Relation between door-to-balloon times and mortality after primary percutaneous coronary intervention over time: a retrospective study


Summary

Background Recent reductions in average door-to-balloon (D2B) times have not been associated with decreases in mortality at the population level. We investigated this seemingly paradoxical finding by assessing components of this association at the individual and population levels simultaneously. We postulated that the changing population of patients undergoing primary percutaneous coronary intervention (pPCI) contributed to secular trends toward an increasing mortality risk, despite consistently decreased mortality in individual patients with shorter D2B times.

Methods This was a retrospective study of STEMI patients who underwent pPCI between Jan 1, 2005, and Dec 31, 2011, in the National Cardiovascular Data Registry (NCDR) CathPCI Registry. We looked for catheterisation laboratory visits associated with STEMI. We excluded patients not undergoing pPCI, patients with D2B times less than 15 min or more than 3 h, and patients at hospitals that did not consistently report data across the study period. We assessed in-hospital mortality in the entire cohort and 6-month mortality in elderly patients aged 65 years or older matched to data from the Centers for Medicare and Medicaid Services. We built multilevel models to assess the relation between D2B time and in-hospital and 6-month mortality, including both individual and population-level components of this association after adjusting for patient and procedural factors.

Findings 423 hospitals reported data on 150 116 procedures with a 55% increase in the number of patients undergoing pPCI at these facilities over time, as well as many changes in patient and procedural factors. Annual D2B times decreased significantly from a median of 86 min (IQR 65–109) in 2005 to 63 min (IQR 47–80) in 2011 (p<0.0001) with a concurrent rise in risk-adjusted in-hospital mortality (from 4.7% to 5.3%; p=0.06) and risk-adjusted 6-month mortality (from 12.9% to 14.4%; p=0.001). In multilevel models, shorter patient-specific D2B times were consistently associated at the individual level with lower in-hospital mortality (adjusted OR for each 10 min decrease 0.92; 95% CI 0.91–0.93; p<0.0001) and 6-month mortality (adjusted OR for each 10 min decrease 0.94; 95% CI 0.93–0.95; p<0.0001). By contrast, risk-adjusted in-hospital and 6-month mortality at the population level, independent of patient-specific D2B times, rose in the growing and changing population of patients undergoing pPCI during the study period.

Interpretation Shorter patient-specific D2B times were consistently associated with lower mortality over time, whereas secular trends suggest increased mortality risk in the growing and changing pPCI population. The absence of association of annual D2B time and changes in mortality at the population level should not be interpreted as an indication of its individual-level relation in patients with STEMI undergoing primary PCI.

Funding National Heart, Lung, and Blood Institute.

Introduction

Door-to-balloon (D2B) time predicts survival in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (pPCI). This relation has been thought to be causal, supported by studies in animals and observational evidence indicating that shorter times to reperfusion are linked to decreased myocardial damage and mortality. As a result, clinical guidelines and national quality initiatives in the past decade have focused on shortening D2B times, including the large D2B Alliance sponsored by the American College of Cardiology (ACC) and the Mission: Lifeline Program led by the American Heart Association (AHA). Yet some studies have reported that contemporary decreases in annual D2B times have not been associated with temporal improvements in mortality in the population of patients undergoing pPCI. These unexpected results have raised uncertainty about the value of existing quality initiatives and questions about the true relation between D2B time and mortality. Results from these studies warrant further assessment. The findings have been interpreted, in some quarters, to suggest that a decrease in D2B times do not result in improved outcomes for individual patients. However, for such an assertion to be true the relation between mortality and patient-specific D2B times (ie, the D2B
time that an individual patient experiences) needs to be disentangled from secular trends in the overall size, profile, and outcomes of the pPCI population that was simultaneously occurring. The expanded use of the procedure in later years through developing STEMI systems of care could have led to a group of patients with an overall increased risk of survival undergoing the procedure (ie, survivor-cohort effect), which might not be fully captured by traditional variables obtained in clinical registries. Although this possibility could mask the effects of shorter D2B times on outcomes at the population level, it would not obviate a clinically meaningful relation between D2B times and mortality for an individual patient.

