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Impact of Delay in Door-to-Needle Time on Mortality in Patients with ST-Segment Elevation Myocardial Infarction

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Abstract

Fibrinolytic therapy remains the most common reperfusion strategy for patients with ST-segment elevation myocardial infarction (STEMI), particularly in smaller centers. Previous studies evaluated the relationship between time to treatment and outcomes when few patients were treated within 30 minutes of hospital arrival and many did not receive modern adjunctive medications. To quantify the impact of delay in door-to-needle time on mortality in a recent and representative cohort of STEMI patients, we analyzed a cohort of 62,470 STEMI patients treated with fibrinolytic therapy at 973 hospitals that participated in the National Registry of Myocardial Infarction from 1999–2002. We employed hierarchical models to evaluate the independent effect of door-to-needle time on in-hospital mortality. In-hospital mortality was lower with shorter door-to-needle times (2.9% for ≤ 30 minutes, 4.1% for 31–45 minutes, and 6.2% for >45 minutes; $p < 0.001$ for trend). Compared with those experiencing door-to-needle times ≤ 30 minutes, the adjusted odd ratios (OR) of dying were 1.17 (confidence interval (CI) 1.04–1.31) and 1.37 (CI 1.23–1.52; p for trend < 0.001) for those patients with door-to-needle times of 31–45 minutes and >45 minutes, respectively. This relationship

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was particularly pronounced in those presenting within 1 hour of symptom onset to presentation time [OR: 1.25 (CI 1.01–1.54) and 1.54 (CI 1.27–1.87) respectively; p for trend <0.001]. In conclusion, timely administration of fibrinolytic therapy continues to significantly impact mortality in the modern era, particularly in patients presenting early after symptom onset.

Keywords

myocardial infarction; mortality; reperfusion; fibrinolysis; thrombolysis

Introduction

Shorter time from symptom onset to treatment in patients with ST-segment elevation myocardial infarction (STEMI) who are administered fibrinolytic therapy has repeatedly been shown to lower mortality (1–7). As the ability to decrease symptom onset-to-door time is limited (8), national organizations have placed substantial emphasis on decreasing door-to-reperfusion time (9,10). Although primary percutaneous interventions are increasing in frequency, treatment with fibrinolytic therapy remains a more common mode of reperfusion (11,12). To quantify the impact of door-to-needle time on mortality in a recent cohort, we used detailed patient-level data from the National Registry of Myocardial Infarction (NRMI) 3 and 4 (13) for a national cohort of patients with STEMI admitted from 1999 to 2002. This cohort has high rates of evidence-based therapy, including aspirin, beta-blockers and angiotensin-converting enzyme inhibitors (14), with nearly half of patients who receive fibrinolytic therapy treated within the recommended 30-minute door-to-needle time (12).

Methods

We used NRMI, a voluntary acute myocardial infarction (AMI) registry sponsored by Genentech, Inc. (South San Francisco, CA), to define a cohort of patients with STEMI who received acute fibrinolytic reperfusion therapy. The NRMI criteria (13,14) include a diagnosis of AMI according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (code 410.X1) and any of the following criteria: total creatine kinase or creatine kinase MB that was ≥ 2 times the upper limit of the normal range or elevations in alternative cardiac markers; electrocardiographic evidence of AMI; or nuclear medicine testing, echocardiography, or autopsy evidence of AMI. During our study period of January 1, 1999 to December 31, 2002, there were 830,473 AMI admissions in NRMI. Of those, 294,474 were diagnosed with ST elevation of 2+ leads or left bundle branch block. From this cohort, the following patients were excluded sequentially: patients who did not receive primary fibrinolytic therapy, including fibrinolytic therapy times that were negative, missing, or >6 hours ($n=182,406$); patients transferred from another acute care institution ($n=31,879$); patients with time from symptom onset-to-diagnostic electrocardiogram (ECG) that was negative, >6 hours or missing ($n=7,743$); and patients with a diagnostic ECG time that was not the first ECG time, that was >1 hour before admission, or >6 hours after admission ($n=5,189$). In addition, patients treated in hospitals outside the US ($n=22$) or reporting <20 patients over the 4-year time period ($n=4,765$) were excluded. The final cohort included 62,470 patients from 973 hospitals. Mortality status at the time of discharge was known for all patients.

