Relationship of Symptom-Onset-to-Balloon Time and Door-to-Balloon Time With Mortality in Patients Undergoing Angioplasty for Acute Myocardial Infarction

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IN THE TREATMENT OF ACUTE MYOCARDIAL infarction (MI), rapid time to treatment with thrombolytic therapy and rapid achievement of reperfusion of the infarct-related artery with thrombolytic therapy (the "open artery theory") is beneficial.1-5 Angiographic studies have supported the link between higher 90-minute (but not 180-minute) infarct-related artery patency and improved survival,4,6 suggesting that small differences in time to achieving reperfusion make clinically important differences in mortality. Primary (or "direct") angioplasty has been found to be a useful means of achieving reperfusion in acute ST-elevation MI compared with thrombolytic therapy in randomized clinical trials.7-10 However, no mortality benefit of primary angioplasty over thrombolysis was observed in several registries in which the delays in performing primary angioplasty were longer.11-14 In these studies, the time between hospital arrival and performance of the primary angioplasty, the so-called door-to-balloon time,3 was on average between 2 and 3 hours,11,14 much longer than in the initial clinical trials.7,8 We hypothesized that, in accord with experimental15 and clinical studies,13,14 the more rapidly reperfusion is achieved with primary angioplasty the better the survival, and conversely, that delays in achieving reperfusion would result in higher mortality. Because prior studies of primary angioplasty have involved only 2007 to 130016-18 patients, the delays in performing primary angioplasty were longer.11-14 In these studies, the time between hospital arrival and performance of the primary angioplasty, the so-called door-to-balloon time,3 was on average between 2 and 3 hours,11,14 much longer than in the initial clinical trials.7,8 We hypothesized that, in accord with experimental15 and clinical studies,13,14 the more rapidly reperfusion is achieved with primary angioplasty the better the survival, and conversely, that delays in achieving reperfusion would result in higher mortality. Because prior studies of primary angioplasty have involved only 2007 to 130016-18 pa...
TIME TO ANGIOPLASTY IN ACUTE MI

METHODS

The NRMI-2 was an observational study conducted at 1474 hospitals across the United States between June 1994 and March 1998. The protocol specified that all consecutive patients with the diagnosis of acute MI were to be enrolled, resulting in a total of 767,409 participants. The protocol was approved at each participating institution, by the institutional review board where applicable. Myocardial infarction was defined as a patient history suggestive of MI accompanied by either creatine kinase or creatine kinase-MB fraction at least 2 times the upper limit of normal or electrocardiographic (ECG) evidence of MI. If enzyme or ECG data were inconclusive, alternative enzymatic, scintigraphic, or echocardiographic evidence of MI or an International Classification of Diseases, Ninth Revision, Clinical Modification discharge diagnosis code of 410.00-410.92 also qualified patients for the registry. There were no exclusion criteria.

Patient Population

From the total group of hospitals, 661 had the capability and performed primary angioplasty for acute MI. The population for this analysis was prospectively specified as patients with onset of chest pain outside of a hospital within 24 hours, which was associated with ST-segment elevation of at least 0.1 mV in 2 or more ECG leads or left bundle-branch block, and who underwent primary angioplasty. Data recorded on all patients included demographics, ECG findings, a detailed timeline including time of onset of chest pain, time of arrival at the hospital (“door” time) and time of first balloon inflation of the primary angioplasty procedure (“balloon” time). If the exact time of the first balloon inflation could not be obtained from the chart, the time of the start of the catheterization/angioplasty procedure was recorded.

Outcome Measures

Patients were divided into several pre-specified groups, first by time from MI symptom onset to first balloon inflation and then by door-to-balloon time. Baseline characteristics and mortality rates were examined across these time categories. The primary end point of this analysis was in-hospital mortality.