Accordingly, the goal of this study was to unravel the relation between patient-specific D2B time and mortality from secular trends in outcomes for the pPCI population. Our hypothesis was that the changing population of patients undergoing pPCI contributed to secular trends toward an increasing mortality risk, despite consistently lower mortality in individual patients with shorter D2B times. With support from the National Cardiovascular Data Registry (NCDR) CathPCI Registry, we included a cohort of patients identical to that of a previous study, but extended this previous work by examining both in-hospital and 6-month mortality outcomes, incorporating more recent data than that used before, and using multilevel models as a principal part of our methods. Multilevel models are invaluable in this setting as they allow for the individual-level relation of D2B times to be examined in the context of broader changes at the population level, and to study both these associations separately. By providing access to the same data sources, this study also represents an open science approach by the NCDR programme by allowing other investigators to build on important issues raised by a previous publication using the same data source.

Methods
Data sources and study sample
We obtained data sources from the NCDR CathPCI Registry, co-sponsored by the American College of Cardiology (ACC) and the Society for Cardiovascular Angiography and Interventions (SCAI). The NCDR CathPCI Registry is the largest national registry of patients undergoing PCI in the USA, with a rapid doubling in participation from about 600 hospitals in 2005 to over 1400 hospitals by 2011. Although large, participation of hospitals in the NCDR CathPCI Registry is done voluntarily and, therefore, not population-based. The NCDR CathPCI Registry employs trained personnel who obtain detailed information on patient and hospital characteristics, coronary angiographic and procedural findings, and outcomes using standardised data elements—a process overseen by an established data-quality programme. The data-quality programme attempts to ensure that data submitted are complete, consistent, and accurate. Every year, 25 sites are selected randomly for a comprehensive on-site data audit. Because PCI practices change quickly, several registry modifications have occurred over time, with recent versions including well over 200 data fields. Definitions and specifications for these data fields are available online. Data in the NCDR CathPCI Registry are recorded up to the time of hospital discharge, with long-term follow-up unavailable, which is a potential limitation.

For this study, we looked for catheterisation laboratory visits associated with STEMI. We excluded patients not undergoing pPCI, transfer patients for pPCI, patients with D2B times less than 15 min or more than 3 h (to focus on patients who had the most gain with myocardial salvage), and patients at hospitals that did not consistently report data across the study period. This selection process created a pPCI population for analysis and was identical to that used to create a cohort from the most recent study to assess this question. No patients were excluded for non-system delays unlike current accountability measures. We noticed variations in these selection criteria over time that were associated with expansion of STEMI systems of care nationally. For example, the proportion of patients undergoing pPCI out of the total PCIs at a hospital grew from 4·3% in 2005 to 6·8% in 2011, and non-transfer patients grew from 62·3% to 78·3% of all pPCIs. The Institutional Review Board at Yale University granted us a waiver to use de-identified data and provided authorisation for this study.

Study variables
We calculated patient-specific D2B times for every case and then used them to determine annual D2B times at the population level for every year. Patient-specific D2B times were based on data from catheterisation laboratory visits and defined as the time from hospital arrival to first device use during PCI (eg, balloon or thrombectomy catheter). We identified annual D2B times by calculating the median of patient-specific D2B times during the year the procedure was done in the pPCI population. We examined both in-hospital and 6-month mortality. We obtained all-cause in-hospital mortality from the NCDR CathPCI Registry, and we assessed 6-month mortality in a group of patients aged 65 years or older in the NCDR CathPCI Registry who had been successfully matched to CMS claims data, with similar patient characteristics noted between linked and unlinked individuals.

An extensive list of patient and procedural factors related to the pPCI were available from the NCDR Cath PCI Registry for risk adjustment (appendix). Missing data were rare for most variables (<1%) with the exception...
Patient demographics, history and cardiac status

