View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Elsevier - Publisher Connector

Journal of the American College of Cardiology Vol. 56, No. 5, 2010
© 2010 by the American College of Cardiology Foundation
Published by Elsevier Inc.
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.04.020

ACUTE MYOCARDIAL INFARCTION

When Is Door-to-Balloon Time Critical?

Analysis From the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) and CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) Trials

Bruce R. Brodie, MD,* Bernard J. Gersh, MB, ChB, DPhil,† Thomas Stuckey, MD,* Bernhard Witzenbichler, MD,‡ Giulio Guagliumi, MD,§ Jan Z. Peruga, MD,‖ Dariusz Dudek, MD,¶ Cindy L. Grines, MD,# David Cox, MD,** Helen Parise, ScD,†† Abhiram Prasad, MD,† Alexandra J. Lansky, MD,†† Roxana Mehran, MD,†† Gregg W. Stone, MD††

Greensboro, North Carolina; Rochester, Minnesota; Berlin, Germany; Bergamo, Italy; Lodz and Krakow, Poland; Royal Oak, Michigan; Allentown, Pennsylvania; and New York, New York

Objectives Our objective was to evaluate the impact of door-to-balloon time (DBT) on mortality depending on clinical risk and time to presentation.

Background DBT affects the mortality rate in ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention, but the impact may vary across subgroups.

Methods The CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) and HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trials evaluated stent and antithrombotic therapy in patients undergoing primary percutaneous coronary intervention. We studied the impact of DBT on mortality in 4,548 patients based on time to presentation and clinical risk.

Results The 1-year mortality rate was lower in patients with short versus long DBT (≤90 min vs. >90 min, 3.1% vs. 4.3%, p = 0.045). Short DBTs were associated with a lower mortality rate in patients with early presentation (≤90 min: 1.9% vs. 3.8%, p = 0.029) but not those with later presentation (>90 min: 4.0% vs. 4.6%, p = 0.47). Short DBTs showed similar trends for a lower mortality rate in high-risk (5.7% vs. 7.4%, p = 0.12) and low-risk (1.1% vs. 1.6%, p = 0.25) patients. Short DBTs had similar relative risk reductions in patients with early presentation in high-risk (3.7% vs. 7.0%, p = 0.08) and low-risk (0.8% vs. 1.5%, p = 0.32) patients, although the absolute benefit was greatest in high-risk patients.

Conclusions Short DBTs (≤90 min) are associated with a lower mortality rate in patients with early presentation but have less impact on the mortality rate in patients presenting later. The absolute mortality rate reduction with short DBT is greatest in high-risk patients presenting early. These data may be helpful in designing triage strategies for reperfusion therapy in patients presenting to non–percutaneous coronary intervention hospitals. (J Am Coll Cardiol 2010;56:407–13) © 2010 by the American College of Cardiology Foundation

Short door-to-balloon (DBT) times are associated with reduced mortality in patients with ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI), but the importance of DBT may differ across subgroups (1–3). Previous studies suggested that delays in DBT may affect the mortality rate

From the *LeBauer Cardiovascular Research Foundation, Greensboro, North Carolina; †Mayo Clinic, Rochester, Minnesota; ‡Charité Campus Benjamin Franklin, Berlin, Germany; §Ospedali Riuniti di Bergamo, Bergamo, Italy; ‖Silesian Center for Heart Disease, Lodz, Poland; ¶Jagiellonian University, Krakow, Poland; #William Beaumont Hospital, Royal Oak, Michigan; **Lehigh Valley Hospital, Allentown, Pennsylvania; and the ††Columbia University Medical Center and the Cardiovascular Research Foundation, New York, New York. This study was supported by the Cardiovascular Research Foundation, with grant support from Boston Scientific and the Medicines Company, Guidant Corporation, and Lilly Research Laboratories. Dr. Gersh has served on the advisory board of Abbott Vascular and Boston Scientific. Dr. Stuckey has served as a consultant to and been on the Speakers' Bureau and advisory board of Boston Scientific. Dr. Witzenbichler is a consultant for and on the Speakers' Bureau of The Medicines Company, Boston Scientific, and Abbott Vascular. Dr. Guagliumi has served as a consultant to Boston Scientific and Volcano and received research grants from Boston Scientific, Medtronic, LightLab, and Abbott Vascular. Dr. Cox has served on the advisory board of Abbott Vascular and Boston Scientific and the Speakers' Bureau of Abbott Vascular, Boston Scientific, and The Medicines Company. Dr. Lansky has received unrestricted research support from Abbott Vascular and The Medicines Company. Dr. Mehran has received grant support from Bristol-Myers Squibb/Sanofi and Bracco, and has served as a consultant to and received honoraria from Abiomed, Abbott, Accumetrics, Bracco, Cordis, Eli Lilly/Daichii Sankyo, Gileau, Guerbet, Regado, and Therox. Dr. Stone has served on the advisory board of Abbott Vascular and Boston Scientific.

