Published in final edited form as:
Am J Med. 2008 April ; 121(4): 316–323. doi:10.1016/j.amjmed.2007.11.017.

Delay in Presentation and Reperfusion Therapy in ST-Elevation Myocardial Infarction

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Abstract

Background—We studied the relationship between longer delays from symptom onset to hospital presentation and the use of any reperfusion therapy, door-to-balloon time, and door-to-drug time.

Methods—Cohort study of patients with ST-elevation myocardial infarction enrolled in the National Registry of Myocardial Infarction from January 1, 1995 to December 31, 2004. Delay in hospital presentation was categorized into 1 hour intervals as ≤1 hour, >1 to 2 hours, >2 to 3 hours, etc., and >11 to 12 hours. The study analyzed 3 groups: 440,398 patients for the association between delay and use of any reperfusion therapy; 67,207 patients for the association between delay and door-to-balloon time; 183,441 patients for the association between delay and door-to-drug time.

Results—In adjusted analyses, patients with longer delays between symptom onset and hospital presentation were less likely to receive any reperfusion therapy, had longer door-to-balloon times, and had longer door-to-needle times (all $p<0.0001$ for linear trend). For patients presenting ≤1 hour, >1 to 2 hours, and >2 to 3 hours, >9 to 10 hours, >10 to 11 hours, and >11 to 12 hours after symptom onset, the use of any reperfusion therapy were 77%, 77%, 73%, 53%, 50%, and 46% respectively; door-to-balloon times were 99, 101, 106, 123, 125, and 123 minutes respectively; door-to-drug times were 33, 34, 36, 46, 44, and 47 minutes respectively.

Conclusions—Longer delays from symptom onset to hospital presentation were associated with reduced likelihood of receiving primary reperfusion therapy, and even among those treated, late presenters had significantly longer door-to-balloon and door-to-drug times.

Keywords

myocardial infarction; reperfusion; angioplasty; fibrinolysis; quality

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Introduction

Timely reperfusion therapy with fibrinolytic therapy or primary percutaneous coronary intervention reduces infarct size and adverse clinical consequences, including mortality, for patient with ST-elevation myocardial infarction.[1–11] The guidelines state that patients with ST-elevation myocardial infarction who present within 12 hours from onset of symptoms should be treated with reperfusion therapy and target a door-to-balloon time <90 minutes and door-to-drug time <30 minutes.[12] Recently, quality improvement initiatives have focused attention on where hospital delays occur and strategies to reduce door-to-balloon time.[13–14]

Rapid and appropriate treatment with reperfusion therapy, in accordance with the guidelines, requires a consistent approach to all eligible patients. In particular, patients who are eligible for reperfusion therapy but who present later after the onset of symptoms may not elicit the same response from the health care system. According to the guidelines, recommendations for reperfusion therapy are not different for patients with ST-elevation myocardial infarction presenting earlier versus later within the 12 hours interval after the onset of symptoms.[12] However, whether patients presenting later in the interval are less likely to be treated with reperfusion therapy is not known. Moreover, among those who are treated, whether there is less urgency associated with their care, resulting in longer door-to-balloon and door-to-drug times has not been documented. If present, these gaps may contribute to worse outcomes in late presenting patients. Knowledge of these patterns would emphasize the importance of earlier presentation and focus attention on logistical and system issues that contribute to lower use of any reperfusion therapy and longer delays in treatment for patients presenting later after the onset of symptoms.

To address these issues, we undertook a study to evaluate the relationship between longer delays from symptom onset to hospital presentation and the use of any reperfusion therapy, door-to-balloon time, and door-to-drug time among patients with ST-elevation myocardial infarction between 1995 to 2004 from National Registry of Myocardial Infarction. This database is ideally positioned to address this question because it is comprised of contemporary, diverse, and national data.

Methods

Study Design and Sample

The study sample included patients enrolled in National Registry of Myocardial Infarction, a voluntary, prospective registry of patients with acute myocardial infarction, from January 1, 1995 to December 31, 2004. Participating hospitals, data collection methods, verification methods, and reliability have been previously described.[15–16] Criteria for diagnosis of acute myocardial infarction used the *International Classification of Diseases, 9th Revision, Clinical Modifications* discharge diagnosis code of 410.X1 and was confirmed with one of the following criteria: (1) two-fold or greater elevation of cardiac biomarkers; (2) electrocardiogram evidence; and (3) echocardiographic, scintigraphic, or autopsy evidence. Participating hospitals, if required, obtained Institutional Review Board approval for data abstraction.

During our study period from 1995 to 2004, there were 1,926,108 admissions for acute myocardial infarction. The following patients were excluded sequentially: patients who did not have new or presumed new ST-segment elevation in 2 or more leads or left bundle branch block on the first electrocardiogram (n=1,161,187); patients who developed symptoms for acute myocardial infarction after hospital admission date and time (n=14,433); patients who had an unknown time of symptom onset (n=173,051); patients who had a first electrocardiogram time that was not the diagnostic electrocardiogram time for ST-elevation

myocardial infarction (n=71,842); patients who had an unknown time of first electrocardiogram (n=23,268); and patients who had a delay from symptom onset to hospital arrival >12 hours (n=41,929). The remaining group of 440,398 patients with ST-elevation myocardial infarction who presented to the hospital within ≤12 hours from symptom onset comprised our study population for the analysis of the association between delay and use of any reperfusion therapy.