<table>
<thead>
<tr>
<th></th>
<th>Total (n=150 116)</th>
<th>2005 (n=15 730)</th>
<th>2006 (n=19 612)</th>
<th>2007 (n=21 183)</th>
<th>2008 (n=22 681)</th>
<th>2009 (n=22 550)</th>
<th>2010 (n=23 911)</th>
<th>2011 (n=24 449)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean patient age, years (SD)</td>
<td>66.9 (13.0)</td>
<td>60.5 (13.1)</td>
<td>60.5 (13.0)</td>
<td>60.7 (13.1)</td>
<td>60.9 (13.2)</td>
<td>61.1 (13.0)</td>
<td>61.2 (12.9)</td>
<td>61.3 (12.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean BMI (SD)</td>
<td>28.9 (6.0)</td>
<td>28.6 (5.8)</td>
<td>28.7 (5.9)</td>
<td>28.8 (5.9)</td>
<td>28.9 (6.0)</td>
<td>28.9 (6.0)</td>
<td>29.0 (6.1)</td>
<td>29.1 (6.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>16.6% (n=24 944)</td>
<td>15.6% (n=22 681)</td>
<td>16.4% (n=23 911)</td>
<td>16.5% (n=22 681)</td>
<td>16.8% (n=22 550)</td>
<td>17.1% (n=23 911)</td>
<td>17.4% (n=24 449)</td>
<td>17.7% (n=24 449)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Renal failure, dialysis</td>
<td>18% (n=27 320)</td>
<td>17.7% (n=22 681)</td>
<td>18.0% (n=23 911)</td>
<td>18.1% (n=22 681)</td>
<td>18.4% (n=22 550)</td>
<td>18.7% (n=23 911)</td>
<td>19.0% (n=24 449)</td>
<td>19.3% (n=24 449)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No Stent</td>
<td>53.6% (n=81 252)</td>
<td>53.6% (n=22 681)</td>
<td>53.7% (n=23 911)</td>
<td>53.8% (n=22 681)</td>
<td>54.0% (n=22 550)</td>
<td>54.2% (n=23 911)</td>
<td>54.5% (n=24 449)</td>
<td>54.8% (n=24 449)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Direct thrombin inhibitors</td>
<td>34.4% (n=51 380)</td>
<td>34.0% (n=22 681)</td>
<td>34.5% (n=23 911)</td>
<td>34.6% (n=22 681)</td>
<td>34.8% (n=22 550)</td>
<td>35.1% (n=23 911)</td>
<td>35.4% (n=24 449)</td>
<td>35.7% (n=24 449)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Heparin plus GPI Ib/IIa</td>
<td>33.3% (n=50 351)</td>
<td>33.4% (n=22 681)</td>
<td>33.5% (n=23 911)</td>
<td>33.6% (n=22 681)</td>
<td>33.7% (n=22 550)</td>
<td>33.9% (n=23 911)</td>
<td>34.1% (n=24 449)</td>
<td>34.3% (n=24 449)</td>
<td>0.0001</td>
</tr>
<tr>
<td>LMWH plus GPI Ib/IIa</td>
<td>48.9% (n=73 116)</td>
<td>49.6% (n=22 681)</td>
<td>49.9% (n=23 911)</td>
<td>50.0% (n=22 681)</td>
<td>50.1% (n=22 550)</td>
<td>50.3% (n=23 911)</td>
<td>50.5% (n=24 449)</td>
<td>50.7% (n=24 449)</td>
<td>0.0001</td>
</tr>
<tr>
<td>LMWH</td>
<td>74.6% (n=112 593)</td>
<td>75.3% (n=22 681)</td>
<td>75.6% (n=23 911)</td>
<td>75.7% (n=22 681)</td>
<td>75.9% (n=22 550)</td>
<td>76.1% (n=23 911)</td>
<td>76.4% (n=24 449)</td>
<td>76.6% (n=24 449)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Other</td>
<td>11.8% (n=17 859)</td>
<td>11.6% (n=22 681)</td>
<td>11.8% (n=23 911)</td>
<td>11.9% (n=22 681)</td>
<td>12.1% (n=22 550)</td>
<td>12.4% (n=23 911)</td>
<td>12.7% (n=24 449)</td>
<td>13.0% (n=24 449)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>11.8% (n=17 859)</td>
<td>11.6% (n=22 681)</td>
<td>11.8% (n=23 911)</td>
<td>11.9% (n=22 681)</td>
<td>12.1% (n=22 550)</td>
<td>12.4% (n=23 911)</td>
<td>12.7% (n=24 449)</td>
<td>13.0% (n=24 449)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other</td>
<td>11.8% (n=17 859)</td>
<td>11.6% (n=22 681)</td>
<td>11.8% (n=23 911)</td>
<td>11.9% (n=22 681)</td>
<td>12.1% (n=22 550)</td>
<td>12.4% (n=23 911)</td>
<td>12.7% (n=24 449)</td>
<td>13.0% (n=24 449)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>11.8% (n=17 859)</td>
<td>11.6% (n=22 681)</td>
<td>11.8% (n=23 911)</td>
<td>11.9% (n=22 681)</td>
<td>12.1% (n=22 550)</td>
<td>12.4% (n=23 911)</td>
<td>12.7% (n=24 449)</td>
<td>13.0% (n=24 449)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Thrombectomy catheters</td>
<td>39.6% (n=61 586)</td>
<td>39.9% (n=22 681)</td>
<td>40.2% (n=23 911)</td>
<td>40.4% (n=22 681)</td>
<td>40.6% (n=22 550)</td>
<td>40.8% (n=23 911)</td>
<td>41.0% (n=24 449)</td>
<td>41.3% (n=24 449)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Catheterisation laboratory visit and coronary anatomy