Manuscript received November 4, 2009; revised manuscript received April 9, 2010, accepted April 13, 2010.

Abbreviations and Acronyms

DBT = door-to-balloon time
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction

most in patients presenting early after the onset of symptoms and in patients at high clinical risk, but the data are limited and conflicting (2,3). Improved understanding of how delays in DBT affect the mortality rate in subgroups may help in triaging STEMI patients presenting at non-PCI hospitals.

The purpose of this study was to evaluate the impact of delays in DBT on mortality in patients with early versus late presentation and in patients with high and low clinical risk from the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) and HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trials (4,5).

Methods

Study population. The CADILLAC trial evaluated abciximab and coronary stenting and the HORIZONS-AMI trial evaluated bivalirudin and drug-eluting stents in STEMI patients undergoing primary PCI (4,5). The current study population included all patients randomized in these trials who underwent primary PCI and had DBT data available (n = 4,548).

Definitions. DBT was the time from hospital arrival until balloon inflation. Time to presentation was the time from symptom onset until arrival at the first hospital. Clinical risk was assessed using a modified Thromobolysis In Myocardial Infarction (TIMI) risk score (6). Selected variables were assigned points weighted as follows: age 75 years and older (3 points), age 65 years and older (2 points), Killip class II to IV (2 points), anterior infarction (1 point), diabetes (1 point), weight <67 kg (1 point), and these were summed for each patient to give a modified TIMI risk score.

Statistical analyses. Baseline categorical variables were compared using chi-square testing, and continuous variables were compared using *t* tests. Mortality rates at 1 year were determined by Kaplan-Meier estimates, and comparisons between categories of DBT were performed with univariate and multivariate Cox regression analyses. In the multivariate Cox regression models, all clinical variables in Tables 1 and 2 were entered into the models.

Table 1 Baseline Variables by Door-to-Balloon Time

	Door-to-Balloon Time		
	≤90 min (n = 1,611)	>90 min (n = 2,937)	p Value
Clinical variables			
Age, yrs	60.1 (11.8)	60.3 (12.0)	0.62
Age ≥65 yrs	35.1%	35.8%	0.64
Age ≥75 yrs	12.5%	13.5%	0.35
Female	22.7%	26.1%	0.011
Diabetes	14.6%	17.0%	0.032
Prior infarction	10.1%	12.6%	0.012
Anterior infarction	40.1%	40.0%	0.92
Killip class II to IV	8.8%	10.1%	0.16
Weight, kg	81.6 (15.4)	82.6 (16.4)	0.058
Weight <67 kg	15.9%	15.3%	0.58
Time to presentation ≤90 min	41.1%	42.0%	0.55
TIMI risk score	1.7 (1.6)	1.8 (1.7)	0.19
Angiographic variables			
Infarct artery location			
Left anterior descending	40.1%	40.0%	0.98
Circumflex	16.2%	18.6%	0.042
Right coronary artery	46.9%	44.4%	0.10
Left main	0.3%	0.1%	0.23
3-vessel disease	17.5%	19.8%	0.061
Index LVEF, %	58.1 (12.7)	57.8 (12.8)	0.62
Index LVEF <40%	9.5%	9.7%	0.31
TIMI flow grade 2 to 3 pre-PCI	27.9%	37.7%	<0.0001

Values are mean (SD) or percent.
LVEF = left ventricular ejection fraction; PCI = percutaneous coronary infarction; TIMI = Thrombolysis In Myocardial Infarction.

