Trends in Door-to-Balloon Time and Mortality in Patients With ST-Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

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Background: In patients with acute ST-elevation myocardial infarction (STEMI) who are undergoing percutaneous coronary intervention, current guidelines for reperfusion therapy recommend a door-to-balloon (DTB) time of less than 90 minutes. Considerable effort has focused on reducing DTB time with the assumption that a reduction in DTB time translates into a significant reduction in mortality; however, the clinical impact of this effort has not been evaluated. Therefore, our objective was to determine whether a decline in DTB time in patients with STEMI was associated with an improvement in clinical outcomes.

Methods: We assessed the yearly trend in DTB time for 8771 patients with STEMI who were undergoing primary percutaneous coronary intervention from 2003 to 2008 as part of the Blue Cross Blue Shield of Michigan Cardiovascular Consortium and correlated it with trends in in-hospital mortality. Patients were stratified according to risk of death using a mortality model to evaluate whether patient risk factors affect the relationship between DTB time and mortality.

Results: Median DTB time decreased each year from 113 minutes in 2003 to 76 minutes in 2008 (P < .001), and the percentage of patients who were revascularized with a DTB time of less than 90 minutes increased from 28.5% in 2003 to 67.2% in 2008 (P < .001). In-hospital mortality remained unchanged at 4.10% in 2003, 4.02% in 2004, 4.40% in 2005, 4.42% in 2006, 4.73% in 2007, and 3.62% in 2008 (P = .69). After the differences in baseline characteristics were adjusted for, there was no difference in the standardized mortality ratios (SMRs) across the study period (SMR, 1.00; 95% confidence interval [CI], 0.74-1.26 in 2003 compared with SMR, 0.95; 95% CI, 0.77-1.13 in 2008).

Conclusions: There has been a dramatic reduction in median DTB time and increased compliance with the related national guideline. Despite these improvements, in-hospital mortality was unchanged over the study period. Our results suggest that a successful implementation of efforts to reduce DTB time has not resulted in the expected survival benefit.

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Methods: We assessed the yearly trend in DTB time for 8771 patients with STEMI who were undergoing primary percutaneous coronary intervention from 2003 to 2008 as part of the Blue Cross Blue Shield of Michigan Cardiovascular Consortium and correlated it with trends in in-hospital mortality. Patients were stratified according to risk of death using a mortality model to evaluate whether patient risk factors affect the relationship between DTB time and mortality.

Background: In patients with acute ST-elevation myocardial infarction (STEMI) who are undergoing percutaneous coronary intervention, current guidelines for reperfusion therapy recommend a door-to-balloon (DTB) time of less than 90 minutes. Considerable effort has focused on reducing DTB time since multiple studies have demonstrated better outcomes in patients with shorter DTB times. Although several studies suggest improved in-hospital mortality with early revascularization, the clinical impact of improved adherence with the current guideline has not been evaluated. Therefore, we assessed the temporal trend in DTB time for patients with STEMI who were undergoing PCI as part of a regional consortium of hospitals in Michigan to determine if improved DTB time corresponded to a reduction in mortality.

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### Table 1. Baseline Demographics and Clinical Characteristics for Patients With ST-Elevation Myocardial Infarction Who Were Undergoing Percutaneous Coronary Intervention From 2003 to 2008