To analyze the relationship between delay in hospital presentation and timeliness of reperfusion therapy, the following patients were additionally excluded from the previous study population: patients who were transferred-in from another hospital (n=98,064) and patients who received reperfusion therapy >12 hours after hospital arrival (n=2,491). Then, patients who did not receive primary percutaneous coronary intervention (n=272,636) were excluded to create a study group of 67,207 patients to analyze the association between delay and door-to-balloon time. Similarly, patients who did not receive fibrinolytic therapy (n=156,402) were excluded to create a study group of 183,441 patients to analyze the association between delay and door-to-drug time.

Data Collection and Measures

Delay in hospital presentation was calculated from the documented date and time of symptom onset to the documented date and time of hospital arrival. Use of any reperfusion was defined as receiving either fibrinolytic therapy or primary percutaneous coronary intervention as a primary reperfusion strategy within ≤12 hours of hospital arrival. Door-to-balloon time was defined as time from hospital arrival to first balloon inflation and door-to-drug time was defined as time from hospital arrival to administration of fibrinolytic therapy. For the outcomes of door-to-balloon time and door-to-drug time, we log transformed the outcome measures and performed parametric analysis because their distributions were skewed. To improve the clinical interpretability of the results, we converted the logged values from the models back to their original units, i.e., minutes, using geometric means[17–18] and simulation with 10,000 reiterations.[19] The geometric mean gives less weight to outlying values and thus better reflects the median as compared with the arithmetic mean.

To evaluate the independent effect of delay in hospital presentation on use of any reperfusion, door-to-balloon time, door-to-drug time, and in-hospital mortality, we adjusted for the following patient and hospital variables. Patient variables included: sociodemographic (age; gender; race/ethnicity classified as white, Black, Hispanic, Asian, and other; and payer type categorized as commercial insurance, Medicare only, Medicare and any other insurance, Medicaid or self pay, and other); medical history (current smoker, diabetes, hypertension, hypercholesterolemia, family history of coronary artery disease, prior myocardial infarction, prior congestive heart failure, prior percutaneous coronary intervention, prior coronary artery bypass surgery, prior stroke, prior angina, absence of chest pain at presentation, congestive heart failure at time of presentation, cardiogenic shock at presentation, systolic blood pressure <90 mmHg at presentation, heart rate >100 beats per minute at presentation); time of day and day of week at presentation (weekdays were defined as Monday to Friday and included daytime from >8am– 4pm, evening from >4pm–12midnight, and night from >12 midnight-8am; weekends were defined as Saturday and Sunday and included daytime from >8am-4pm, evening from >4pm–12midnight, and night from >12 midnight–8am). Hospital variables included: U.S. census region (West, South, Midwest, Northeast), teaching hospitals defined as participation in an accredited residency or fellowship training program, and type of cardiac facilities (interventional, interventional without surgery on site, invasive but not interventional, and non-invasive). All these variables were selected based on their clinical and statistical significance from previous studies.[11,20–21]

Statistical Analyses

For the outcomes of door-to-balloon time and door-to-drug time as a function of delay in hospital presentation, multivariable generalized linear models were constructed for each outcome to estimate the associations between delay in hospital presentation adjusted for all patient and hospital characteristics. The time from symptom onset to hospital presentation was categorized into 1 hour intervals as ≤1 hour, >1 to 2 hours, >2 to 3 hours, etc., and >11 to 12 hours. By introducing 11 dummy variables representing these categories into the generalized linear models (with the first category as reference group), we estimated the unadjusted outcomes and adjusted outcomes in these categories. We constructed the test of overall differences and also linear trend in outcomes among these categories in the models.

For the outcome of use of any reperfusion, multivariable logistic regression models were constructed to estimate the associations between delay in hospital presentation adjusted for all patient and hospital characteristics. The multivariate models were repeated after excluding patients who were transferred in from another hospital and after excluding patients who had documented contraindications to fibrinolytic therapy or who were treated with emergent coronary artery bypass surgery. These results were not reported separately because the direction and magnitude of the effects were similar to the prior analyses and did not change the conclusions.

For the outcome of in-hospital mortality, multivariable logistic regression models were constructed in the group of patients who were treated with primary percutaneous coronary intervention and in the group who were treated fibrinolytic therapy as the primary reperfusion strategy, and the associations between delay in hospital presentation and in-hospital mortality were estimated and adjusted for all patient and hospital characteristics as well as door-to-balloon time or door-to-drug time respectively.

Statistical analyses were performed using SAS versions 9.1 (SAS, Inc, Cary, NC) and Stata version 8.0 (Stata Corp, College Station, TX).

Results

Study Population

Baseline characteristics of the 3 groups, namely for the use of any reperfusion therapy, those treated with primary percutaneous coronary intervention, and those treated with fibrinolytic therapy are shown in Table 1. Patient and hospital characteristics were generally similar for all 3 groups with a majority being younger (age <70 years), men, and white patients. Diabetic patients comprised 18% to 21% and those with prior myocardial infarction comprised 17% to 19%. Patients treated with primary percutaneous coronary intervention were more likely to be treated during weekday daytime hours 8am-4pm (41%) or have cardiogenic shock (3%) as compared with patients treated with fibrinolytic therapy during weekday daytime (29%) or have cardiogenic shock (1%).