Our outcome was in-hospital mortality and the principal independent variable was the door-to-needle time, which is the time from hospital arrival to administration of fibrinolytic therapy, derived from the corresponding date/time noted in the medical record and recorded in the NRMI case report form. Patients who were transferred to another facility were counted as survivors. Other patient-level variables included age (<65 , $65-79$, ≥ 80 years), sex, race/ethnicity (white, black, Hispanic, other), insurance status, and clinical characteristics. Clinical characteristics

consisted of medical history (current smoker, chronic renal insufficiency, previous AMI, hypertension, family history of coronary artery disease, hypercholesterolemia, congestive heart failure, previous percutaneous transluminal coronary angioplasty, previous coronary artery bypass graft surgery, chronic obstructive pulmonary disease, stroke, angina, diabetes); presentation characteristics (whether a pre-hospital ECG was performed, the admission time of day [day, evening, or night], admission day of week [weekday or weekend], chest pain at presentation, systolic blood pressure, heart rate, heart failure); and the results of the diagnostic ECG (number of leads with ST-elevation, AMI location, ST depression, nonspecific ST/T-wave changes, Q-wave).

To assess the independent effect of door-to-balloon time on in-hospital mortality and of symptom onset-to-door time on in-hospital mortality, we employed a multivariable hierarchical logistic regression model using in-hospital death as the dependent variable. Because NRMH enrolls hospitals that then report information about their patients, we could not assume that patient observations were independent of hospital; assessment of intraclass correlations indicated that variation in both the logarithm of time to treatment ($p = 0.0876$, 95% Confidence Interval (CI) [0.0780, 0.0971]) and mortality ($p = 0.0073$, 95% CI [0.0052, 0.0935]) was partially explained by hospital. Thus, we used hierarchical models to account for clustering of patients within hospitals; a random effect was specified for the main intercept. We replicated the model in each of the 3 strata of symptom onset-to-door time. The stratification variable was not included in the corresponding subgroup model. Because 54% of the patients were transported to another hospital after receiving fibrinolytic therapy (median length of stay for patients transferred to another hospital was 1.1 days; 12% staying ≤ 2 hours), we conducted 3 secondary analyses to assess the robustness of our results. First, we re-estimated the main analysis using a cohort excluding patients transferred to another hospital; next, we repeated this analysis using only patients from hospitals with a transfer rate $\leq 15\%$. Finally, to account for any association between time to fibrinolytic therapy and length of stay that may affect in-hospital mortality, we repeated the analysis using survival models, with censoring for patients who were transferred, with standard errors adjusted for clustering by hospital. Statistical analyses were performed using HLM 6.02 for Windows (SSI, Lincolnwood, IL), and Stata version 9.2 (Stata Corp., College Station, TX).

Results

Table 1 gives demographic, clinical and presentation characteristics of the cohort. Nearly half (47%) of patients were treated within the guideline-recommended 30 minutes (Figure 1). In unadjusted analysis, shorter door-to-needle time was associated with lower in-hospital mortality ($p < 0.001$ for trend) (Figure 2). In-hospital mortality was 8.2% in patients with door-to-needle times > 100 minutes and 2.5% in patients treated within 15 minutes (test for trend, $p < 0.001$). Shorter door-to-needle time was associated with lower in-hospital mortality in all 3 symptom onset-to-door groups (test for trend all $p < 0.001$) (Figure 3). The association of mortality with symptom onset-to-door time was less consistent within the subgroups based on door-to-needle times (Figure 3).