Table 2 Baseline Variables by Time to Presentation

	Time to Presentation		
	≤90 min (n = 1,917)	>90 min (n = 2,700)	p Value
Clinical variables			
Age, yrs	58.4 (11.7)	61.6 (11.9)	<0.0001
Age ≥65 yrs	29.6%	40.2%	<0.0001
Age ≥75 yrs	10.1%	15.2%	<0.0001
Female	21.1%	27.2%	<0.0001
Diabetes	12.9%	18.3%	<0.0001
Prior infarction	12.8%	11.0%	0.064
Anterior infarction	41.6%	38.9%	0.07
Killip class II to IV	9.1%	10.0%	0.32
Weight, kg	83.4 (16.3)	81.5 (15.9)	<0.0001
Weight <67 kg	14.1%	16.6%	0.02
TIMI risk score	1.6 (1.6)	1.9 (1.7)	<0.0001
Angiographic variables			
Infarct artery location			
Left anterior descending	41.4%	39.1%	0.11
Circumflex	16.3%	18.8%	0.029
Right coronary artery	45.2%	45.2%	0.97
Left main	0.1%	0.2%	0.34
3-vessel disease	16.5%	21.2%	<0.0001
Index LVEF, %	58.2 (12.6)	57.9 (12.7)	0.46
Index LVEF <40%	8.5%	9.4%	0.44
TIMI flow grade 2 to 3 pre-PCI	35.2%	33.6%	0.25

Values are mean (SD) or percentage.
Abbreviations as in Table 1.

Results

Median time to presentation was 112 min (interquartile range 60 to 205 min) and median DBT, including both transferred and nontransferred patients, was 107 min (interquartile range 79 to 146 min).

Table 3 Cut-Point Analyses for DBT, Time to Presentation, and TIMI Risk Score

	1-Year Mortality (%)*		Hazard Ratio†	95% CI	p Value
DBT cut points	Short DBT	Long DBT			
60 min	3.0	4.0	0.75	0.45–1.22	0.25
90 min	3.1	4.3	0.72	0.52–0.99	0.045
120 min	3.7	4.1	0.87	0.65–1.16	0.35
Time to presentation cut points	DBT ≤90 min	DBT >90 min			
≤60 min (n = 1,122)	2.3	3.3	0.68	0.31–1.52	0.34
>60 min (n – 3,327)	3.4	4.6	0.73	0.51–1.05	0.09
≤90 min (n = 1,853)	1.9	3.8	0.49	0.26–0.93	0.029
>90 min (n = 2,596)	4.0	4.6	0.86	0.58–1.28	0.47
≤120 min (n = 2,472)	2.4	3.5	0.69	0.42–1.14	0.15
>120 min (n = 1,977)	4.0	5.2	0.76	0.49–1.19	0.24
Modified TIMI risk cut points	DBT ≤90 min	DBT >90 min			
TIMI risk score <2 (n = 2,402)	1.1	1.6	0.64	0.30–1.37	0.25
TIMI risk score ≥2 (n = 2,047)	5.7	7.4	0.75	0.51–1.02	0.12
TIMI risk score <3 (n = 3,067)	1.4	2.1	0.65	0.36–1.18	0.16
TIMI risk score ≥3 (n = 1,382)	7.2	9.0	0.78	0.52–1.14	0.20
TIMI risk score <4 (n = 3,738)	2.0	2.5	0.73	0.46–1.15	0.17
TIMI risk score ≥4 (n = 711)	9.7	13.1	0.75	0.47–1.19	0.22

*1-year mortalities are Kaplan-Meier estimates. †Hazard ratios are unadjusted and compare mortality with short versus long door-to-balloon times (DBTs).
CI = confidence interval; other abbreviations as in Table 1.

Baseline variables by DBT and time to presentation. The frequency of female sex, diabetes, and previous infarction was higher in patients with long versus short DBT (Table 1).

Patients with late versus early time to presentation were older, more often female, and more often diabetic; weighed less; and had a higher modified TIMI risk score (Table 2).

Cut-point analyses. On the basis of previous experiences (1–3), comparisons of mortality with short versus long DBT were assessed at cut points of 60, 90, and 120 min. A cut point of 90 min gave the lowest hazard ratio (HR) for mortality comparing short and long DBTs (Table 3).