<table>
<thead>
<tr>
<th>Variable</th>
<th>2003 (n=976)</th>
<th>2004 (n=970)</th>
<th>2005 (n=1318)</th>
<th>2006 (n=1381)</th>
<th>2007 (n=1862)</th>
<th>2008 (n=2264)</th>
<th>P Valuea</th>
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<td><strong>Demographic variable</strong></td>
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<td>Female</td>
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<td>Lean (BMI &lt;25)</td>
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<td>Obese (BMI ≥30)</td>
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<td>15</td>
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<td>7.2</td>
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<td>.29</td>
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<td>1.1</td>
<td>1.1</td>
<td>1.2</td>
<td>1.2</td>
<td>1.1</td>
<td>.17</td>
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<tr>
<td>Baseline creatinine level ≥1.5 mg/dL</td>
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<td>12.3</td>
<td>11.0</td>
<td>11.8</td>
<td>10.6</td>
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<td>WHO anemia</td>
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<td>17.9</td>
<td>18.7</td>
<td>21.1</td>
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<td>Mean ejection fraction</td>
<td>46.4</td>
<td>46.4</td>
<td>44.9</td>
<td>45.5</td>
<td>45.7</td>
<td>45.3</td>
<td>.02</td>
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<tr>
<td>Ejection fraction &lt;50%</td>
<td>53.3</td>
<td>50.2</td>
<td>55.9</td>
<td>54.4</td>
<td>52.6</td>
<td>53.3</td>
<td>.89</td>
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</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CABG, coronary artery bypass grafting; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; MI, myocardial infarction; PCI, percutaneous coronary intervention; WHO, World Health Organization.

SI conversion factor: To convert creatinine values to micromoles per liter, multiply by 88.4.

a P values were determined by the means of the continuous trend test.

Consortium (BMC2), a multihospital regional quality improvement collaborative. The study period from January 2003 to December 2008 was selected because these years were most likely to reflect the impact of focused efforts to improve DTB time. A standardized form was used to collect baseline clinical, demographic, procedural, angiographic, and medication data as well as procedural and in-hospital outcomes. Details of the data collection are described in previous publications, and the registry was approved by the institutional review boards of all participating hospitals. Exclusion criteria included symptom-to-balloon time of greater than 12 hours, use of thrombolytic agents, and patients transferred from another hospital for primary PCI.

The primary end point for this analysis was in-hospital mortality, which was defined as death from any cause. Major adverse cardiovascular events (MACEs) were defined as the composite of death, myocardial infarction (MI), transient ischemic attack or stroke, coronary artery bypass grafting, and target lesion revascularization. Death included mortality from both cardiac and noncardiac causes. Stroke was defined as a new focal neurologic deficit lasting longer than 24 hours, and contrast nephropathy was defined as an increase in postprocedural serum creatinine levels greater than or equal to 0.5 mg/dL (to convert to micromoles per liter, multiply by 88.4). Vascular complications included pseudoaneurysm, arteriovenous fistula, femoral neuropathy, retroperitoneal hematoma, hematoma at the access site, and any access site complication requiring surgical repair. Transfusion was defined as the transfusion of any blood product regardless of the number of units transfused.

Discrete variables are expressed as percentages, and continuous variables are expressed as mean (SD). The χ² test and the Fisher exact test were used to determine differences in discrete variables between years. The Wilcoxon rank sum test and the t test were used to evaluate continuous variables. Trends in outcome were evaluated using the Cochran-Armitage test. To adjust for differences in baseline characteristics, we divided patients into quartiles of predicted mortality using the modified BMC2 death prediction model. The variables in the mortality model included age categories 60 through 69 years, 70 through 79 years, and 80 years or older; sex; history of congestive heart failure; history of extracardiac vascular disease; history of significant valve disease; and presenting variables (emergency PCI, baseline MI [≤7 days prior], cardiac arrest, cardiogenic shock, World Health Organization anemia, baseline creatinine level 1.0-1.9 mg/dL, baseline creatinine level ≥2.0 mg/dL, and left ventricular ejection fraction <50%). Two variables (emergency PCI and baseline MI ≤7 days prior) were
Baseline procedural characteristics were also compared each year and showed an increase in the percentage of patients with restenotic lesions; however, cardiac arrest, cardiogenic shock, contrast load, visible thrombus, and calcification decreased (Table 2). The prevalence of ventricular tachycardia and ventricular fibrillation showed significant differences between years but did not trend consistently. Treatments administered before PCI showed a trend toward increased use of clopidogrel, lipid-lowering agents, angiotensin-converting enzyme inhibitors, calcium channel blockers, and warfarin as time progressed. Use of an intra-aortic balloon pump, low-molecular-weight heparin, and unfractionated heparin decreased over the study period. The percentage of patients per year treated with glycoprotein IIb/IIIa inhibitors did not change over the study period. The percentage of patients treated with stent placement was lowest at 85.8% in 2003 and peaked at 94.4% in 2006. The percentage of patients treated with bare metal stents was highest at 71.1% in 2003, with a nadir of 24.9% in 2006, and drug-eluting stents were placed in 14.7% of