After adjusting for patient characteristics including symptom onset-to-door time, the odds of dying were 1.17 (CI 1.04–1.31) and 1.37 (CI 1.23–1.52; p for trend < 0.001) for those patients with door-to-needle times of 31–45 minutes and > 45 minutes, respectively, compared with those experiencing door-to-needle times ≤ 30 minutes. This higher mortality for delayed door-to-needle times was seen for all 3 subgroups of patients based on symptom onset-to-door time, and was particularly pronounced for those patients presenting within 1 hour, with odds of 1.25 (CI 1.01–1.54) and 1.54 (CI 1.27–1.87) respectively; p for trend < 0.001] (Figure 4). In secondary analyses, the relationship between door-to-needle time and mortality was found in 2 subcohorts, 1 excluding the transferred patients and the other excluding patients from those

hospitals with high (>15%) transfer rates (Table 2). In addition, a similar relationship was seen in the survival analyses, suggesting no substantial effect of length of stay.

Discussion

Fibrinolytic therapy remains the most common form of reperfusion therapy for patients presenting with STEMI (12). In this large, well characterized and recent cohort of patients with STEMI with a high rate of proven therapies, in-hospital mortality was significantly lower for patients treated within shorter door-to-needle times. This association was found regardless of time from symptom onset to hospital presentation, being particularly strong in those presenting within 1 hour of symptom onset. The findings suggest that improving time to fibrinolytic therapy could have an important effect on improving survival rates for patients presenting with STEMI.

Multiple studies evaluating fibrinolytic therapy in patients with STEMI have found improved survival for shorter time from symptom onset to hospital presentation (1,2,6,15,16) and from symptom onset to treatment (including both symptom onset-to-door time and door-to-needle time (3,5). In a meta-analysis (17), the absolute reduction in mortality with the use of fibrinolytic therapy compared with placebo was greatest among patients who presented within 1 hour after symptom onset. The evidence concerning the specific association between door-to-needle time and mortality is less well established. The Global Utilization of Streptokinase and tPA for Occluded Coronary Arteries (GUSTO) trial (15) did find in-hospital mortality to increase with increasing door-to-needle times. However, these patients were highly selected, and the analysis was not adjusted for time to presentation or patient characteristics. In the GUSTO trial, which enrolled patients from 1990–1993, only 7% were treated within 30 minutes of arrival. The Cooperative Cardiovascular Project (CCP) (18) 30-day mortality significantly increased from 12.5% for those treated within 30 minutes, to 14.1% for those treated 31–90 minutes, and 19.9% for those treated after 90 minutes (18). In the CCP, which evaluated patients >65 years old with AMIs in 1994 to 1996, only 22% were treated within 30 minutes. In the first years of NRM, average time from presentation to the administration of fibrinolytic therapy (door-to-needle) decreased from 62 minutes in 1990 to 38 minutes in 1999 (11). In our current NRM cohort (1999–2002), 46% of patients were treated within 30 minutes (12). Thus, although the GUSTO trial and the CCP both showed a clear increase in mortality with increased door-to-needle time, our study confirms this relationship in the current era with much shorter mean door-to-needle time.

We found that when stratified into groups based on door-to-needle time, the association between in-hospital mortality and symptom onset-to-door time was not consistent. The reliability of the time from symptom onset likely explains this lack of consistent association. First, symptom onset time is retrospectively estimated by the patient upon hospital arrival, likely introducing inaccuracy. Secondly, the changing nature of the symptoms may make accurate estimation difficult. Very likely, some patients initially experienced symptoms due to nonocclusive disease or temporarily occlusive disease but presented only when more severe symptoms from total persistent occlusion occurred. In that case, the true time from occlusion to reperfusion would be overestimated. Whether due to patient recall difficulty or pathophysiologic reasons, any inaccuracy in timing estimation would bias the relationship between symptom onset-to-presentation and mortality to the null. More accurate symptom onset times may increase the strength of the relationship between time from symptom onset-to-door as well as the increased importance of door-to-needle time for those presenting earlier.