Multivariable Analysis of Delay and Use of Any Reperfusion

In adjusted analyses, patients with longer times between symptom onset and hospital presentation were significantly less likely to receive any reperfusion therapy (Figure 1, $p<0.0001$ for linear trend). For early presenters with times from symptom onset to hospital presentation of ≤1 hour, >1 to 2 hours, and >2 to 3 hours, patients with ST-elevation myocardial infarction were treated with any reperfusion therapy in 77% (reference group), 77% (odds ratio 1.0, $p=0.81$), and 73% (odds ratio 0.88, $p<0.0001$) respectively. In late presenters with times >9 to 10 hours, >10 to 11 hours, and >11 to 12 hours, the use of any reperfusion therapy was

53% (odds ratio 0.36, p<0.0001), 50% (odds ratio 0.33, p<0.0001), and 46% (odds ratio 0.27, p<0.0001) respectively.

Multivariable Analysis of Delay and Timeliness of Reperfusion Therapy

In adjusted analyses, among patients who were treated with primary percutaneous coronary intervention, those with longer time from symptom onset to hospital presentation had significantly longer door-to-balloon times (Figure 2, p<0.0001 for linear trend). For early presenters with times from symptom onset to hospital presentation of ≤1 hour, >1 to 2 hours, and >2 to 3 hours, patients were treated with door-to-balloon times of 99, 101, 106 minutes respectively. In late presenters with times of >9 to 10 hours, >10 to 11 hours, and >11 to 12 hours, door-to-balloon times were 123, 125, and 123 minutes respectively.

Among patients who received fibrinolytic therapy, those with longer delay in hospital presentation also had significantly longer door-to-drug times (Figures 3, p<0.0001 for linear trend). For time intervals from symptom onset to hospital presentation of ≤1 hour, >1 to 2 hours, >2 to 3 hours, >9 to 10 hours, >10 to 11 hours, and >11 to 12 hours, patients were treated with door-to-drug times of 33, 34, 36, 46, 44, and 47 minutes respectively.

Multivariable Analysis of Delay and In-hospital Mortality

Among patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention, the time interval from symptom onset to hospital presentation was associated with increased in-hospital mortality even after adjusting for door-to-balloon time (Figure 4, p<0.0001 for linear trend). For early presenters with times from symptom onset to hospital presentation of ≤1 hour, >1 to 2 hours, and >2 to 3 hours, in-hospital mortality rates were 4.9% (reference group), 4.0% (odds ratio 0.82, p<0.0001), and 4.0% (odds ratio 0.76, p<0.0001) respectively. In comparison, late presenters with times >9 to 10 hours, >10 to 11 hours, and >11 to 12 hours had in-hospital mortality rates of 5.4% (odds ratio 0.91, p=0.62), 6.9% (odds ratio 1.2, p=0.34), and 6.6% (odds ratio 1.2, p=0.37) respectively.

Among patients with ST-elevation myocardial infarction treated with fibrinolytic therapy, the time interval from symptom onset to hospital presentation was associated with increased in-hospital mortality even after adjusting for door-to-drug time (Figure 5, p<0.0001 for linear trend). For early presenters with times from symptom onset to hospital presentation of ≤1 hour, >1 to 2 hours, and >2 to 3 hours, in-hospital mortality rates were 4.1% (reference group), 4.1% (odds ratio 0.93, p=0.022), and 4.8% (odds ratio 0.98, p=0.52) respectively. In comparison, late presenters with times of >9 to 10 hours, >10 to 11 hours, and >11 to 12 hours had in-hospital mortality rates of 7.1% (odds ratio 1.5, p<0.0001), 6.7% (odds ratio 1.3, p=0.067), and 6.3% (odds ratio 1.2, p=0.17) respectively.

Discussion

In our study of patients with ST-elevation myocardial infarction spanning a 10 year period (1995–2004), we found that longer time intervals from symptom onset to hospital presentation were associated with reduced likelihood of receiving primary reperfusion therapy, and even among those treated, late presenters had significantly longer door-to-balloon and door-to-drug times. Although guidelines state that patients with ST-elevation myocardial infarction who present within 12 hours after onset of symptoms should be treated with rapid reperfusion therapy, we found longer times to hospital presentation may contribute to downstream hospital delays in administration of reperfusion therapy and consequently, delay may represent a novel risk factor associated with poorer quality of hospital care for ST-elevation myocardial infarction.

Our study is the largest contemporary report of the relationship between time from symptom onset to hospital presentation and subsequent treatment with and timeliness of reperfusion therapy and advances the existing research in several respects. Previous studies have shown that patients with longer door-to-balloon times[6,11], longer door-to-drug times[2], and longer total ischemic times between symptom onset and reperfusion therapy[3,8] were associated with higher in-hospital mortality rates. However, our study is the first to demonstrate the independent effect of longer time intervals from symptom onset to hospital presentation among patients with ST-elevation myocardial infarction. We demonstrated that longer times to hospital presentation were associated with significantly lower use of any reperfusion therapy, longer door-to-balloon times, and longer door-to-drug times. The novel finding from our study is that longer times to hospital presentation is a risk factor for additional downstream hospital delays in treatment with and timeliness of any reperfusion therapy.

Furthermore, among patients treated with primary percutaneous coronary intervention or fibrinolytic therapy, longer times to hospital presentation were associated with increased in-hospital mortality rates, even after adjusting for other clinical factors and door-to-balloon time or door-to-drug time respectively. The high mortality rates observed among patients presenting within <2 hours of symptom onset may represent those who are at highest clinical risk such as those with cardiogenic shock. Despite the survival bias among late presenters (some late presenters who died out of hospital would not be included in this observational registry), there was still a linear trend for increased mortality rates among patients who presented late.