Statistical Analyses

Univariate analyses were conducted to evaluate differences in baseline characteristics across the different time categories. For these analyses, the Wald χ² test was used to evaluate differences between dichotomous variables. All statistical analyses were performed using SAS statistical software version 6.12. Means were compared using a general linear model (PROC GLM in SAS), which was formally equivalent to an analysis of variance model, and medians were compared using a standard nonparametric median test (NPARIWAY) available in SAS.

Multivariate logistic regression analyses were conducted to evaluate the adjusted effect estimates associated with the symptom-onset-to-balloon and door-to-balloon time variables. For these analyses, multivariate logistic regression models were fit (using PROCLOGISTIC in SAS), for which mortality was the dependent (outcome) variable of interest and the various baseline characteristics were included in these models. Initial logistic regression models were fit using a forward, stepwise automated method. Subsequent logistic regression models were developed to include clinically as well as statistically significant covariates, and to address specific questions of interest regarding subgroups or restricted analyses. Model fit was assessed using the difference in the log-likelihood scores between models.

Two models were developed, one with the time variable of symptom onset to balloon and the second with 2 mutually exclusive time intervals, symptom-onset-to-door time and door-to-balloon time. The final logistic regression models developed to analyze the relationship between symptom-onset-to-balloon and mortality and door-to-balloon time and mortality included the variables shown in Table 1. The 2 models had similar odds ratios (ORs) for the nontime variables, and thus only the model with door-to-balloon time is shown. The OR for symptom onset to door time was 0.99 (95% confidence interval [CI], 0.98-1.01; P = .58). Possible interactions were also examined but no a priori interactions were posited, and inclusion of the possible interactions between the primary exposure and other covariates in the logistic regression model improved the overall fit as evidenced by a statistically significant change in the log-likelihood score.

In addition to the analyses described above, a propensity score analysis was conducted to evaluate the balance of covariates between the exposure groups.

RESULTS

Time From Symptom Onset to Angioplasty

Among the 27,080 patients with acute ST-elevation or left bundle-branch block MI, the median time from onset of chest pain to hospital arrival was 1.6 hours, and the median time from onset of chest pain to primary angioplasty was 3.9 hours. Patients treated earlier were younger and more likely to be male, to have had previous angioplasty, or presented in cardiogenic shock (Table 2). In contrast, those treated later were more likely to be female, diabetic, and transferred from another institution. Although unadjusted mortality was higher in the patients treated later, the multivariate-adjusted odds of in-hospital mortality did not increase over the 24-hour period (Figure 1).

Door-to-Balloon Time

The median door-to-balloon time in this cohort was 1 hour 56 minutes (interquartile range, 1 hour 25 minutes to 2
hours 43 minutes). Only 8% of patients had a door-to-balloon time of 60 minutes or less (Table 3). Patients who underwent primary angioplasty rapidly after hospital arrival were younger and more likely to be male. In contrast, patients with longer door-to-balloon times more often had a contraindication to thrombolytic therapy or were transferred from another institution.

Unadjusted mortality rose from 4.2% to 8.5% with increasing door-to-balloon time (P<.001) (Table 3). Controlling for differences in baseline characteristics, the multivariate-adjusted odds of in-hospital mortality were not significantly increased if door-to-balloon time was 2 hours or less (Figure 1). However, the adjusted odds of mortality were significantly increased by 41% to 62% for patients with door-to-balloon times longer than 2 hours.

### Subgroups and Propensity Score Analysis

No significant interactions by subgroups were observed (Table 4). For the subgroup of 22483 patients eligible for thrombolysis, the increases in mortality by time categories were for 121 to 150 minutes: OR, 1.44 (P=.02); for 151 to 180 minutes: OR, 1.77 (P<.001). Similar increases in mortality were observed when excluding patients transferred from other hospitals (OR, 1.37, P=.02; OR, 1.61, P=.001; and OR, 1.47, P=.006 for the 3 time intervals, respectively). For the 25990 patients without cardiogenic shock, the increases in mortality were similar to the overall group, whereas for the 988 patients in cardiogenic shock, mortality increased more sharply as time increased (for 121-150 minutes: OR, 1.29, P=.41; for 151-180 minutes: OR, 1.85, P=.06; and for >180 minutes: OR, 2.45, P=.003).