### RESULTS

A total of 8771 patients with STEMI underwent PCI from 2003 to 2008 and were followed up in the BMC2. Baseline demographics and clinical characteristics for each year are shown in Table 1. The mean age of the study population per year ranged from 59.2 to 60.6 years, and 69.8% to 72.5% of the patients were male. The proportion of older patients increased over the course of the study period. Also, comorbidities such as hypertension, prior MI, diabetes, congestive heart failure, and atrial fibrillation were more prevalent as time progressed, and the percentage of patients with prior PCI increased toward the end of the study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>2003 (n=976)</th>
<th>2004 (n=970)</th>
<th>2005 (n=1318)</th>
<th>2006 (n=1381)</th>
<th>2007 (n=1862)</th>
<th>2008 (n=2264)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median DTB time, min</td>
<td>113</td>
<td>110</td>
<td>98</td>
<td>89</td>
<td>80</td>
<td>76</td>
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</tr>
<tr>
<td>Length of stay, d</td>
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<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>.41</td>
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<tr>
<td>Cardiac arrest</td>
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<td>7.6</td>
<td>8.7</td>
<td>6.7</td>
<td>7.1</td>
<td>7.3</td>
<td>.02</td>
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<td>Cardiogenic shock</td>
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<td>11.9</td>
<td>15.0</td>
<td>14.1</td>
<td>9.0</td>
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<tr>
<td>VT/ VF</td>
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<td>7.8</td>
<td>6.7</td>
<td>7.9</td>
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<td>&lt;.001</td>
</tr>
<tr>
<td>Total contrast, mL</td>
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<td>215</td>
<td>208</td>
<td>211</td>
<td>211</td>
<td>205</td>
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<td>2.2</td>
<td>2.1</td>
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<td>GP IIb/IIla</td>
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<td>3.5</td>
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<td>93.6</td>
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<td>96.1</td>
<td>94.3</td>
<td>.53</td>
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Abbreviations: ACE, angiotensin-converting enzyme; DTB, door-to-balloon; GP IIb/IIIA, glycoprotein IIb/IIia inhibitors; MACD, maximum allowed contrast dose; PCI, percutaneous coronary intervention; TIMI-3, thrombolysis in myocardial infarction grade 3; VF, ventricular fibrillation; VT, ventricular tachycardia.

*P* values were determined by the means of the continuous trend test.
patients in 2003 compared with 69.5% of patients in 2006. The percentage of patients with postprocedural normal flow, defined as thrombolysis in MI grade 3 flow, did not differ much between the years of the study. Also, procedural outcomes did not differ between years, with the exception of vascular complications, which increased before peaking in 2006 (Table 3).

Median DTB time significantly decreased each year from 113 minutes in 2003 to 76 minutes in 2008 (P < .001), and the percentage of patients who were revascularized with a DTB time of less than 90 minutes increased from 28.5% in 2003 to 67.2% in 2008 (P < .001) (Figure 1). This change represents a greater than 100% increase in patients meeting the current ACC/AHA guideline over the study period. Despite improved compliance with the national guideline, in-hospital mortality remained unchanged, with 4.10% in 2003 compared with 3.62% in 2008 (P = .69) (Figure 1). Furthermore, the rates of most adverse events remained unchanged, with no difference in MACEs over the study period (10.25% in 2003 and 9.54% in 2008; P = .98).