<table>
<thead>
<tr>
<th></th>
<th>Total (n=150 116)</th>
<th>2005 (n=15 730)</th>
<th>2006 (n=19 612)</th>
<th>2007 (n=21 183)</th>
<th>2008 (n=22 681)</th>
<th>2009 (n=22 550)</th>
<th>2010 (n=23 911)</th>
<th>2011 (n=24 449)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ejection fraction % (SD)</td>
<td>46.6 (12.6)</td>
<td>46.6 (12.7)</td>
<td>46.6 (12.6)</td>
<td>46.6 (12.6)</td>
<td>46.7 (12.5)</td>
<td>46.8 (12.5)</td>
<td>46.9 (12.5)</td>
<td>46.9 (12.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Radial access</td>
<td>26.1% (n=39 157)</td>
<td>26.6% (n=15 730)</td>
<td>27.0% (n=19 612)</td>
<td>27.4% (n=21 183)</td>
<td>27.8% (n=22 681)</td>
<td>28.1% (n=22 550)</td>
<td>28.4% (n=23 911)</td>
<td>28.7% (n=24 449)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
of ejection fraction (about 25%) and glomerular filtration rate (about 8% of creatinine assessments before and after procedure). In both cases, values for these variables were imputed for missing data through a standardised procedure. In both cases, values for these variables were imputed for missing data through a standardised procedure.}

**Statistical analysis**

We compared baseline demographic and clinical characteristics of patients undergoing pPCI across years. For these analyses, we defined 7 years in the study period: 2005, 2006, 2007, 2008, 2009, 2010, and 2011. We compared continuous variables across years using analysis of variance and categorical variables with the \( \chi^2 \) test. We plotted the annual D2B time in the pPCI population against unadjusted in-hospital mortality for each year to examine the population-level relation across years. Next, we plotted patient-specific D2B times (grouped by deciles) against unadjusted in-hospital mortality within each of the periods to examine the individual patient-level relation within years. Fitted linear trend lines were used to aid with visual comparison.

We then built multilevel logistic regression models to estimate both individual and population-level components of the association between D2B time and mortality, after accounting for differences in recorded patient and procedural factors. Models simultaneously included as predictors of mortality, the patient-specific D2B time (ie, the D2B time the individual patient experienced), and the annual D2B time (ie, the median D2B time in the year in which the PCI for that patient was done). Neither of these variables was centred before inclusion. The coefficient estimate for patient-specific D2B time represented the individual-level relation between D2B time and mortality after accounting for other factors, including annual D2B time. The coefficient estimate for annual D2B time represented the population-level relation or secular trend between decreasing average D2B time and mortality after accounting for other factors, such as patient-specific D2B time. We also constructed models that only included annual D2B time for every patient. The coefficient estimate for annual D2B time obtained from this model represented the aggregate relation that consisted of both the individual and population-level relations of D2B time.

**Role of the funding source**

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. BKN, YW, and HMK had full access to all the data in the study, and all authors had final responsibility for the decision to submit for publication.