Possible explanations for the relationship between delay in hospital presentation and use of any reperfusion and timeliness of reperfusion therapy include: (a) patients who present early after onset of symptoms may elicit more urgency from providers to initiate reperfusion therapy; and (b) patients who present late may exhibit more atypical or no symptoms which subsequently lead to missed or late diagnosis as well as confusion or reluctance to administer reperfusion therapy. Among patients with ST-elevation myocardial infarction eligible to receive reperfusion, an optimal system of care should not exclude patients from reperfusion therapy or incur incremental delays in door-to-balloon or door-to-drug times simply because of longer times to hospital presentation.

Recently, there is great interest in strategies to reduce door-to-balloon time[13] and to develop systems of care to transfer and increase number of patients who are eligible to receive primary percutaneous coronary intervention across large geographic regions.[14] These innovative approaches have focused on coordinating and streamlining processes within a hospital and between hospital networks to reduce door-to-balloon time. In concert with these initiatives, reliable systems that deliver timely reperfusion to all eligible ST-elevation myocardial infarction patients should be developed regardless of the duration of delay in hospital presentation.[22–23] With the knowledge that delay in hospital presentation negatively impacts use of any and timeliness in administering reperfusion therapy, attention should be focused on logistical and system issues for providers and patients. Providers should seek to eliminate hospital delays in reperfusion therapy for patients who present late after the onset of symptoms. Moreover, it will also be important to understand which patient groups are at greatest risk for longer delays[24–27] as well as to evaluate novel interventions aimed at reducing delays in hospital presentation.

Acknowledgements

Funding: Research supported by grant R01 HL072575 of National Heart, Lung, and Blood Institute.

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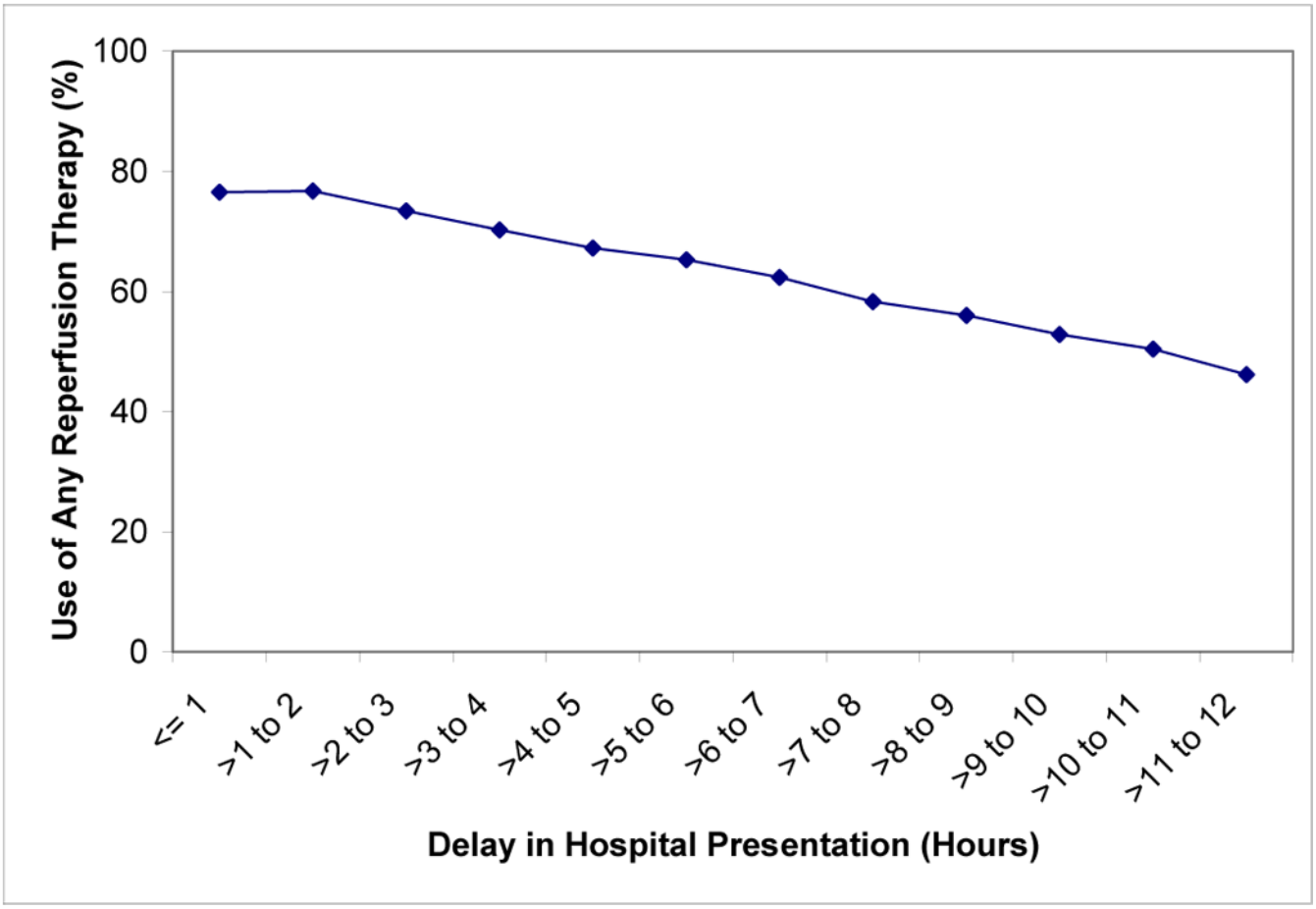


