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PREHOSPITAL DELAY TIME IN ACUTE MYOCARDIAL INFARCTION: RELATIONSHIP TO COST OF CARE

by

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DISSERTATION

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Dedication

The stresses and strains of producing a dissertation are felt by the author, but they also greatly affect those closest to them. Steve Weiss, my husband, my best friend, my partner in all things personal and professional, provided constant support during the process. He exalted with me during the high points, and gave me perspective during low points. He has been patient throughout, helping me sort out jumbled thoughts and ideas, cajoling me when I needed it, prodding me when I was tired, editing drafts, and rewarding my efforts. His knowledge of the health care field and enthusiasm for my topic provided constant sources of wisdom, motivation, and reassurance. For this, I dedicate this Dissertation to him.

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PRE-HOSPITAL DELAY TIME IN ACUTE MYOCARDIAL INFARCTION:

RELATIONSHIP TO COST OF CARE

Mary Alice Caldwell, RN, MBA, PhD

University of California, San Francisco, 1998

Abstract

Coronary angioplasty and thrombolytics reduce or eliminate damage during myocardial infarction. However, patients must arrive at the hospital in less than six hours from symptom onset to realize these benefits. Public campaigns to reduce delay have consumed time and dollars with minimal success. While studies have demonstrated improved clinical benefits with short delay times, there are no studies investigating the impact of delay time on hospitalization cost.

Methods: A historic prospective study using two existing databases, the National Registry of Myocardial Infarction and the cost accounting system from two hospitals. Chi-squares and t-tests examined differences between groups. Linear regression determined the association of delay time to cost. Using logistic regression, delay and 4 sets of variables–demographic, cardiac history, risk factor, and hospitalization characteristics -were tested to predict cost. A final model controlling for age and gender used significant variables from the four sets of variables. There were 298 patients in the sample.

Results: Short (<6 hours) and long delayers (≥6 hours) were similar in demographics, cardiac history, risk factors, and hospitalization characteristics. Cost was not different between short and long delayers. Of treatment-eligible patients arriving within six hours, only 45% received reperfusion therapy. Delay time (*ln*) was not associated with cost (*ln*) (r=–0.02). Delay time did not predict high cost, however the use of diagnostic procedures (RR 2.9, 95%CI 1.7, 5.2; p=<0.00) and complications (RR 3.4, 95%CI 2.0, 5.8; p=<0.00) did. Post hoc analyses revealed that, while only 45% of short delayers received treatment, the maximum treatable population may have been reached; diagnostic methods for identifying impending MI may not be optimal; there was a trend toward lower costs in

the group delaying less than one hour; and, cost per day yields more information than cost alone.

Conclusions: Short delay time does not ensure that a therapy will be administered, hospital outcomes will be improved, or costs can be reduced. While efforts to decrease delay time should not change until further research is performed, this study raises important questions with respect to delay, rapid diagnosis and treatment of MI, and cost.

APPROVED:

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CHAPTER ONE: Study Problem And Significance

Background

The Phenomenon of Delay in Seeking Care for Symptoms of Myocardial Infarction

The amount of time that a patient delays before seeking care after the onset of symptoms of a myocardial infarction (MI) has become critically important in the last decade because of the availability of drugs and technology that mitigate or prevent the effects of MI. Successful outcomes are predicated on early treatment. Even before the advent of thrombolysis, it was recognized that shorter delay times were important in reducing morbidity and mortality.[1] More recently, large scale clinical trials investigating the benefits of thrombolytics have established the importance of early initiation of treatment for MI.[2,3]

Physiologic Consequences of Delay

Delaying treatment for MI leads to irreversible myocardial damage. The myocardium (heart muscle) is highly dependent on oxygen from the coronary arteries for normal functioning. Under normal circumstances, blood flow (supply) to the heart muscle closely approximates metabolic demand despite wide fluctuations in oxygen consumption.[4,5] When an imbalance between supply and demand occurs such as the case with atherosclerotic occlusions, ischemia results with a build-up of toxic metabolic wastes leading to tissue dysfunction. A chain reaction occurs as myocardial cells develop acidosis, creatine kinase levels drop, and intercellular potassium levels rise. Cell membranes become dysfunctional and lactate is produced because of anaerobic glycolysis. The severity of the dysfunction depends on the size of the ischemic segment, which is a function of the location of the obstruction in the coronary artery.[6]

Ultimate viability of myocardium after coronary occlusion is limited and dependent on duration and severity of ischemia.[7,8] If the ischemic period persists, the cellular changes mentioned above lead to irreversible injury, necrosis and myocardial infarction.