**Results**

**Study sample**

For this study, we identified 512,321 catheterisation laboratory visits associated with STEMI between Jan 1, 2005, and Dec 31, 2011. We excluded patients not undergoing pPCI (n=52,372), transfer patients for pPCI (n=129,579), patients with D2B times less than 15 min or

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**Table 1: Patients characteristics stratified by calendar year**

<table>
<thead>
<tr>
<th></th>
<th>2005 (n=15,730)</th>
<th>2006 (n=19,612)</th>
<th>2007 (n=21,183)</th>
<th>2008 (n=22,681)</th>
<th>2009 (n=22,550)</th>
<th>2010 (n=23,911)</th>
<th>2011 (n=24,440)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>D2B time and outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual D2B time, median (IQR)</td>
<td>69 (52–89)</td>
<td>86 (65–109)</td>
<td>80 (61–102)</td>
<td>72 (55–90)</td>
<td>68 (52–85)</td>
<td>66 (50–83)</td>
<td>64 (48–81)</td>
<td>62 (47–80)</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>7062 (4.7%)</td>
<td>751 (4.8%)</td>
<td>888 (4.5%)</td>
<td>996 (4.7%)</td>
<td>1045 (4.6%)</td>
<td>1047 (4.6%)</td>
<td>1103 (4.6%)</td>
<td>1232 (5.0%)</td>
</tr>
<tr>
<td>6-month mortality</td>
<td>520 (13.5%)</td>
<td>509 (13.3%)</td>
<td>596 (13.2%)</td>
<td>687 (14.1%)</td>
<td>803 (13.6%)</td>
<td>818 (13.7%)</td>
<td>837 (13.3%)</td>
<td>880 (13.4%)</td>
</tr>
</tbody>
</table>

Data are n (％) or mean (SD％), unless otherwise indicated. Most variables are categorical. CAD=coronary artery disease. BMI=body-mass index. MI=myocardial infarction. CHF=congestive heart failure. CPR=cardiopulmonary resuscitation. TIMI=thrombolysis in myocardial infarction. D2B=door-to-balloon. STEMI=ST-segment elevation myocardial infarction. CMS=Centers for Medicare & Medicaid Services.

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**Articles**

The approach used in previous studies including the NCDR CathPCI Registry. We included random intercepts for each hospital to account for the clustering effects of procedures within hospitals. We built analogous models for both in-hospital and 6-month mortality. We generated odds ratios (ORs) and 95% CIs for mortality for reporting. For patient-specific D2B times, we reported these ORs as a change per 10 min decrease whereas we reported annual D2B time as a change per year. We used the SAS software version 9.2 (Cary, NC, USA) for all analyses. We used the SAS GLIMMIX procedure for all analyses related to the multilevel models.
more than 3 h (n=45 391), and patients at hospitals that
did not consistently report data in each year across the
study period (n=134 863).

150 116 pPCI procedures were done in 146 940 patients
at 423 hospitals during Jan 1, 2005, to Dec 31, 2011;
37 954 procedures in 37 445 patients aged 65 years or
older at 359 hospitals were also available in the CMS
claims data-matched cohort for the assessment of
6-month mortality. Annual D2B times in the pPCI
population decreased significantly from a median of
86 min (IQR 65–109) in 2005 to 63 min (IQR 47–80) in
2011 (p<0·0001). Overall, unadjusted in-hospital mort-
ality was 4·7% in the total cohort and unadjusted
6-month mortality was 13·5% in the cohort of patients
aged 65 years or older (table 1). During this time period,
risk-adjusted in-hospital mortality rose non-signifi-
cantly (from 4·7% to 5·3%; p=0·06) whereas risk-adjusted
6-month mortality increased signifi cantly (from 12·9%
to 14·4%; p=0·001).

Table 1 shows a full list of patient and procedural factors,
stratifi ed by year. We noted signifi cant, but modest
differences across years in several demographic features
(eg, age >75 years) and clinical features (eg, diabetes
mellitus, history of PCI, and New York Heart Association
[NYHA] Class IV status) in the pPCI population.

Treatment patterns associated with pPCI also differed
signifi cantly across years with some large differences
noted. We also noted a substantial increase in the total
number of patients treated every year at these 423 hospitals:
overall, 55% more patients underwent pPCI in 2011 than
Rates of direct thrombin inhibitor use increased more
than four-fold from 10% to 42% and manual thrombectomy
use rose from 12% to 39%, whereas use of glycoprotein
IIb/IIIa dropped from 73% to 45%, and drug-eluting stent
use dropped from 76% to 53% (table 1).