Figure 1.
Delay in Hospital Presentation and Use of Any Reperfusion Therapy

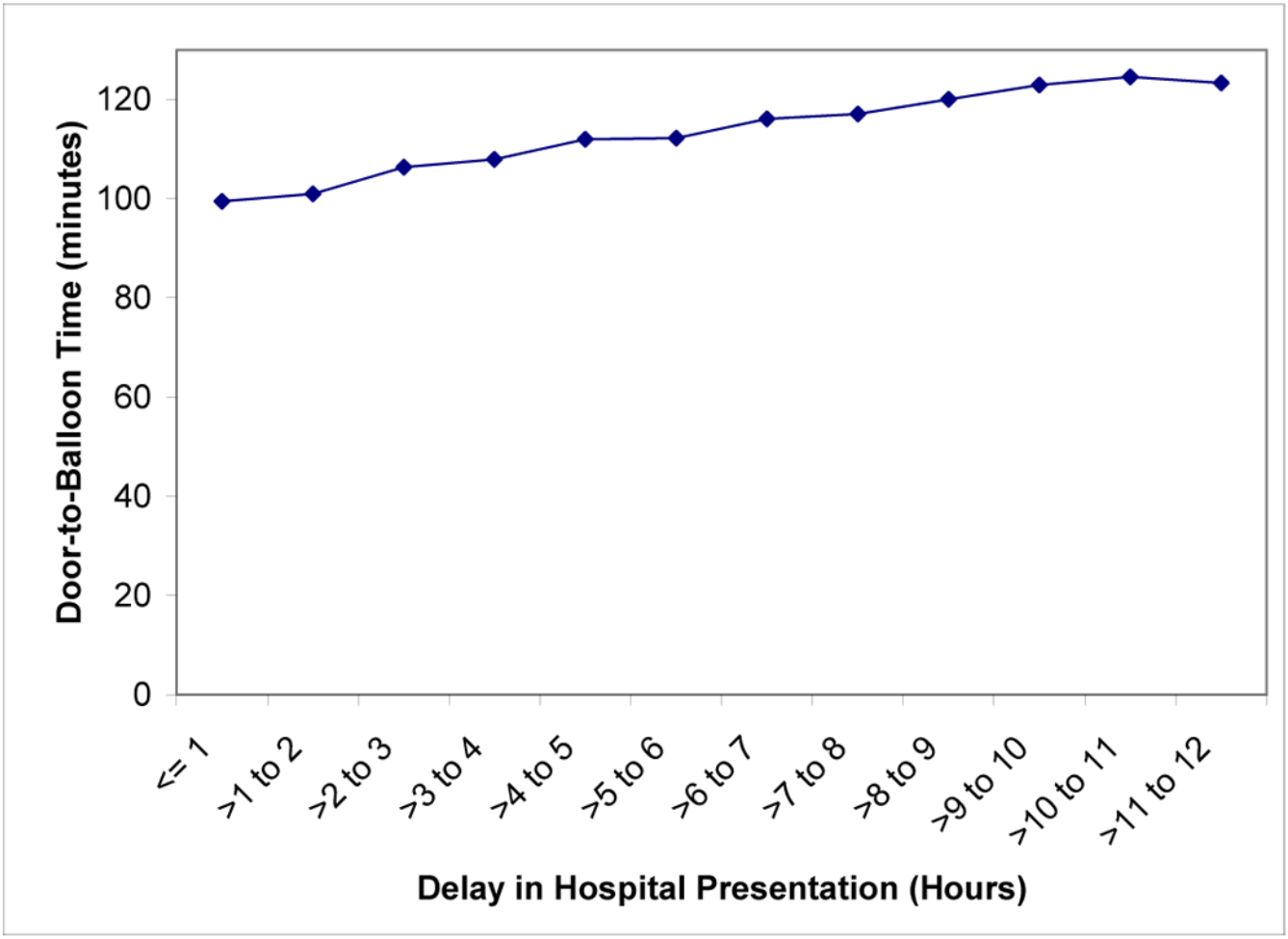


Figure 2.