After the difference in baseline characteristics was adjusted for, there was no difference in annual mortality, and the standardized mortality ratio remained close to unity across the study period (Figure 2). The use of hierarchical modeling to adjust for clustering also demonstrated similar results (data not shown). Furthermore, the number of participating hospitals in the registry increased throughout the study period (Table 1). An analysis restricted to the 15 hospitals participating in the BMC2 for the entire study period demonstrated similar results, with a statistically significant decrease in median DTB time over the study period (P < .001) but no associated survival benefit (P = .67).

Patients were stratified into quartiles according to risk of death using their predicted mortality; quartiles 1 and 4 represent the lowest- and highest-risk patients, respectively. The C statistic for the mortality model in the cohort was 0.91, suggesting excellent discrimination. The mortality per year within each quartile ranged from 0% to 0.4% in quartile 1, 0% to 1.2% in quartile 2, 0.9% to 2.9% in quartile 3, and 11.9% to 16.5% in quartile 4 (Figure 3). The highest-risk patients, who were strati-
fied to quartile 4, were associated with 79% to 91% of the deaths in the cohort each year, whereas the patients in quartile 3 represented 5% to 17% of the deaths each year.

Yearly median DTB time was evaluated within each quartile to determine whether higher-risk patients had increased DTB times or a reduced rate of change in DTB time relative to lower-risk patients. The patients in the highest-risk quartile had a longer DTB time compared with lower-risk patients. Quartile 4 patients had a median DTB time of 120 minutes in 2003 compared with a median DTB time of 109 minutes in 2003 for quartile 1 patients. The difference in median DTB time between high- and low-risk quartiles was present in each study year, and the median DTB time in 2008 was 82 minutes for quartile 4 patients compared with 72 minutes for quartile 1 patients (Figure 4). However, the median DTB time uniformly decreased within each quartile over the study period. In quartile 4, the median DTB time decreased from 120 minutes in 2003 to 82 minutes in 2008; furthermore, the percentage of patients in the highest-risk quartile who met a DTB time of less than 90 minutes increased from 25% in 2003 to 62% in 2008 (Figure 4).

Despite the improvement in DTB time over the study period, the percentage of deaths each year within each quartile remained unchanged with time. No significant trend in mortality was noted in any subgroup by post hoc analysis (cardiogenic shock [P=.89], no cardiogenic shock [P=.08], anterior MI [P=.79], age <75 years [P=.87], and age >75 years [P=.50]) and by categorizing patients into those with symptoms to a procedure duration of less than 3 hours (P=.35), 3 to 6 hours (P=.37), and longer than 6 hours (P=.71).

Although the DTB times decreased significantly over the study period (P<.001), the symptom-to-doors times remained unchanged for most of the study period (P=.16). High-risk patients had longer median symptom-to-door times than low-risk patients for all years in the study, with the exception of 2008 (Figure 5). In a post hoc analysis, we calculated that to determine a 5% relative annual reduction in mortality with α = .05, our study would have required 808 patients in the first year and 1615 patients by the last year for a power of 80%.16

**COMMENT**

In our study, we evaluated the trends in median DTB times in patients with STEMI who were undergoing primary PCI from 2003 to 2008 and evaluated the effect of DTB time on in-hospital mortality. Our data showed a linear decrease in yearly median DTB time and increased compliance with the national guideline of a DTB time of less than 90 minutes; however, in-hospital mortality was unchanged over the study period. The highest-risk patients were responsible for most deaths each year in the study population, and the mortality each year did not decrease despite an improvement in yearly DTB time within the highest-risk quartile.

The national effort to improve compliance with the current ACC/AHA guideline for DTB time is based on the assumption that improved DTB time has substantial potential to improve survival. The introduction of initiatives such as the ACC DTB quality alliance demonstrates the emphasis that has been placed on reducing
DTB time to improve outcomes in patients with STEMI who are undergoing PCI. However, previous studies suggest that several factors may have an effect on the relationship between DTB time and mortality. Healthier patients may be treated with shorter DTB times, and this immigration bias may strongly influence the relationship between DTB time and mortality. Furthermore, multiple lines of evidence suggest a marked decline in myocardial salvage with time and identify a critical time-dependent period for revascularization within the first several hours of symptom onset. If DTB time begins outside this critical time-dependent period, decreased DTB time may not have a major impact on survival. Also, the extent of benefit from earlier reperfusion may reach a point of diminishing returns, which leaves little room for improvement in mortality despite a considerable reduction in DTB time.