The individual-level relation between D2B times and
mortality showed that decreases in patient-specifi-
c D2B times were consistently associated with decreased
in-hospital mortality within each year of the study period (figure 1). The population-level relation showed little correlation between decreases in annual D2B times and mortality across years. Additionally, an increase in mortality was noted across years, as the fitted linear trend lines are generally higher during later years, and predominately diverge during later deciles of patient-specific D2B times. For example, the last decile of patient-specific D2B times in 2005, was 154 min with an unadjusted in-hospital mortality of 8.1% whereas the last decile of patient-specific D2B times in 2011, was 127 min with an unadjusted in-hospital mortality of 11.0% (figure 1). Lastly, longer delays in patient-specific D2B time were associated with increasing mortality over the years of the study. For example, patients with D2B times longer than 90 min had an in-hospital mortality of 6.1% in 2005 and of 10.3% in 2011.

Table 2 displays results of estimates from the multilevel models that simultaneously examined associations between D2B time and mortality at the individual patient level and the population level (the appendix shows full model results that include all of the variables accounted for during risk-adjustment; the c-statistics for the models for in-hospital mortality were 0.893 and for 6-month mortality 0.812). Adjusted for observed patient and procedural factors and population D2B times, reduced patient-specific D2B times over the study period were consistently associated with reduced in-hospital mortality and 6-month mortality (table 2, figure 2). However, decreases in annual D2B times were associated with increased risk-adjusted in-hospital mortality and significantly higher 6-month mortality, representing worsening mortality risk across years of the study period (table 2). Figure 3 displays secular trends in predicted in-hospital and 6-month mortality for the pPCI population across years, keeping all other covariates constant, including patient-specific D2B times. In models that only included annual D2B time for every patient, we found that the aggregate relation (comprised of both the individual and population-level relations of D2B time) suggested no association with either in-hospital mortality (0.99; 95% CI 0.96–1.02; p=0.54) or 6-month mortality (0.99; 0.96–1.03; p=0.78).

Discussion

Previous studies linked a decrease in patient-specific D2B times with a decrease in mortality after pPCI at the individual level. However, recent decreases in annual D2B times at the population-level have not been associated with decreases in mortality as predicted (panel). The purpose of this study was to offer additional insights on this seemingly paradoxical finding and its implications for STEMI care. Through multilevel models, which simultaneously estimated both the individual and population-level components of the association of mortality with D2B time, we uncovered several key findings. First, we confirmed that recent decreases in annual D2B times at the population-level have not been associated with decreases in mortality as predicted (panel). The purpose of this study was to offer additional insights on this seemingly paradoxical finding and its implications for STEMI care. Through multilevel models, which simultaneously estimated both the individual and population-level components of the association of mortality with D2B time, we uncovered several key findings. First, we confirmed that recent decreases in annual D2B times at the population-level have not been associated with decreases in mortality as predicted (panel). The purpose of this study was to offer additional insights on this seemingly paradoxical finding and its implications for STEMI care. Through multilevel models, which simultaneously estimated both the individual and population-level components of the association of mortality with D2B time, we uncovered several key findings. First, we confirmed that recent decreases in annual D2B times at the population-level have not been associated with decreases in mortality as predicted (panel). The purpose of this study was to offer additional insights on this seemingly paradoxical finding and its implications for STEMI care. Through multilevel models, which simultaneously estimated both the individual and population-level components of the association of mortality with D2B time, we uncovered several key findings. First, we confirmed that recent decreases in annual D2B times at the population-level have not been associated with decreases in mortality as predicted (panel). The purpose of this study was to offer additional insights on this seemingly paradoxical finding and its implications for STEMI care. Through multilevel models, which simultaneously estimated both the individual and population-level components of the association of mortality with D2B time, we uncovered several key findings. First, we confirmed that recent decreases in annual D2B times at the population-level have not been associated with decreases in mortality as predicted (panel). The purpose of this study was to offer additional insights on this seemingly paradoxical finding and its implications for STEMI care. Through multilevel models, which simultaneously estimated both the individual and population-level components of the association of mortality with D2B time, we uncovered several key findings. First, we confirmed that recent decreases in annual D2B times at the population-level have not been associated with decreases in mortality as predicted (panel). The purpose of this study was to offer additional insights on this seemingly paradoxical finding and its implications for STEMI care. Through multilevel models, which simultaneously estimated both the individual and population-level components of the association of mortality with D2B time, we uncovered several key findings. First, we confirmed that recent decreases in annual D2B times at the population-level have not been associated with decreases in mortality as predicted (panel). The purpose of this study was to offer additional insights on this seemingly paradoxical finding and its implications for STEMI care. Through multilevel models, which simultaneously estimated both the individual and population-level components of the association of mortality with D2B time, we uncovered several key findings. First, we confirmed that recent decreases in annual D2B times at the population-level have not been associated with decreases in mortality as predicted (panel). The purpose of this study was to offer additional insights on this seemingly paradoxical finding and its implications for STEMI care. Through multilevel models, which simultaneously estimated both the individual and population-level components of the association of mortality with D2B time, we uncovered several key findings. First, we confirmed that recent decreases in annual D2B times at the population-level have not been associated with decreases in mortality as predicted (panel).
we also showed that shorter patient-specific D2B times are strongly and consistently associated with lower risk-adjusted in-hospital and 6-month mortality at the individual level.