Comparisons of mortality by DBT in patients with early versus late time to presentation were assessed at time to presentation cut points of 60, 90, and 120 min (2,3). A cut point of 90 min resulted in the greatest difference in HRs for mortality rate with short versus long DBTs between patients with early and late presentation (Table 3).

Comparisons of mortality by DBT in patients at low and high clinical risk were assessed at TIMI risk score cut points

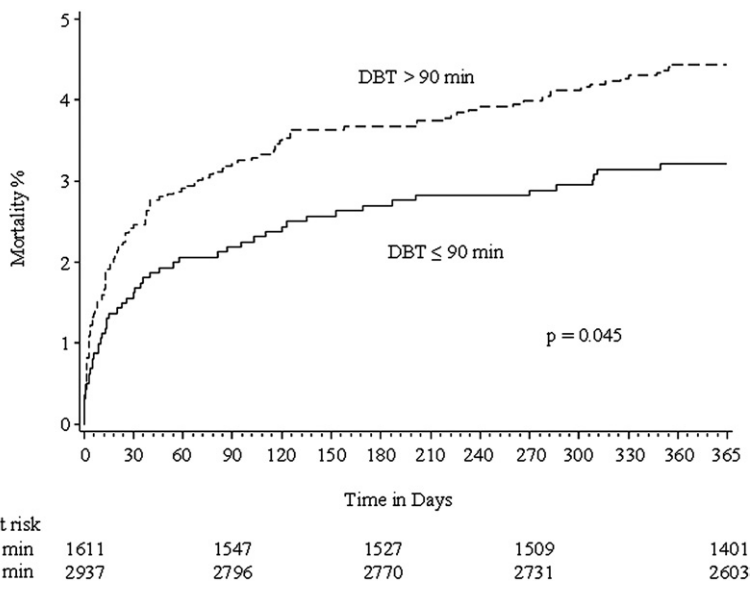

Figure 1 DBT and 1-Year Mortality Rate

Kaplan-Meier estimates for mortality rate in ST-segment elevation myocardial infarction patients with a door-to-balloon time (DBT) of ≤90 min versus >90 min.

of 2, 3, and 4. All cut points demonstrated similar HRs for high- and low-risk groups (Table 3).

Impact of DBT on 1-year mortality by time to presentation and TIMI risk score. In the entire cohort, short DBTs (≤90 min) were associated with significantly lower mortality rates (3.1% vs. 4.3%, HR: 0.72, 95% confidence interval [CI]: 0.52 to 0.99, p = 0.045) (Table 3, Fig. 1). After adjusting for differences in baseline variables, study differences, and treatment assignment, the differences were not quite significant (HR: 0.72, 95% CI: 0.52 to 1.01, p = 0.058).

In patients with early time to presentation (≤90 min), short DBTs (≤90 min) were associated with lower mortality rate (1.9% vs. 3.8%, HR: 0.49, 95% CI: 0.26 to 0.93, p = 0.029), whereas in patients with late time to presentation (>90 min), the DBT had no significant impact on the mortality rate (4.0% vs. 4.6%, HR: 0.86, 95% CI: 0.58 to 1.28, p = 0.47) (p value for interaction = 0.14) (Table 3, Fig. 2). The impact of short DBTs on patients with early presentation remained significant after adjusting for differences in baseline variables (HR: 0.51, 95% CI: 0.26 to 0.98, p = 0.044).

