Door-to-Balloon Time in Primary Percutaneous Coronary Intervention Predicts Degree of Myocardial Necrosis as Measured Using Cardiac Biomarkers

Reduced door-to-balloon time in primary percutaneous coronary intervention for the treatment of ST-elevation myocardial infarction has been associated with lower cardiac mortality rates. However, it remains unclear whether door-to-balloon time is predominantly a surrogate for overall peri-myocardial infarction care and is not independently predictive of outcomes, particularly when differences in door-to-balloon time have narrowed and previous studies have contained myocardial infarction-selection bias.

We analyzed 179 consecutive patients who presented emergently at our cardiac catheterization laboratory with ST-elevation myocardial infarction within 12 hours of symptom onset and who underwent primary percutaneous coronary intervention within 3 hours of presentation. Our curve estimation regression model used the natural logarithm (ln) of area under the curve (AUC) of creatine kinase to evaluate the effect of door-to-balloon time on cardiac biomarker levels. We correlated ln (AUC–creatinine kinase) with improvement of left ventricular ejection fraction at follow-up and with the intermediate-term mortality rate.

Median door-to-balloon time was 87 minutes (interquartile range, 65–113 min). The ln (AUC–creatinine kinase) correlated significantly with door-to-balloon time (r=0.2, P=0.02). Upon propensity-score analysis, door-to-balloon time remained a significant independent predictor of ln (AUC–creatinine kinase) (β=0.15, P=0.03). Upon use of a Cox regression model, ln (AUC–creatinine kinase) independently predicted death (P=0.04) and recovery of left ventricular function (P=0.001) at follow-up (mean, 14 mo).

Longer door-to-balloon time independently predicts increased myocardial cell damage, and ln (AUC–creatinine kinase) predicts improvement in left ventricular systolic function and intermediate-term death after ST-elevation myocardial infarction. (Tex Heart Inst J 2010;37(2):161-5)

Primary percutaneous coronary intervention (PCI) is the preferred method of treatment for ST-elevation myocardial infarction (STEMI) if it can be performed in a timely manner. The American College of Cardiology/American Heart Association guidelines for the treatment of STEMI state that PCI is the favored approach if an institution can achieve a door-to-balloon time (DBT) of no longer than 90 minutes.1 This benchmark time is derived from multiple studies that show that shorter DBTs are associated with improved clinical outcomes.2-14 However, nearly all of these studies have been multicenter trials, which makes it unclear whether DBT is a surrogate of volume and overall institutional expertise rather than an independent predictor of outcomes. It has been shown that high-volume cardiac-care institutions have shorter DBTs, which may drive the primary results of multicenter data.15 Primary PCI volume also strongly correlates with post-myocardial infarction (MI) survival. Since all-cause death is typically the endpoint and is a variable that often depends upon overall quality of care in STEMI, institutional expertise in MI management is a strong confounder and a hidden predictor in these studies. For instance, when comparing off-hours care with weekday care (during which in-hospital MI care would be similar within the same institution), previous studies have reported similar outcomes despite significantly longer DBTs in the off-hours patient groups.16,17 More-
over, many of these trials have included patients with DBTs of longer than 3 hours, which likely adds MI-selection bias.

In this study, we have considered the amount of myocardial necrosis, as measured by the creatine kinase (CK) area under the curve (AUC), to be the most accurate measure of the direct, independent, and immediate benefit of reduced DBT. Moreover, by analyzing outcomes from a single institution and narrowing the criteria to include only truly emergent STEMI cases with early intervention, we have eliminated both the confounder of the treating institution and that of MI-selection bias. We sought to determine whether DBT is independently predictive of myocardial necrosis after STEMI and whether that myocardial necrosis predicts intermediate-term death and recovery of left ventricular ejection fraction (LVEF).