Ranges of Delay Times

The median range of delay times varies from study to study. Most studies reporting delay use the median rather than the mean or average time. Median times are more appropriate than the mean since delay time is skewed to the right. Average or mean times, when reported, tend to be substantially higher than median times, reflecting the small proportion of patients who have very long delays.[9-12]

Table 1 contains a listing of studies reporting median delay times from onset of symptoms to hospital arrival (except where noted by an asterisk). Median delays range from one and one-half hours to five hours. This is a large variation considering the relationship of time to treatment and infarct size and mortality. While one and one-half hours is probably a short enough delay to minimize infarct size, at five hours significant cell death is certain. This range could merely reflect what is actually true from study to study or other factors could be influencing the extreme delays. A possible reason for the wide range of delay times is the lack of clear definition of what constitutes onset of symptoms.

Table 1. Median Delay Times

Reference	Study Years	*n*	Median * (hr.)	Comment
Turi[1]	1978-83	778	2.0	
Ridker[13]	1982-88	258	1.8	(MDs only)
Ridker[13]	1982-88	240	4.9	
Hofgren[12]	1982	47	4.8	19% > 24 hr.
Karlson[14]	1986-87	921		
men			2.8	
women			3.8	

Reference	Study Years	*n*	Median * (hr.)	Comment
Blohm[15]	1986-88	1,553		
pre campaign			3.0	
during campaign			2.3	
Ho[16]	1986-87	135	2.6	34% > 6 hr.
Leitch[17]	1987	87	2.0	29% > 4 hr.
Clark[11]	1988-89	315	3.2	30% > 6 hr.
Schmidt[18]	1988-89	126	2.0	21% > 6 hr.
Weaver[19]	1988-89	3,256	2.0	
Herlitz[20]	1989-90	1,018		24% > 6hrs
thrombolytics			1.7	
no thrombolytics			2.7	
GISSI[10]	1990	5,301	3.3	* total delay
Bleeker[21]	1990-91	300	0.5	† 10% > 6hrs
Ottesen[9]	1990-92	5,978	3.2	30% > 6 hr.
Rogers[22]	1990-93	240,989	2.2	25% > 6 hr.
GUSTO[23]	1990-93	41,021	1.5	
Moses[24]	1991	66	1.7	
Rawles[25]	not stated	450	2.0	
Reilly[26]	not stated	77	5.0	60% > 3 hr.
Trent[27]	not stated	93	2.1	

* = onset of symptoms to hospital arrival or treatment location unless noted otherwise

† = onset of symptoms to call to a physician

It is particularly noteworthy in Table 1 that, where reported, there is a high percentage of patients presenting after six hours of symptom onset. This is clinically

relevant in the face of studies demonstrating that treatment after six hours yields similar results to no treatment at all, that is, treatment is ineffective after that point.[28]

Impact of Delay on Infarct Size

Infarct size has an important influence on outcome after MI and the patient's eventual return to productivity and a reasonable quality of life. As mentioned previously, animal experiments have related the duration and severity of coronary occlusion to eventual percentage of subendocardial necrosis.[7,8] Focusing on the subendocardium fed by the left anterior descending artery, DeBoer et al.[7] demonstrated that there was no necrosis when flow deprivation (flow in the ischemic zone ÷ flow in the normal zone) was less than 18 minutes. Beyond 18 minutes there were varying degrees of significant necrosis that spread in a parabolic pattern.