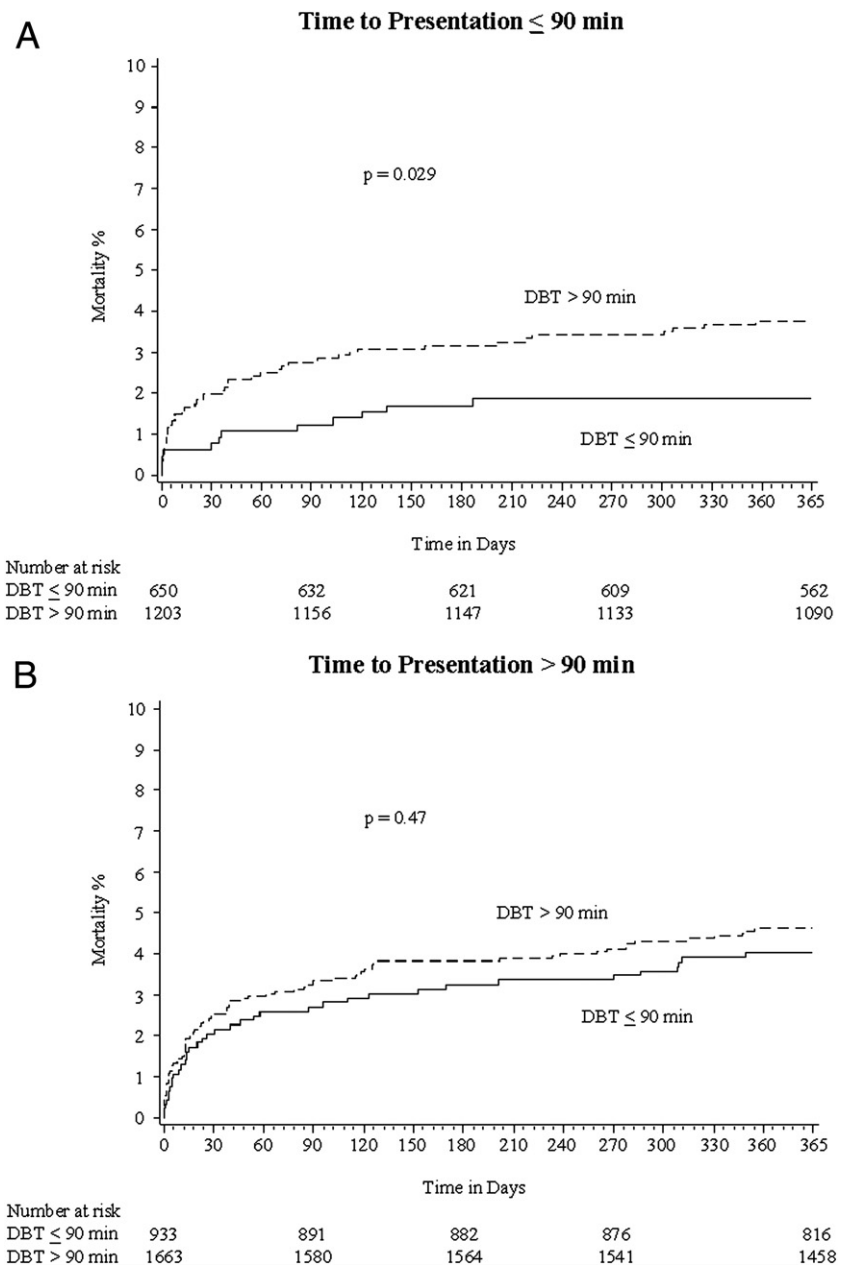

Figure 2 DBT and 1-Year Mortality Rate in Early and Late Presenters

Kaplan-Meier estimates for mortality comparing door-to-balloon time (DBT) of ≤90 min versus >90 min in patients with time to presentation ≤90 min **(A)** and in patients with time to presentation >90 min **(B)**.