A propensity score analysis also was carried out.24-26 In a logistic regression analysis, the adjusted odds of in-hospital mortality were significantly increased if door-to-balloon time was 2 hours or less (Fig-
model analogous to that in Table 1 that also included adjustment for the derived propensity score, the adjusted OR for door-to-balloon time longer than 2 hours (vs <2 hours) was 1.28 (95% CI, 1.13-1.44) (P < .001).

Institutional Volume of Primary Angioplasty

Because the institutional volume of elective angioplasties performed has been shown to influence outcome, a separate multivariate model was run that included variables for the volume of primary angioplasty procedures performed at each hospital, categorized as less than 1 (referent group), 1 to 3, and more than 3 per month. Interestingly, the overall adjusted mortality was lower as institutional volume increased (Figure 2). In the new multivariate model, when accounting for institutional volume, the adjusted odds of mortality for door-to-balloon times longer than 2 hours were similar to the original model.

COMMENT

This study demonstrates that an increase in door-to-balloon time for primary angioplasty is associated with increased mortality. We found that in this cohort of more than 27,000 patients treated with primary angioplasty, the multivariate-adjusted odds of mortality were approximately 40% to 60% higher for longer door-to-balloon times.
higher if the door-to-balloon time was longer than 2 hours. This relationship was observed in thrombolytic-eligible patients and when excluding patients transferred from other hospitals or excluding those in cardiogenic shock. The institutional volume of primary angioplasty cases appeared to independently influence mortality, with higher volume associated with better outcomes.

It thus appears that door-to-balloon time and institutional volume of primary angioplasty are 2 important and modifiable factors relating to survival of patients treated with primary angioplasty. Our data suggest that physicians, hospitals, and health care systems should work to reduce door-to-balloon time, as has been recommended for “door-to-drug” time by the National Heart, Lung, and Blood Institute's National Heart Attack Alert Program, and for primary angioplasty in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of acute MI. Our data support the current guideline recommendation of a door-to-balloon time of 90 ± 30 minutes.

**Pathophysiology**

The importance of rapid reperfusion has been established in experimental models and clinical studies. In thrombolytic therapy, the relative benefit on mortality between tissue-type plasminogen activator and streptokinase is believed to be due to more rapid achievement of early patency in the infarct-related artery (ie, at 60 minutes and at 90 minutes after the start of therapy). Using these findings as a foundation, the relative benefits of rapid vs delayed primary angioplasty can be evaluated. When door-to-balloon time is rapid (eg, 60-80 minutes as in initial trials), nearly 95% of arteries would be patent by 90 minutes after hospital arrival. In contrast, if the door-to-balloon time is 2 hours or longer, as observed over all 4 years in this large multicenter study, and in other registries of current practice, patency would be achieved at the 90-minute point in only 30% to 40% of patients. Thus, door-to-balloon time would have a profound influence on early patency of the infarct-related artery. It is not surprising that there is no difference in mortality comparing thrombolytic therapy with relatively delayed primary angioplasty.

Based on our data, and as suggested by others, it appears that to afford patients the full benefit of primary angioplasty, the door-to-balloon times should be less than 2 hours. If logistical constraints exist (eg, need for transfer to another facility that is too far away to meet this timeline, or nighttime delay in getting the catheterization team onsite), immediate treatment with thrombolytic therapy in patients without contraindications would appear to be the preferred means of reperfusion therapy. (In patients with contraindications to thrombolysis, there is no time cut-off since primary angioplasty is the only option.)

There also is emerging a concept of “facilitated coronary intervention” in which patients are treated with a glycoprotein IIb/IIIa inhibitor, reduced-
dose thrombolytic therapy,46 or both53,57 in the emergency department prior to transporting the patient for primary angioplasty to achieve the benefits of earlier patency.