So why have anticipated decreases in mortality over time not occurred in the pPCI population despite reductions in annual D2B time and a consistent association between patient-specific D2B time and outcomes? The results of this study suggest that the most likely explanation is expanding use of pPCI and the changing population of patients with STEMI undergoing the procedure. This is supported by the finding that the annual number of pPCIs reported within this stable cohort of hospitals increased by more than 50% between 2005 and 2011—a period during which estimates of pPCI use grew from 40% to 80% of patients with STEMI in the USA, whereas STEMI incidence decreased nationally. Additionally, we noted that several patient and procedural factors varied across years, with unobserved factors potentially modifying patient case-mix as well. For example, manual aspiration thrombectomy and bivalirudin use increased by roughly four times in the pPCI population during this study period, and whether (or how) these changes affected outcomes is unclear since clinical trials of these therapies have reported mixed results. Lastly, we noted increasing mortality over the study period in patients with the longest D2B times. We postulate that some of these patients might have not reached the cardiac catheterisation laboratory in earlier years when STEMI systems of care were less common, a phenomenon Terkelsen and colleagues have referred to as the survivor-cohort effect. Thus, the increased mortality of this high-risk cohort might offset gains in patients with shorter D2B times.

These findings have several implications for patients and the cardiology community. The results caution against misinterpretation of the absence of association between decreasing annual D2B times and mortality at a population level as evidence that improvements in patient-specific D2B time have not affected mortality at an individual level. Such an interpretation, as asserted in a recent review of this topic with a more contemporary Medline search using the search terms “door-to-balloon time” and “mortality”. Generally, we found that longer door-to-balloon times have been correlated with worse outcomes in several, but not all, reports that have used observational data. Many reports have suggested that delays might be most important early after symptom onset (eg, within first 2–3 h) or in high-risk patients (eg, cardiogenic shock). Others have raised the issue that worse outcomes due to delays might largely result from confounding—that is, high-risk patients need stabilisation and have longer door-to-balloon times than do low-risk patients. In this context, a recent study suggested that contemporary decreases in annual D2B times in the population undergoing primary PCI have not been associated with temporal improvements in mortality. This population-level association has been construed as suggesting shorter door-to-balloon times in individual patients have not improved care—a potential misinterpretation consistent with an ecological fallacy.

Interpretation

The goal of this retrospective study was to unravel the association between D2B time and mortality at both the population level and individual level simultaneously. We postulated that the changing population of patients contributed to secular trends toward an increasing mortality risk, despite consistently lower mortality in individual patients with shorter D2B times. For this study, we used data between Jan 1, 2005, and Dec 31, 2011, in the National Cardiovascular Data Registry (NCDR) CathPCI Registry. By contrast with the recent study discussed above that examined contemporary reductions in annual D2B times at the population level only, we built multilevel models to assess the relation between D2B time and in-hospital and 6-month mortality that included both individual and population-level components of this association. Overall, our findings revealed that shorter D2B times were consistently correlated with lower mortality at the individual level within every year of our study period, whereas secular trends suggested an increased mortality risk over time at the population level. Thus, the absence of association of annual D2B time and changes in mortality at the population level should not be interpreted as an indication of its individual-level relation in patients with STEMI undergoing primary PCI.