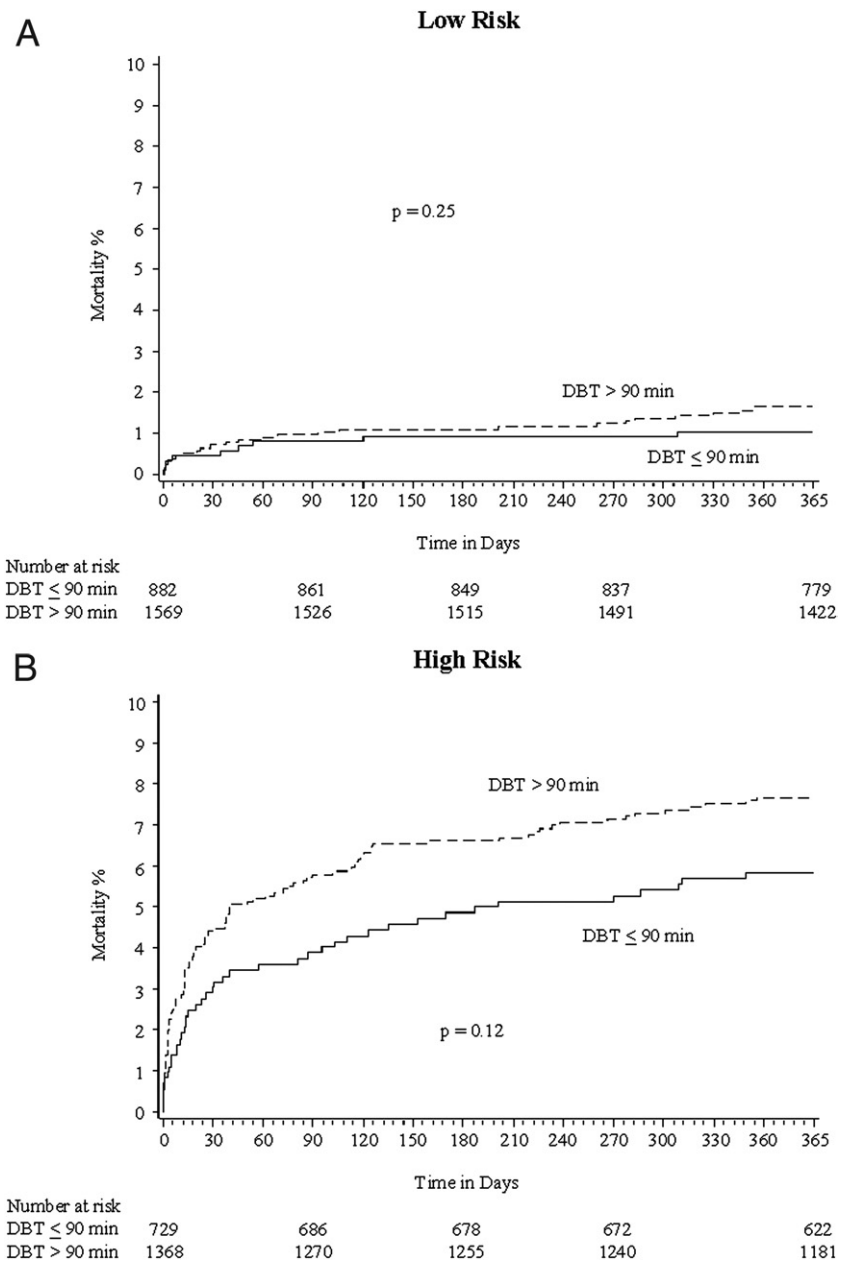

Figure 3 **DBT and 1-Year Mortality Rate in Low- and High-Risk Patients**

Kaplan-Meier estimates for mortality comparing door-to-balloon time (DBT) of ≤90 min versus >90 min in patients at low risk (modified Thrombolysis In Myocardial Infarction [TIMI] risk score <2) **(A)** and in patients at high risk (modified TIMI risk score ≥2) **(B)**.

The HRs of short and long DBTs for 1-year mortality rate were similar in high- and low-risk patients (modified TIMI risk score ≥2 vs. <2) (p value for interaction = 0.71) (Table 3, Fig. 3). However, the absolute reduction in mortality rate with short DBTs was greater in high-risk than low-risk patients (1.7% vs. 0.5%) (Table 3).

In patients presenting early (≤90 min), the HRs for mortality rate in patients with short versus long DBTs were identical for high- versus low-risk patients, but the absolute mortality rate differences were greater in high-risk patients (3.3% vs. 0.7%) (Table 4, Fig. 4). In patients presenting late (>90 min), mortality was similar with short and long DBTs in both high- and low-risk patients (Table 4).

Discussion

The major finding of this study is that short DBTs (<90 min) are associated with a lower 1-year mortality rate in patients presenting early after the onset of symptoms but appear to have