There are limited data regarding the mortality benefit, as compliance with the national guideline has improved over time. Gibson et al. performed an analysis of the National Registry of Myocardial Infarction data for patients with STEMI who were undergoing PCI or thrombolytic therapy. Results from their study showed a linear decline in DTB time in patients who were undergoing PCI from 111 minutes in 1994 to 79 minutes in 2006 (P < .001). The decline in DTB time corresponded to an improvement in in-hospital mortality from 8.6% to 3.1% (P < .001), which is not consistent with the results from our study. However, there has been a great improvement in pharmacologic and interventional therapies from 1994 to the present, which may have contributed to the mortality benefit observed by Gibson et al. In contrast to these results and in accordance with our findings, a recent study by Wang et al. involving 5881 patients with STEMI who were undergoing PCI showed that the median DTB time from January to December 2005 was 101 minutes, and this decreased to a median DTB time of 87 minutes during a later period, from July 2006 to June 2007. The improved DTB time was not associated with an improvement in mortality.

The benefit of early reperfusion on mortality in patients treated with thrombolytic therapy has been clearly established in several randomized trials; however, studies have shown conflicting evidence regarding the importance of DTB time on mortality in patients with STEMI who were treated with PCI. In the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes Trial, Berger et al. showed that 30-day mortality was lowest in patients who were treated with a DTB time of less than 60 minutes. Furthermore, they showed a statistically significant increase in mortality with increasing DTB time, which remained significant after adjustment for differences in baseline characteristics. Cannon et al. evaluated the relationship between DTB time and mortality in a large-scale, multicenter observational study using data from the Second National Registry of Myocardial Infarction, and their analysis showed that a DTB time of longer than 2 hours was associated with increased in-hospital mortality. In contrast, in an observational study of patients treated with primary PCI as part of the Stent Primary Angioplasty in Myocardial Infarction Trial, Brodie et al. showed no correlation between DTB time and 1- or 6-month mortality. In a single-center observational study of patients with STEMI who were treated with primary PCI, De Luca et al. showed the absence of any relationship between DTB time and mortality.

The discrepancies between the results of the aforementioned studies could potentially be explained by differences in the analysis of confounding risk factors. High-risk patients have characteristics that may require stabilization before they undergo PCI, thereby contributing to a delay in time to revascularization. Therefore, patients with an increased risk of mortality may have increased DTB times relative to low-risk patients, and the delay required for stabilization in high-risk patients would have an impact on the interpretation of DTB time and in-hospital mortality. To address this effect on the data, we stratified patients into quartiles based on risk of death using a mortality model.

Patients in the higher-risk quartiles (quartiles 3 and 4 combined) were responsible for 91% to 100% of deaths in the cohort each year, with no significant change in yearly mortality over the study period. Interestingly, the higher-risk quartiles showed yearly improvement in median DTB time and a similar rate of change when compared with lower-risk quartiles during the study period. Our data show that progress has been made in reducing DTB time in the highest-risk patients who represent most deaths in the cohort, but the improvement in DTB time in these patients had no effect on mortality. However, higher-risk patients in our study had increased symptom-to-door times relative to lower-risk patients, who showed no improvement in symptom-to-door time over most of the study period.