Additionally, this study highlights the importance of an open science approach and reproducible research, a growing movement in other fields that is also gaining traction in medicine. We had the opportunity to do these analyses because of access to the same data sources used in a previous study also supported by the NCDR CathPCI Registry. This access allowed us to build on the earlier work using more years of data and long-term outcomes. However, it also eliminated the possibility that differences in the findings we report here merely portrayed variability in data collection methods, study populations, or health-care systems. These same data sources were made available to us from the NCDR CathPCI Registry with funds also provided to perform these additional analyses. The process itself shows the value of a collaborative research framework that is aimed to advance scientific progress through an iterative process for the ultimate benefit of patients and clinicians.

The study findings should be interpreted with the following limitations in mind. First, the inference of a causal relation between shorter patient D2B times and
lower mortality cannot be proven conclusively by this study, or any other study based on observational data. However, the individual-level relation we noted lends support to the causal hypothesis that ischaemia time affects outcomes. Additional work will be needed to examine how this relation extends to other key components of total ischaemia time, such as time from symptom onset to first medical contact, and use of pre-hospital electrocardiography and emergency medical services. All of these areas are logically becoming the next stage for focus as D2B times have dropped substantially in recent years and recognition of the importance of system delay has grown.11

Second, the risk-adjustment methods we used have several limitations, some of which, in fact, might help explain the seemingly paradoxical results we discuss. We used the NCDS PCI risk model to be consistent with a previous study,12 but this risk model was developed in a broad population of patients that mainly included non-emergent PCI.22 It might not capture all the patient and procedural factors that changed in the pPCI population over time, and more recent models have been developed incorporating better variable definitions around high-risk patients. We unfortunately could not use these newer models as such information was inconsistently available over the study period.

Third, these hospitals that consistently participated in the NCDS CathPCI Registry over this study period might not be representative of all hospitals performing PCI either in the USA or worldwide, although we have no reason to suspect that the clinical association between D2B time and outcomes would differ for patients at these centres. Fourth, we provide data only until 2011 even as the use of pPCI continues to grow. Fifth, evidence exists that the relation between time-to-treatment and outcomes in STEMI is non-linear with benefits of reperfusion diminishing over time.16,17 Estimation of per-minute survival benefits made directly from our data and over a broad range of delays should be done cautiously.

Finally, this study cannot determine all of the specific reasons for rises in in-hospital mortality or 6-month mortality for the pPCI population over time. The results indicate, however, expansion in the pPCI population and substantial changes in treatment and patient characteristics over time. The population-level trend in outcomes therefore should not be taken as evidence against the clinical benefits of pPCI, as established in clinical trials.18 The expanded use of pPCI in later years in a larger number of patients with STEMI, particularly in the USA, indicates its use in those who would have previously received fibrinolysis or no reperfusion therapy with a potentially increased risk for worse outcomes. However, we cannot comment on whether this policy is appropriate or effective for a population, especially where resources required for pPCI might differ and alternative therapeutic options exist (eg, pharmacoinvasive strategy with fibrinolytic therapy followed by non-emergent PCI).

In conclusion, we noted that decreases in D2B times were consistently associated with decreases in in-hospital and 6-month mortality in patients with STEMI undergoing pPCI. However, mortality has not decreased and might even be increasing over time in the growing subset of patients with STEMI undergoing pPCI, despite reductions in annual D2B time. This finding seems to indicate secular trends in the pPCI population toward increased mortality risk in later years that coincides with expansion in the use of the procedure during STEMI, as well as changes in patient and procedural factors. These findings highlight the importance of continued vigilance with D2B times and caution against misinterpretation of the absence of association between annual D2B time and changes in mortality at the population level as an indication of its individual-level relation in patients with STEMI.

Contributors
All authors were responsible for the critical revision of the work for important intellectual content and gave final approval of the version to be published. BKN and HMK were responsible for conception and design of the work; the acquisition, analysis, and interpretation of the data; and the drafting of the report. S-LTN was responsible for conception and design of the work, and the analysis and interpretation of the data. YW was responsible for design of the work and the analysis and interpretation of the data. TPH was responsible for design of the work and the interpretation of the data. JEB Jr was responsible for interpretation of the data. EHB was responsible for interpretation of the data. JCM was responsible for interpretation of the data.

Declaration of interests
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