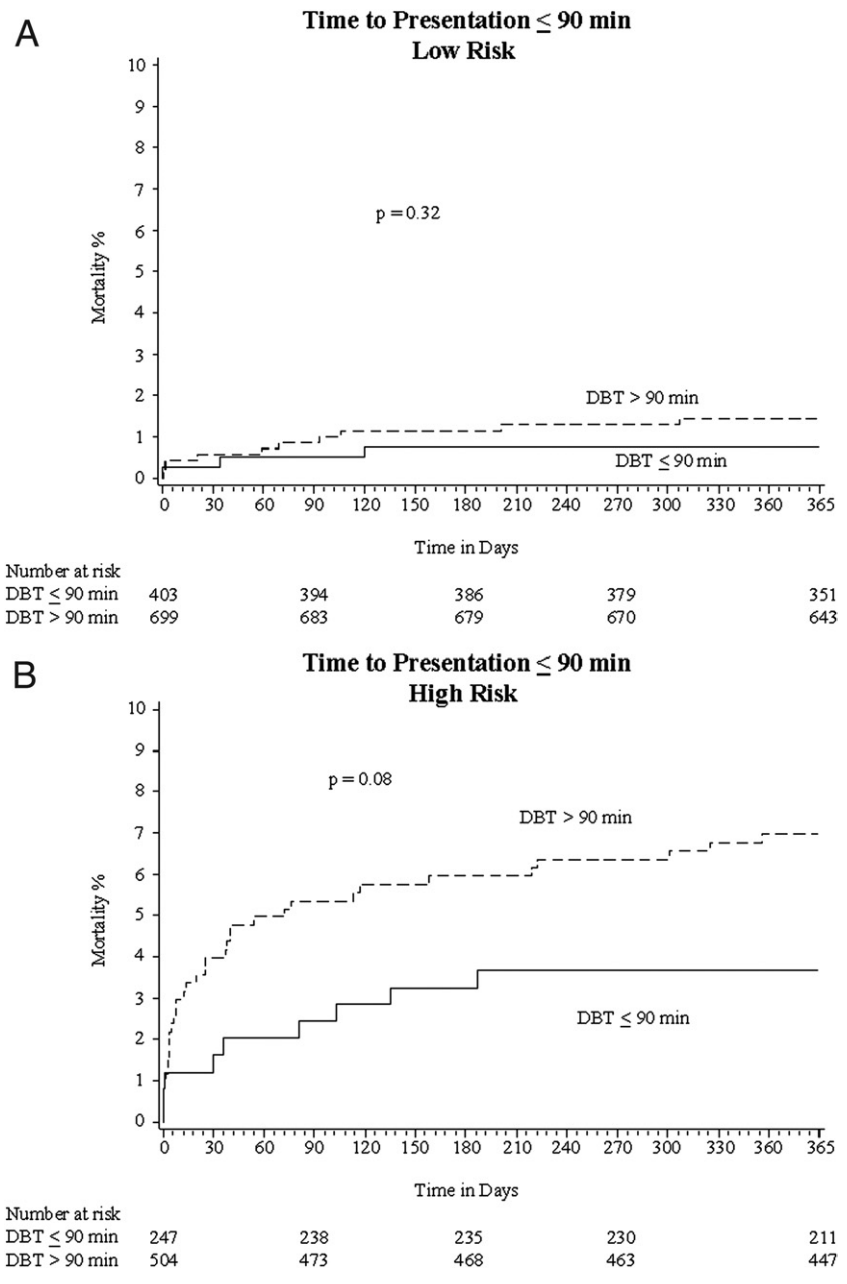

Figure 4 **DBT and 1-Year Mortality Rate in Low- and High-Risk Patients Presenting Early**

Kaplan-Meier estimates for mortality comparing DBT of ≤90 min versus >90 min in patients with time to presentation ≤90 min in patients at low risk (modified TIMI risk score <2) **(A)** and in patients at high risk (modified TIMI risk score ≥2) **(B)**. Abbreviations as in Figure 3.

less impact on the mortality rate in patients presenting later. A second finding of our study is that short DBTs are associated with similar relative reductions in mortality rate in low- and high-risk patients, although the absolute reduction in mortality rate is greatest in high-risk patients.

These data are consistent with the mechanism of benefit of reperfusion therapy described by Gersh et al. (7), which states that the greatest benefit of reperfusion occurs when reperfusion is achieved within the first 2 to 3 h, during which time incremental delays result in considerable loss of myocardial salvage and survival. After 2 to 3 h, incremental delays have much less impact on outcomes. Accordingly, short DBTs should be most beneficial in patients presenting early after the onset of symptoms when reperfusion can be achieved within the time window of maximal benefit.