**Quality-of-Care Indicators**

Recently, door-to-drug time in patients receiving thrombolytic therapy has been adopted as a measure of quality of care by the Joint Commission for Accreditation of Hospitals Organization. A similar measure has been suggested in the ACC/AHA MI guidelines for primary angioplasty, but no data were available to support this consensus.31,32 Our data provide evidence that door-to-balloon time may be a useful marker of quality of care for patients treated with primary angioplasty. In addition, institutional volume of primary angioplasty cases was found to influence mortality in acute MI, similar to observations made in elective angioplasty in other studies.27–29,63 Thus, institutional volume of primary angioplasty may also be a useful indicator of quality of care for hospitals.

**Symptom-Onset-to-Balloon Time**

An unexpected finding of our study was that adjusted mortality was not increased with longer overall time to treatment, whereas several studies of thrombolytic therapy have shown unadjusted2,5,33,34 and multivariate-adjusted37 mortality to be higher with increasing time to treatment. The difference in outcome between the 2 strategies with increasing time from symptom onset may be due to high rates of complete reperfusion achieved by primary angioplasty in these late-presenting patients,18 whereas artery patency is reduced in patients treated later with thrombolysis.38,49 Interestingly, this hypothesis is supported by 2 reports in which primary angioplasty was superior to thrombolysis in patients treated more than 4 hours after symptom onset.49,50 Methodologically, door-to-balloon time may have emerged as predictive while time from symptom onset was not because the latter is a much less precise measure that depends on patient recall. In addition, there may be a difference in ascertainment of outcomes in the 2 cohorts: for the analysis of door-to-balloon, all patients in the cohort analysis are included in the registry, and hence 100% ascertainment of outcome is feasible. On the other hand, for time to treatment, we do not have information in this registry on patients in the catchment areas who had out-of-hospital MI and died prior to hospital arrival. Hence, there may be a survivor-cohort effect, wherein those who present to the hospital after 6 to 12 hours have already survived the highest risk period of death, the first several hours. Thus, the denominator for the symptom-onset-to-balloon analysis is not fully defined, whereas that for the analysis of door-to-balloon time is a complete cohort, lending support to our findings.

**Limitations**

Several limitations of this study should be considered. This large database is an observational study and did not randomize patients to rapid vs slower door-to-balloon times. However, one study has suggested that the development of a critical pathway to reduce door-to-balloon time can improve mortality in primary angioplasty,31 lending support to our observations. Participation in this industry-sponsored registry was voluntary and no independent on-site monitoring of the data was performed. However, computer edit checks of the data were carried out and queries were sent to the research coordinators for clarification. More importantly, the internal validity of the NRMI-2 database has recently been demonstrated31 in a comparison of more than 25,000 patients enrolled in both NRMI-2 and the Cooperative Cardiovascular Project, the latter of which involved rigorous centralized chart review.32 Most hospitals in this cohort are relatively low-volume primary angioplasty sites. However, even when accounting for hospital volume in the multivariate model, the relationship between door-to-balloon time longer than 2 hours and multivariate-adjusted mortality was present. It should be noted, however, that our findings might not apply to “expert” centers with very high angioplasty volume. Nonetheless, this 4-year, multicenter experience, involving 661 (56%) of the 1190 hospitals in the United States that perform angioplasty, provides a good estimate of current practice with primary angioplasty across the country. Finally, other factors that are not captured in this database may influence outcome,28 such as physician experience.10,53,54 and angiographic success.35

**CONCLUSIONS**

In this cohort of more than 27,000 patients treated with primary angioplasty, door-to-balloon time longer than 2 hours was an important factor related to mortality, a finding consistent with the pathophysiology of acute MI and prior studies of time to treatment with thrombolysis. Given the importance of time delays, our data suggest that physicians and health care systems should monitor door-to-balloon times and work to reduce them to less than 2 hours. Furthermore, when clinicians are faced with a patient having an acute MI, these data suggest that door-to-balloon time should be considered when choosing a revascularization strategy.

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