Delay in Hospital Presentation and Door-to-Balloon Time

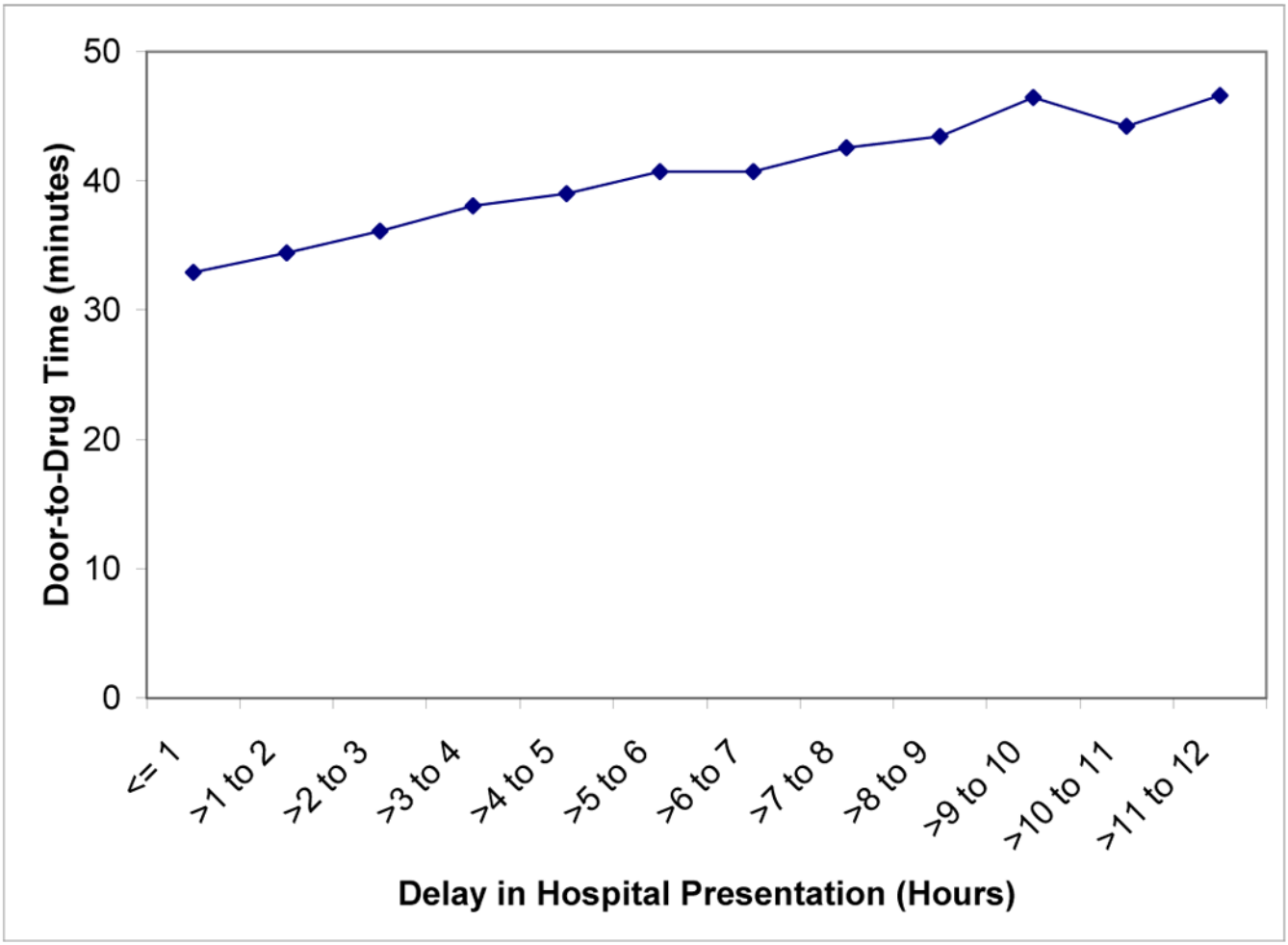
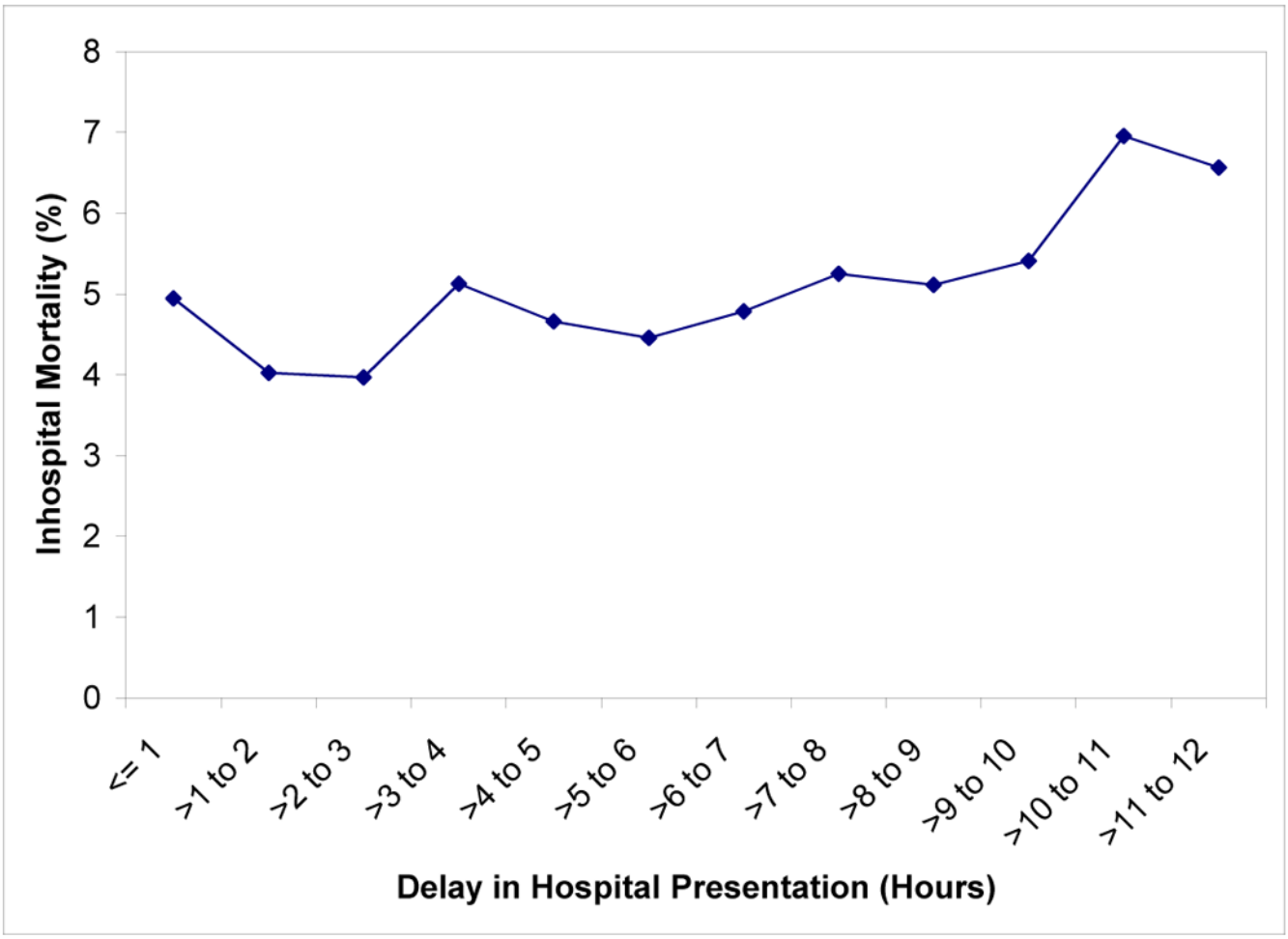