Other investigators looking at subendocardial and epicardial salvage after left circumflex artery occlusion in animals showed that at 15-30 minutes of coronary occlusion, there was no significant myocardial damage.[8] After 40 minutes of occlusion, necrosis was present but limited to the subendocardium. After 3-6 hours of occlusion, necrotic areas became progressively larger and extended into the mid-myocardium and sub-epicardium. At six hours of temporary occlusion, necrotic patterns were similar to those of permanent occlusions.[8] The study further found that an average of 55% of the myocardium at risk was still salvageable if reperfused at 40 minutes. However, this number declined exponentially to 33% at three hours and 16% at six hours.

In humans, only indirect methods have been used to determine the association of delay (or ischemia duration) and infarct size due to the difficulties in obtaining direct measurements. When results from four Washington State trials of thrombolytics were pooled and evaluated it was found that final infarct size (as measured by thallium imaging) was highly dependent on duration of symptoms before thrombolysis.[28] Each 30 minute increase in duration was associated with an increase in infarct size, in a somewhat linear pattern. The investigators further found that in patients at the highest end of the range of

delay times (four to six hours), final infarct size was indistinguishable from patients who received no thrombolysis, indicating that patients should be treated within this time frame.[28] This finding confirms the animal work mentioned previously.

In another study, an exponential rise in median infarct size was demonstrated. Those treated within the first hour had significantly greater reductions in infarct size. More than half of this benefit was lost when treatment was delayed more than 75 minutes. Beyond two hours, median infarct size began to plateau.[29] Lastly, in another study measuring the effects of a public education campaign, infarct size (as measured by peak serum aspartate amino-transferase and creatine kinase) was significantly reduced when delay time shortened.[15]

Impact of Delay on Mortality

Early administration of thrombolytics or percutaneous transluminal coronary angioplasty procedures (PTCA) are associated with lower overall mortality.[2, 3, 30, 31] While shorter delay times appear to have positive effects in both short and long term mortality,[1, 20] one study noted a difference between short term (six day) and long term (one, two, and three year) mortality.[9] While early mortality was not affected by delay in that study, long term mortality declined significantly with shorter delay times.

The Grampian Region Early Anistreplase Trial (GREAT) examined and quantified the benefits of early thrombolysis by comparing patients treated on an emergent basis at home with those whose treatment was delayed until arrival at the hospital. At 30 days, there was no statistical difference between groups. However, at three months the difference became significant. In patients who received thrombolytics two hours after the start of symptoms, each hour's delay increased the mortality risk by 21 lives per 1,000 within 30 days (95% CI = 1, 94 lives) and 69 lives per 1,000 within 30 months (95% CI = 16, 141 lives).[32] A statistically significant mortality difference of 11% favoring those in the early treatment group was achieved at one year[33] and was maintained through five years.[34] Although the one year results appear to represent an impressive increase in mortality risk

with lengthened delays, the findings may be somewhat unstable as the confidence intervals are large and the total sample size was only 311.

An earlier study revealed that for the first four hours of patient delay, a reduction of mortality as great as 27% to as low as 9% was seen. However, the highest mortality of any group (38%) was in those presenting at four to eight hours. The next highest mortality (32%) was among the patients who presented more than 64 hours after onset of symptoms.[25] The authors hypothesized that the mortality reduction in the first four hours was probably due to a decline in incidence of ventricular fibrillation after the first few hours. An alternative, though not mutually exclusive hypothesis is that the length of time that the pain of MI is tolerated is inversely related to the size of the infarct. This hypothesis however has not been conclusively proven.

One of the most cited commentaries on mortality and delay has been provided by the Fibrinolytic Therapy Trialists Collaborative Group (FTT).[35] An overview of nine randomized trials of >1,000 patients comparing placebo with thrombolysis revealed a time related benefit of thrombolysis. However the gradient derived by the FTT Group was so low as to question whether efforts (and assumedly dollars) should be expended in expediting delivery of thrombolytics. This analysis has subsequently been criticized on several levels: use of a linear statistical model when data were non-linear, under-representation of early-treated patients, and non-random determination of time of treatment.[34, 36]

The relationship between symptom intensity and delay is an interesting issue and should be considered when evaluating the effect of early treatment on short term mortality rates. Because the most severely afflicted patients may have symptoms that compel them to seek earlier treatment, their naturally higher mortality rates from fatal arrhythmias in the first hour may mask short term results of early treatment. The corollary to this may also be true. That is, that there may be a natural selection bias in that patients with lesser, more

vague, symptoms may not seek treatment at all. It is likely that only when large cohorts of patients have been followed several months that the true mortality benefit can be viewed.