**Patients and Methods**

Using our institution’s PCI registry, we analyzed a study population of 179 consecutive STEMI patients who presented at our emergency department from January 2005 through December 2008 in whom primary PCI was performed. Patients were selected for analysis if their symptoms were of no longer than 12 hours’ duration and their DBT was shorter than 3 hours. Patients were included only when there was documented electrocardiographic evidence of ST-segment elevations in leads V1 and V2 (with R>S in lead V1 or V2), or a documented new left bundle branch block. Serial, timed CK levels were obtained for all patients and plot-fitted, and the AUC was integrated and measured. A curve estimation regression model using the natural logarithm (ln) of AUC was used to evaluate the effect of DBT on the cardiac biomarker level of CK. Angiographic and clinical variables, including the presence of multivessel coronary artery disease (defined as ≥2 epicardial vessels with stenoses ≥70%), baseline LVEF on ventriculography, infarct location (anterior or other), and Thrombolysis in Myocardial Infarction (TIMI) risk score for STEMI were determined for 79% of the patients. The median DBT was 87 minutes (interquartile range, 65–113 min) and the mean TIMI STEMI risk score was 3.6 ± 2.6. Figure 1 shows the relationship between DBT and ln (AUC–CK), and the significant, linear correlation of ln (AUC–CK) with respect to DBT (r=0.2, P=0.02). Figure 2 shows the mean ln (AUC–CK) for the DBT quartiles. Upon propensity-score analysis with

**Results**

Table I shows the mean TIMI STEMI scores for the 179 patients, and the frequencies and means of the clinical and angiographic variables. Mortality rate data were obtained for all patients, and LVEF recovery data were determined for 79% of the patients. The mean DBT was 87 minutes (interquartile range, 65–113 min) and the mean TIMI STEMI risk score was 3.6 ± 2.6. Figure 1 shows the relationship between DBT and ln (AUC–CK), and the significant, linear correlation of ln (AUC–CK) with respect to DBT (r=0.2, P=0.02). Figure 2 shows the mean ln (AUC–CK) for the DBT quartiles. Upon propensity-score analysis with

**Table I. Baseline Characteristics and Angiographic Variables of the 179 Patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yr</td>
<td>62 ± 14</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>70</td>
</tr>
<tr>
<td>Mean baseline LVEF</td>
<td>0.42 ± 0.10</td>
</tr>
<tr>
<td>Mean recovery of LVEF</td>
<td>0.09 ± 0.11</td>
</tr>
<tr>
<td>Multivessel CAD, %</td>
<td>63</td>
</tr>
<tr>
<td>Anterior infarct, %</td>
<td>45</td>
</tr>
<tr>
<td>Shock, %</td>
<td>4</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>16</td>
</tr>
<tr>
<td>Mean body surface area, m²</td>
<td>1.92 ± 0.28</td>
</tr>
<tr>
<td>Mean TIMI STEMI score</td>
<td>3.6 ± 2.6</td>
</tr>
<tr>
<td>DBT, min (median, min)</td>
<td>87 (65–113)*</td>
</tr>
<tr>
<td>CPT, min (median, min)</td>
<td>120 (60–255)*</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; CPT = chest pain-to-presentation time; DBT = door-to-balloontime; LVEF = left ventricular ejection fraction; STEMI = ST-elevation myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction

*Interquartile range, 25%–75%

Values are presented as number, percentage, or mean ± SD.
multiple linear regression of variables (including CPT, multivessel disease, anterior infarct and hemodynamic status, and TIMI STEMI risk score), DBT remained a significant independent predictor of ln (AUC–CK) (β=0.15, P=0.03), as did CPT (β=0.13, P=0.05). Table II shows the standardized coefficients of the model (β). Upon the use of a multivariate Cox regression model, ln (AUC–CK) was a significant independent predictor of recovery of LVEF (P=0.001) and of death (P=0.04) at a mean follow-up time of 14 months (Table III).

![Fig. 1](image1.png) Curve estimation model of the natural logarithm of the area under curve (ln [AUC]) of creatine kinase versus door-to-balloon time.