Previous studies provide no consensus regarding the effect of symptom-to-door or symptom-to-balloon time on mortality in patients with STEMI who undergo treatment with PCI. Cannon et al., in analysis of patients in the Second National Registry of Myocardial Infarction, did not find a correlation between symptom-to-balloon time and in-hospital mortality. Also, Zijlstra et al. analyzed pooled data from 10 randomized trials comparing primary angioplasty and thrombolytic therapy, and although increased symptom-to-balloon time was associated with increased rates of MACEs in patients who were treated with thrombolytic agents, no relationship was found between symptom-to-balloon time and MACEs in patients who were treated with PCI. These results are inconsistent with an analysis by Brodie et al. involving patients enrolled in the Stent Primary Angioplasty in Myocardial Infarction Trial, which showed improvement in 30-day mortality with symptom-to-balloon time of less than 2 hours. Furthermore, De Luca et al. showed improved 1-year mortality among patients with decreased symptom-to-balloon times in a single-center study involving 1791 patients with STEMI who were undergoing angioplasty.

The inconsistencies of these study results are likely attributable to confounding variables, similar to those discussed in the analysis of DTB time. Several studies show differences in the effect of increased symptom-to-door time on mortality between high- and low-risk patients. Brodie et al. showed improved in-hospital survival with de-
creased symptom-to-balloon time in patients with cardio-
genic shock, whereas symptom-to-balloon time did not
affect survival in low-risk patients. Furthermore, Antoni-
ucci et al. stratified patients according to the risk criteria
of the thrombolysis in MI investigators and showed a sta-
tistically significant increase in mortality with increased time
to treatment in high-risk patients, whereas no significant
effect of symptom-to-door time was observed on mortal-
ity in low-risk patients. Furthermore, De Luca et al. showed
a linear increase in 1-year mortality with increasing sym-
ptom-to-balloon times in high-risk patients, which was not
observed in the low-risk category.

Our data show no trend in median symptom-to-door
times over the course of the study period; however, pa-
tients with higher-risk characteristics have increased me-
dian symptom-to-door times relative to lower-risk pa-
tients. Furthermore, our data show greater adherence to
the current AHA/ACC guidelines for a DTB time of less
than 90 minutes without a resultant improvement in over-
all mortality. It could be that the negative impact of the
increased symptom-to-door time among high-risk pa-
tients is sufficient to mask any potential protective effect
of the decreased DTB among this group of patients, who
account for the vast majority of mortality in patients un-
dergoing PCI for STEMI. These data invoke the need to
further evaluate the negative results of our study. It is
possible that total ischemic time, including symptom-
to-door time and DTB time, should be considered in the
development of measures to improve outcomes for pa-
tients with STEMI who are undergoing PCI. Benefits of
reduced DTB time may emerge later, with a reduction
in heart failure and late mortality. Furthermore, it may
be helpful to study cause-specific mortality to better un-
derstand the pathophysiologic processes that are con-
tributing to patient death in the contemporary era. How-
ever, it is equally important to recognize that the drive
to reduce DTB time has not resulted in the expected sur-
vival benefit, and other measures to reduce the mortal-
ity of acute MI need to be investigated.

Several limitations of this study should be noted. First,
our study is an observational study with recognized dif-
fferences in baseline demographic, clinical, and pro-
ducral characteristics noted over the study period. Fur-
thermore, unrecognized differences in baseline variables
that are inherent to observational studies could influ-
ence the data analysis as well. Second, difficulty exists
in ensuring the accuracy of symptom-to-door times owing
to the subjective nature of symptom onset and the possi-
bility of recall bias. Third, the BMC2 collects data regard-
ing in-hospital outcomes only; therefore, the study
cannot evaluate the effect of DTB time or symptom-to-
door time on long-term outcomes.

In conclusion, our study shows a linear decrease in
yearly median DTB time and increased compliance with
the national guideline of a DTB time of less than 90 min-
utes in patients with STEMI who are undergoing PCI. De-
spite these improvements, in-hospital mortality was un-
changed over the study period. Higher-risk patients, as
defined in our mortality model, accounted for most deaths
each year in the study population and also had in-
creased symptom-to-door time relative to lower-risk pa-
tients. Our results suggest that successful implementa-
tion of efforts to reduce DTB time has not translated into
a reduction in in-hospital mortality. Further studies are
warranted to identify strategies that could improve the
outcome of patients undergoing primary PCI.

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and Gurm. Acquisition of data: Moscucci, LaLonde, Changezi,
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