseline variables across categories of door-to-balloon times that may not be accounted for in the multivariable analyses and that may affect the relationship between door-to-balloon time and mortality. Our study spans two decades of experience. Although this allows for long-term follow-up, changes in adjunctive therapies with primary PCI could impact the relationship between door-to-balloon time and outcomes. However, we examined the relationship between door-to- balloon time and late mortality in the period before (1984 to 1995) and after (1996 to 2003) the introduction of stents and glycoprotein IIb/IIIa platelet inhibitors and the relationships were similar. Finally, reperfusion may occur before balloon inflation, either spontaneously or as the result of the administration of heparin and aspirin, and in these patients the time to reperfusion is unknown.

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