Figure 3.
Delay in Hospital Presentation and Door-to-Drug Time



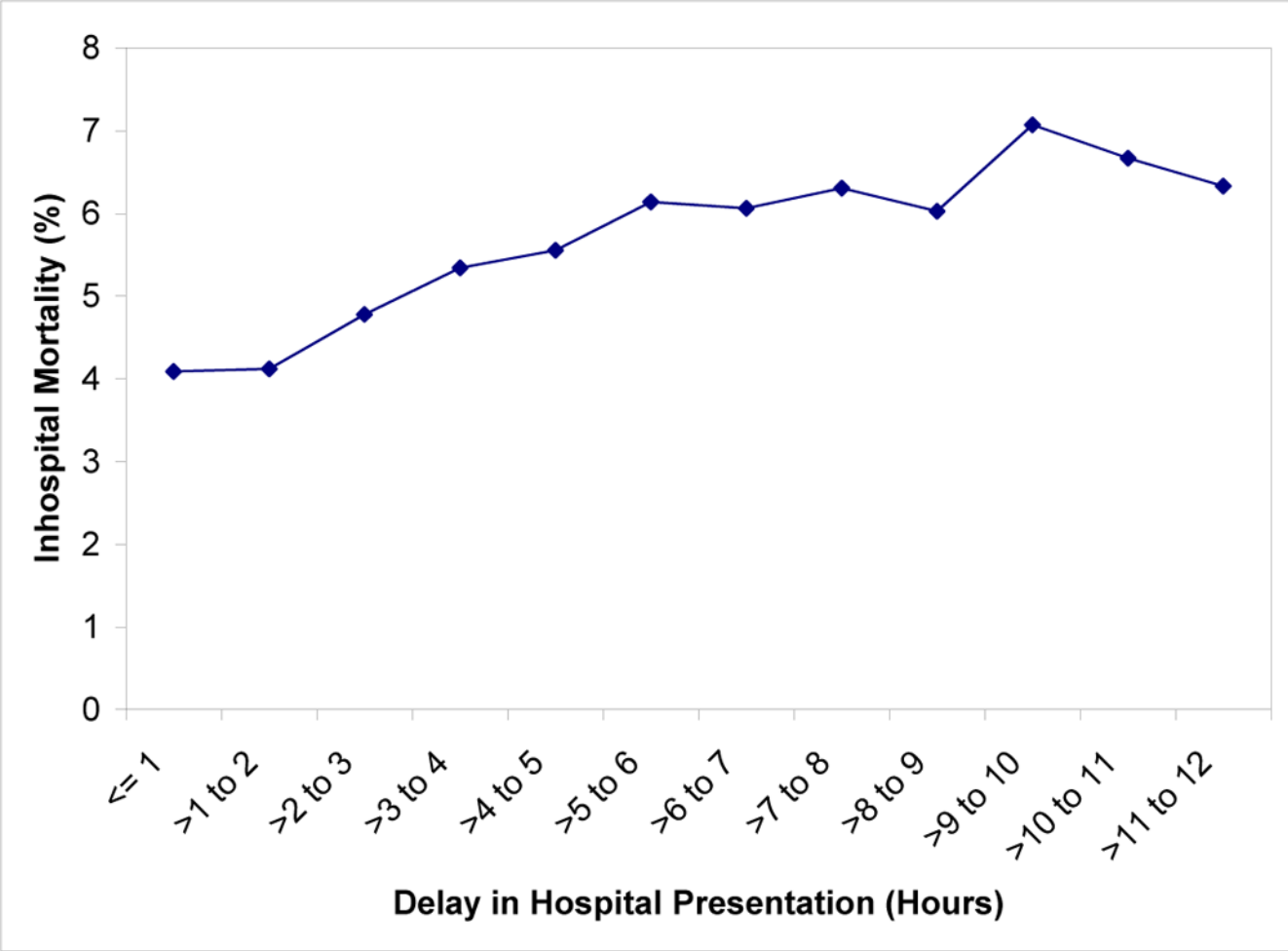


Figure 4.

Figure 4A. Delay in Hospital Presentation and In-Hospital Mortality Among Patients Treated with Primary PCI

Figure 4B. Delay in Hospital Presentation and In-Hospital Mortality Among Patients Treated with Fibrinolytic Therapy