Public Knowledge and Patient Education

The significance of early diagnosis of MI and availability of definitive treatments has generated widespread publicity in virtually all forms of media. Frequent news stories on TV and radio, in newspapers, and in other forms of general publication have heralded thrombolytics and PTCA as effective methods of minimizing or avoiding infarcts. This widespread publicity however, seems to have had little impact on decreasing delay in the United States.

It is discouraging to note that having prior knowledge about the symptoms of MI does not ensure that patients will recognize their symptoms,[11] nor reduce the delay time.[16, 17, 37] Other investigators have found that 36% of patients learned about heart attacks from a physician, 20% had knowledge because of previous MI's, 9% heard about it from radio or TV, 7% from family members, and only 2% from nurses; yet 50% of patients having an MI did not realize that their symptoms were cardiac related.[26] The authors conclude that this, plus the fact that patients' first responses to their symptoms vary, implies that individuals in the community are still unaware of the symptoms of MI and they are unclear about the first actions to take.

There seems to be a difference regarding prior knowledge of MI between health care professionals and the lay public, however. One investigation attempted to evaluate whether people with the ability to recognize cardiac symptoms and, with easy access to medical care, had shortened delay times. Total time interval between symptom onset and hospital arrival in 258 physicians experiencing a first MI participating in the Physicians Health Study were compared to 240 men enrolled in the US cohort of ISIS-2 and other previously published series using lay persons. It was found that physicians had a significantly shorter median delay time as well as a higher percentage presenting earlier after onset of symptoms.[13] This translated into lower mortality rates for physicians. The

authors concluded that the findings support the concept that shorter delay times can be achieved with education. While this study offers some sense of optimism that prior knowledge could shorten delay, the conclusion should be taken with some caution since a physician's education and access to care are substantially different from that of a lay person.

Table 2 outlines studies describing public education efforts to reduce delay times by country. These studies utilized similar campaign strategies, but with differing results.

Table 2. Reduction of Delay Resulting From Public Education Campaigns

	n	Study Year	Country	Type of Campaign	Reduce delay?
Blohm[15]	1,444	1986-88	Sweden	print, 1 radio station	yes
Mitic[38]	471	not stated; ~1982	Canada	radio, TV	yes
Bett[37, 39]	943	not stated	Australia	'national campaign'	no
Ho[16]	890	1986-87	US (Washington State)	newspaper, radio, TV	no
Moses[24]	not stated	not stated; ~1989	US (midwest, rural)	print, TV, radio, public talks, posters	no
Meischke[40]	5,447	1991-1993 (follow-up to Ho[16])	US Seattle	direct mail	only those at highest risk

A radio and print public education campaign decreased median delay time by 40 minutes in a Swedish population and decreased infarct size but did not decrease in-hospital mortality.[15] In another study conducted in Canada, overall delay times at 3 months decreased after a media campaign.[38] However when the results are analyzed with respect to gender, the mean delay times in men decreased 64 minutes while women's increased a remarkable 100 minutes.[38] The authors do not comment on this apparent serendipitous result and it is difficult to deduce a possible cause from the information provided in the

article. Nothing in the study design or implementation suggests a clue as to the reason for this finding.

The National Heart Foundation of Australia conducted surveys about delays before and after a national campaign whose message urged patients with chest pain to seek help promptly.[37, 39] They found among other things, that there was no significant reduction in patient related delay and concluded that reluctance to seek help remained a major cause of delay preceding admission.