Data regarding this are conflicting. A large single-center study found improved survival with short DBTs in patients presenting early but not in patients presenting later (2). In contrast, a large registry found that short DBTs were

Table 4 1-Year Mortality Rate by DBT, Time to Presentation, and TIMI Risk Score

	1-Year Mortality (%)*				
	DBT ≤90 min	DBT >90 min	Hazard Ratio†	95% CI	p Value
Time to presentation ≤90 min					
TIMI risk score <2 (n = 1,102)	0.8	1.5	0.52	0.14–1.89	0.32
TIMI risk score ≥2 (n = 751)	3.7	7.0	0.52	0.24–1.08	0.08
Time to presentation >90 min					
TIMI risk score <2 (n = 1,300)	1.3	1.7	0.76	0.29–2.00	0.58
TIMI risk score ≥2 (n = 1,296)	6.8	7.6	0.88	0.57–.35	0.57

*1-year mortalities are Kaplan-Meier estimates. †Hazard ratios are unadjusted and compare mortality with short versus long DBTs.
Abbreviations as in Tables 1 and 3.

associated with a lower mortality rate in patients with both early and late presentation (3). Hidden biases in registries for patients with long DBTs to have higher mortality may explain the differences between the registry data and the present study.

Clinical implications. Pinto et al. (8) found that the PCI-related delay at which primary PCI loses its advantage over fibrinolytic therapy was shorter in patients presenting early versus later and in anterior versus nonanterior infarction. These data and our data suggest that patients presenting early (and patients at high clinical risk) may benefit from alternative reperfusion strategies such as fibrinolysis or facilitated PCI. Facilitated PCI strategies have not yet shown any advantage over primary PCI, but a retrospective analysis of the FINESSE (Facilitated INtervention with Enhanced Reperfusion Speed to Stop Events) trial found that high-risk patients presenting early at spoke hospitals had better outcomes with facilitated PCI compared with primary PCI (9–11). It remains to be proven whether facilitated PCI might be beneficial in high-risk STEMI patients presenting early after the onset of symptoms.

Study limitations. This is an observational, post hoc analysis of data from 2 randomized trials. We believe that this is a representative group of the overall STEMI population, but we do not have data on patients who were screened but not enrolled to document this. Also, exclusion of patients because of missing DBT data could potentially affect our results.

In analyzing numerous cut points, there is the potential for false-positive results. However, our cut points were based on clinical considerations, which should minimize this error.

Although this is the largest randomized primary PCI database evaluating DBT, the power to detect differences in mortality rate in subgroups is limited. This may be the reason why the adjusted differences in mortality rate between short and long DBTs and the interaction between time to presentation and DBT on mortality rate were not quite significant.

Acknowledgment
The authors thank Susan Barnes for her help in preparation of the manuscript.

Reprint requests and correspondence: Dr. Bruce R. Brodie, 313 Meadowbrook Terrace, Greensboro, North Carolina 27408. E-mail: bbrodie@triad.rr.com.

REFERENCES

1. Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. JAMA 2000;283:2941–7.
2. Brodie BR, Hansen C, Stuckey TD, et al. 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. J Am Coll Cardiol 2006;47:289–95.
3. McNamara RL, Wang Y, Herrin J, et al. Effect of door-to-balloon time on mortality in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol 2006;47:2180–6.
4. Stone GW, Grines CL, Cox DA, et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. N Engl J Med 2002;346:957–66.
5. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358:2218–30.
6. Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation. An intravenous nPA for treatment of infarcting myocardium early II Trial substudy. Circulation 2000;102:2031–7.
7. Gersh BJ, Stone GW, White HD, Holmes DR. Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction. Is the slope of the curve the shape of the future? JAMA 2005;293:979–86.
8. Pinto DS, Kirtane AJ, Nallamothu BK, et al. Hospital delays in reperfusion for ST-elevation myocardial infarction. Implications when selecting a reperfusion strategy. Circulation 2006;114:2019–25.
9. ASSENT-4 PCI Investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI) randomized trial. Lancet 2006;367:569–78.
10. Ellis SG, Tendera M, de Belder MA, et al., for the FINESSE Investigators. Facilitated PCI in patients with ST-elevation myocardial infarction. N Engl J Med 2008;358:2205–17.
11. Herrmann HC, Lu J, Brodie BR, et al., for the FINESSE Investigators. Benefit of facilitated PCI in high risk ST-elevation myocardial infarction patients presenting to non-PCI hospitals. J Am Coll Cardiol Intv 2009;2:917–24.

Key Words: door-to-balloon time ■ myocardial infarction ■ primary percutaneous coronary intervention.