![Fig. 2](image2.png) Categorical relationship of the natural logarithm of the area under curve of creatine kinase (ln [AUC–CK]) versus door-to-balloon time (DBT).

**Discussion**

Our analysis is the first to rigorously evaluate the direct predictive value of DBT on myocardial necrosis, as measured by the AUC of CK, by avoiding biases due to quality of care, institutional expertise, and PCI volume. The lower ln (AUC–CK) observed in patients with shorter DBTs translates into an improvement of LVEF at follow-up and to a reduction in the intermediate-term mortality rate.

Substantial resources have been used by PCI centers to improve outcomes in STEMI, with a particular emphasis on DBT. Door-to-balloon time is easily measurable, and it has been used as a marker of quality of care. The preponderance of the clinical evidence regarding treatment times in STEMI suggests that a shorter DBT translates directly into a more favorable outcome. Numerous studies have shown a correlation between DBT and death. The “time is myocardium” mantra makes intuitive sense, because it is logical to conclude that the more quickly an artery can be opened and the coronary flow restored, the less myocardial damage will occur. This correlation is nearly indisputable, but the presence of a strong direct causation between DBT and outcomes is less clear, particularly if differences in DBT are narrowed to minutes. All prior DBT trials have been retrospective studies that have involved large, multicenter databases, or they have been post hoc analys-
s of randomized trials. The ethics of randomizing patients to a delayed-treatment approach in STEMI are clearly prohibitive, so our data must come from the existing analyses. The results enable us to conclude that cases with short DBTs are associated with superior outcomes.

Nevertheless, the desirability of attaining short DBT should not obfuscate the heavy selection bias that is involved in all of the data to date. Confounders are present in these analyses, foremost among which is whether DBT is simply a surrogate variable for institutional level of expertise. Many studies have shown that centers with higher primary PCI volume or greater expertise in STEMI achieve shorter DBTs. It has also been shown that high-volume institutions have lower mortality rates in primary PCI. These same institutions tend to adhere more to clinical guidelines for overall MI management and have lower mortality rates for cardiac disease in general. However, in the models of these studies, a center’s level of expertise is rarely considered to be a confounder—and, as a result, the independent effect of DBT is less certain. For example, an analysis involving only hospitals that participated in the American Heart Association’s “Get With the Guidelines” program (motivated, high-volume centers) showed that patients who presented with MI during off-hours had longer DBTs but similar rates of major acute cardiac events in comparison with patients who presented during weekday hours. This suggests that outcomes have more to do with overall hospital care (which should be similar whether the initial presentation is during off-hours or on a weekday) rather than with DBT itself. Our study involves only a single institution and eliminates this confounder. Scientifically, a more direct endpoint should be used when attempting to define a DBT effect on outcomes. Our endpoint is not tied to confounders and is more strictly a result of time to coronary reperfusion. Moreover, in our analysis, the higher ln (AUC–CK) that resulted from longer time to coronary reperfusion. Even with the introduction of CPT into our model, CPT and DBT both remained strong predictors of myocardial necrosis. The standardized β-coefficients of DBT and CPT are approximately half the weight of those of shock and LVEF, indicating the relative importance of the first 2 variables compared with the second. Of note, our study considered only patients whose DBTs were shorter than 3 hours, unlike other studies, which directly analyzed myocardial necrosis and included outlying DBTs. Despite our tighter temporal distribution of DBT, there was still a significant linear association of DBT to ln (AUC–CK).

Our study has several important limitations. Because the study is a single-center analysis, the sample size is relatively small and may not fully account for the heterogeneity in infarct size, CK levels, infarct location, and differences in TIMI flow among STEMI. Although we factored in body surface area, differences in cardiac size among patients may also contribute to differences in enzyme levels.

References
is timing (almost) everything? Am J Cardiol 2003;92(7):824-6.