Though this database is large and has been found to be reasonably generalizable (19), there are limitations. First, more than half of the patients who received fibrinolytic therapy were subsequently transferred to another hospital. We do not have the ability to track the outcomes

of these patients at the second hospital. However, while the magnitude of the relationship between time and outcome may change depending on the cohort inclusion criteria and the analytical method, the pattern of the relationship is robust. Second, although there may be other variables that may confound the relationship between door-to-needle time and mortality, the large size and depth of characterization of our population enabled control for a large number of important clinical variables. Finally, door-to-needle time may be a proxy for general quality of care; the relationship with mortality may reflect unobserved quality measures. In NRMI, we have found that time to reperfusion is not closely associated with performance on other quality indicators such as use of aspirin, beta-blockers or angiotensin-converting enzyme inhibitors (14). In addition, to account for any hospital-level confounding, we used an analytic technique (hierarchical generalized linear model, HGLM) that separates hospital-level effects from patient-level effects.

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60,290 patients included with door-to-needle time ≤ 120 minutes
2,181 patients omitted with door-to-needle time > 120 minutes

Figure 1.
Frequency distribution of door-to-needle times for the entire cohort.

Figure 2.
Door-to-needle time and in-hospital mortality for the entire cohort, $p < 0.001$ for trend.

Figure 3.

In-hospital mortality in subgroups based on door-to-needle time (x-axis across the page) and on symptom onset-to-presentation time (y-axis going into the page). For trend across door-to-needle times, p values all <0.001 . For trend across symptom onset-to-presentation times, p <0.001 for door-to-needle time ≤ 30 minutes, p = 0.031 for door-to-needle time 31–45 minutes, and p = 0.758 for door-to-needle time >45 minutes.

DTN = Door-to-needle time
Reference group is DTN ≤30 minutes

Figure 4.

With DTN <30 minutes as the reference, adjusted odds ratios of in-hospital mortality from delay in reperfusion therapy by symptom onset-to-presentation time. For symptom onset-to-presentation time <1 hour, $p < 0.001$; for symptom onset-to-presentation time 1–2 hours, $p < 0.03$; for symptom onset-to-presentation time >2 hours, $p < 0.02$.

DTN = door-to-needle time

Table 1

Patient Characteristics

Characteristic	(n)	Door to Needle Time (minutes)			In-hospital mortality
		<30 (29,434)	31–45 (15,049)	>45 (17,987)	
Total	62,470	100%			4.1%
Age (yrs)					
<65	36,845	59%	57%	52%	1.4%
65–80	20,516	32%	34%	37%	5.7%
>80	5,109	8%	8%	12%	17.7%
Gender					
Female	18,748	30%	32%	37%	7.0%
Male	43,722	70%	68%	63%	2.9%
Insurance					
Medicare	10,054	16%	17%	19%	7.9%
Medicare + another	11,455	18%	19%	21%	7.4%
Medicare/Medicaid	1,251	2%	2%	3%	9.9%
Commercial	29,107	47%	46%	41%	1.9%
Medicaid	1,593	3%	3%	3%	3.0%
Veterans Administration	301	1%	0%	0%	2.3%
Other	2,644	4%	4%	4%	2.3%
Self	5,581	9%	8%	8%	2.2%
Unknown	484	1%	1%	1%	4.6%
Race/Ethnicity					
White	53,940	86%	86%	84%	4.2%
Black	2,963	5%	5%	6%	3.4%
Hispanic	2,139	3%	4%	4%	4.1%
Other/Unknown	3,428	6%	6%	6%	4.0%
Clinical history					
Heart failure	2,378	4%	4%	6%	14.6%
Hypertension	29,660	48%	49%	52%	4.9%
Diabetes	11,967	19%	20%	24%	6.0%
Smoker	24724	40%	38%	35%	2.1%