Table 1

Baseline Characteristics of Study Cohorts

Description	Cohort for Use of Any Reperfusion Therapy		Cohort Treated with Primary PCI		Cohort Treated with Fibrinolytic Therapy	
	#	%	#	%	#	%
N	440398	100.00	67207	100.00	183441	100.00
Demographics						
Age						
Age <60	182894	41.53	31719	47.20	84140	45.87
Age 60 to 69	104765	23.79	16100	23.96	45809	24.97
Age 70 to 79	96045	21.81	13118	19.52	37683	20.54
Age ≥80	56694	12.87	6270	9.33	15809	8.62
Female						
No	297095	67.46	47950	71.35	127956	69.75
Yes	143303	32.54	19257	28.65	55485	30.25
Race						
White	380685	86.44	57060	84.90	159283	86.83
Black	21966	4.99	3626	5.40	9091	4.96
Hispanic	12424	2.82	2114	3.15	5591	3.05
Asian	6292	1.43	1273	1.89	2722	1.48
Other/Unknown	19031	4.32	3134	4.66	6754	3.68
Health insurance						
Commercial (HMO/PPO) only	175229	39.79	30240	45.00	81202	44.27
Medicare only	126381	28.70	15013	22.34	48112	26.23
Medicare with any other insurance	57409	13.04	9024	13.43	18139	9.89
Medicaid or Self	47604	10.81	8043	11.97	21025	11.46
Other/Unknown	33775	7.67	4887	7.27	14963	8.16
Medical history						
Current smoker						
No	279099	63.37	40743	60.62	110986	60.50
Yes	161299	36.63	26464	39.38	72455	39.50
Diabetes						
No	348944	79.23	55174	82.10	148966	81.21
Yes	91454	20.77	12033	17.90	34475	18.79
Prior MI						
No	355765	80.78	55932	83.22	152256	83.00
Yes	84633	19.22	11275	16.78	31185	17.00
Hypertension						
No	226786	51.50	35316	52.55	100187	54.62
Yes	213612	48.50	31891	47.45	83254	45.38
Hypercholesterolemia						
No	299441	67.99	43165	64.23	126308	68.85
Yes	140957	32.01	24042	35.77	57133	31.15
Family history of CAD						
No	303735	68.97	47098	70.08	122896	66.99
Yes	136663	31.03	20109	29.92	60545	33.01
Prior CHF						
No	411373	93.41	65058	96.80	176629	96.29
Yes	29025	6.59	2149	3.20	6812	3.71
Prior PCI						
No	396519	90.04	57705	85.86	167642	91.39
Yes	43879	9.96	9502	14.14	15799	8.61
Prior CABG						
No	406665	92.34	63173	94.00	171814	93.66
Yes	33733	7.66	4034	6.00	11627	6.34
Stroke						

Description	Cohort for Use of Any Reperfusion Therapy		Cohort Treated with Primary PCI		Cohort Treated with Fibrinolytic Therapy	
	#	%	#	%	#	%
No	415298	94.30	64009	95.24	177402	96.71
Yes	25100	5.70	3198	4.76	6039	3.29
Angina						
No	394263	89.52	61096	90.91	166270	90.64
Yes	46135	10.48	6111	9.09	17171	9.36
Presentation						
Chest pain at presentation						
Yes	401564	91.18	63656	94.72	176246	96.08
No	38834	8.82	3551	5.28	7195	3.92
Cardiogenic shock						
No	431855	98.06	65159	96.95	181505	98.94
Yes	8543	1.94	2048	3.05	1936	1.06
Systolic Blood Pressure <90 mmHg						
No	418381	95.00	63427	94.38	174956	95.37
Yes	22017	5.00	3780	5.62	8485	4.63
Pulse >100 beats per minute						
No	375139	85.18	59612	88.70	162563	88.62
Yes	65259	14.82	7595	11.30	20878	11.38
Current CHF						
No	381018	86.52	61275	91.17	164674	89.77
Yes	59380	13.48	5932	8.83	18767	10.23
Time of presentation						
Weekday daytime	141476	32.12	27566	41.02	53905	29.39
Weekday evening	86357	19.61	11168	16.62	36660	19.98
Weekday night	81585	18.53	11293	16.80	34972	19.06
Weekend daytime	59104	13.42	8647	12.87	25867	14.10
Weekend evening	37670	8.55	4597	6.84	16842	9.18
Weekend night	34206	7.77	3936	5.86	15195	8.28
Year of presentation						
1995	56930	12.93	4531	6.74	29352	16.00
1996	59677	13.55	5967	8.88	29950	16.33
1997	56917	12.92	6614	9.84	27697	15.10
1998	54210	12.31	6847	10.19	22930	12.50
1999	58760	13.34	8133	12.10	23952	13.06
2000	44550	10.12	7194	10.70	17524	9.55
2001	40631	9.23	8004	11.91	14797	8.07
2002	27240	6.19	6414	9.54	8871	4.84
2003	23604	5.36	7163	10.66	5454	2.97
2004	17879	4.06	6340	9.43	2914	1.59
Hospital characteristics						
Cardiac facilities						
Non-invasive	65567	14.89	0	0.00	46643	25.43
Invasive but non-interventional	84848	19.27	32	0.04	60167	32.80
Interventional	268030	60.86	61991	92.24	66274	36.13
Interventional without OHS	21953	4.98	5184	7.71	10357	5.65
Teaching Status						
No	250987	56.99	34759	51.72	121258	66.10
Yes	189411	43.01	32448	48.28	62183	33.90
Census division						
West	106378	24.15	19905	29.62	42967	23.42
South	138032	31.34	19439	28.92	56683	30.90
Mid-West	132827	30.16	23063	34.32	48301	26.33
Northeast	63161	14.34	4800	7.14	35490	19.35

Description	Cohort for Use of Any Reperfusion Therapy		Cohort Treated with Primary PCI		Cohort Treated with Fibrinolytic Therapy	
	#	%	#	%	#	%

CHF =congestive heart failure; CABG =coronary artery bypass surgery; CAD =coronary artery disease; HMO =health maintenance organization; MI= myocardial infarction; OHS =onsite heart surgery; PCI =percutaneous coronary intervention; PPO = preferred provider organization;