Characteristic	(n)	Door to Needle Time (minutes)			In-hospital mortality
		<30	31–45	>45	
Stroke	2,073	3%	4%	4%	10.7%
Percutaneous coronary intervention	6,157	10%	10%	10%	3.3%
Coronary artery bypass graft surgery	4021	6%	7%	8%	6.0%
Chronic obstructive pulmonary disease	5,077	8%	8%	10%	6.9%
Hypercholesterolemia	21,225	34%	35%	33%	2.6%
Hormone replacement therapy	1,778	3%	3%	3%	3.8%
Chronic renal insufficiency	1,234	2%	2%	3%	13.3%
Coronary artery disease	1,9592	31%	31%	29%	2.3%
Angina pectoris	4,485	7%	8%	8%	6.0%
Previous myocardial infarction	10,185	16%	16%	19%	5.4%
Presentation					
Prehospital electrocardiogram	3,416	5%	4%	3%	4.5%
Chest pain	59,285	95%	96%	91%	3.6%
No chest pain	2,525	4%	3%	7%	15.5%
No heart failure	55,945	90%	90%	86%	3.0%
Rales/jugular venous distension	4,536	7%	7%	9%	10.0%
Pulmonary edema	1,323	2%	2%	3%	16.2%
Shock	666	1%	1%	1%	35.9%
Systolic blood pressure <100 mmHg	2,966	5%	4%	4%	14.7%
Systolic blood pressure 100–180 mmHg	53,103	85%	85%	83%	3.6%
Systolic blood pressure >180 mmHg	6,256	10%	11%	13%	2.9%
Heart rate <50 beats/minute	3,365	5%	5%	4%	5.4%
Heart rate 50–100 beats/minute	51,555	82%	83%	80%	3.4%
Heart rate >100 beats/minute	7,378	12%	12%	16%	8.6%
Electrocardiogram					
Left bundle branch block	1,199	2%	2%	3%	11.6%
ST elevation 2 leads	6,447	10%	10%	15%	4.2%
ST elevation 3–4 leads	42,080	67%	68%	65%	3.5%
ST elevation >4 leads	11,815	19%	18%	16%	5.4%
Myocardial infarction location					
Anterior	20,329	33%	33%	35%	5.8%

Characteristic	(n)	Door to Needle Time (minutes)			In-hospital mortality
		<30	31–45	>45	
Inferior	38,746	62%	62%	56%	3.2%
Admission time of day/day of week					
Weekday 8–4pm	20,623	33%	32%	32%	4.0%
Weekday 4pm-midnight	12,709	20%	20%	22%	4.3%
Weekday midnight-8am	10,603	17%	18%	17%	4.2%
Weekend 8am–4pm	8,822	14%	14%	13%	4.3%
Weekend 4pm-midnight	5,397	9%	9%	9%	4.4%
Weekend midnight-8am	4,316	7%	7%	7%	3.5%
Time since symptom onset (hours)					
≤1	21,564	34%	33%	28%	3.7%
>1–2	18,300	29%	29%	27%	3.6%
>2	22,606	36%	38%	45%	5.0%

Table 2

Secondary Analyses to Assess Effect of Patient Transfer on In-hospital Mortality

Door-to-needle time (minutes)	Main Cohort (n=62,470) OR (95% CI)	Cohort excluding patients transferred to a second hospital (n=28,942) OR (95% CI)	Cohort excluding patients from hospitals with transfer rates >15% (n=18,466) OR (95% CI)	Survival Analysis (n=62,470) HR (95% CI)
<30	Reference	Reference	Reference	Reference
31–45	1.17 (CI 1.04–1.31)	1.077 (0.95–1.22)	1.19 (0.99–1.42)	1.12 (1.00–1.25)
>45	1.37 (CI 1.23–1.52)	1.196 (1.07–1.34)	1.39 (1.17–1.64)	1.23 (1.11–1.35)
p-value for trend	<0.001	0.007	<0.001	<0.001

CI, Confidence Interval; HR, Hazards Ratio, OR, Odds Ratio

Each analysis is adjusted for patient characteristics