A county-wide multimedia campaign in Washington State did not change delay times, either in the group as a whole or in a subset of confirmed MIs despite a documented heightened awareness among patients presenting to the emergency department (ED).[16] Of the patients who heard new information about MIs, only 5% in the pre-message group and 10% in the post-message group heard about the importance of time and delay and less than half used an Emergency Medical Service (EMS). Over 40% still delayed longer than four hours after the campaign.[16] In a similar finding, a two year public education campaign sponsored by a midwestern rural hospital using several forms of media including brochures, posters, newspaper, TV, and radio did not improve response time of patients with chest pain either in the group as a whole or when examined by subgroups of age, sex, and arrival < 6 hours or > 6 hours after onset.[24]

Meischke implemented a 10 month randomized study with the aim of increasing the use of 911 and decreasing prehospital delay time.[40] Three intervention groups receiving an informational, an emotional, or a social message direct mail brochure were compared to a control group. Only those patients in high risk categories (that is those with a previous history of MI) reduced their delay times compared with the control group.

In an article on the topic of delay in MI patients, Weaver criticized many of the aforementioned studies.[41] Sample sizes were too small to adequately measure an effect, programs were too short in duration to 'penetrate' the audience, and inadequate controls made interpretation of the effectiveness of the media intervention nearly impossible. In

another discussion, Rawles noted that the behavior prompting patients to seek care appears to be based on a more instinctive level with possible cultural influences.[25] He concluded that this may make delay in seeking care unmodifiable in necessarily 'superficial' public education campaigns.

The most obvious difference to be noted in the studies listed in Table 2 is that the only successful media campaigns took place in Scandinavia and Canada. There could be several reasons for this with the most obvious being a difference in health care system philosophies and policies.

It is also interesting to note that there has only been one new study[40] reporting on education campaigns in the US in the 1990's despite visibility of the high incidence and prevalence of heart disease, the success of revascularization strategies, and continued long patient delays. However, the American Heart Association (AHA) and Boehringer Mannheim Corporation (BMC) recently issued a press release describing the launch of a new public education program directed toward early heart attack awareness and response.[42] This program was prompted by a nationwide survey conducted by BMC that revealed lack of public awareness of the symptoms and appropriate responses, as well as the lack of reduction of delay time since 1990.

In scanning a sampling of print literature available to the lay public through the AHA (Understanding Angina; The Silent Epidemic; and, Take Charge!), the issue of delay was either not mentioned or only give one paragraph on one of the last pages. While this survey of AHA patient literature was not exhaustive, it suggests that there is minimal emphasis in lay public literature about delay by the most prominent cardiovascular disease organization. This, despite AHA's active involvement in professional programs that target delay.

Finally, there is a possible dilemma that should not be overlooked with respect to educating the public. Health care providers have expressed concern regarding a possible increase in the number of false alarms presenting to EDs after public education campaigns,

however this has not been found to be a long term problem. There was an impressive increase in the number of patients with chest pain and no suspicion of MI in the first week immediately following the initiation of the ad campaign that declined rapidly thereafter.[15] It has also been noted that there was a statistically significant decrease in the number of confirmed MIs, as a percentage of the total, in a post campaign group compared with a pre-campaign group indicating an increase in false alarms.[16] In another study, there was no statistically significant increase in ED visits during a 2 year campaign however the percent of the study population that resulted in non-cardiac complaints increased 26% from baseline.[24] And finally, although there was an increase in the number of persons who presented at the ED during another campaign, the percent of persons who were admitted to the Coronary Care Unit (CCU) before, during or after the campaign changed very little.[38] These data would indicate that concern over increased numbers of patients flooding emergency departments after media campaigns are largely unfounded. Some short term rise in patient presentation could be expected but no long term impact should be anticipated.

The increase in false positives, as well as the ratio of false positives to the total number identified has been a concern for decades in other programs of this sort. It is the same issue that has been put forth when discussing the merits and costs of mass screening programs for cardiovascular as well as other diseases. If public education programs aimed at shortening delay times were to be utilized on a wide scale, consideration should be given to determining the cost (clinical and financial) of false positives versus the cost of MIs that are potentially missed or arrive too late for intervention.

Study Problem

In order for patients experiencing an MI to receive maximum benefit from reperfusion therapies, they must arrive at the hospital in less than six hours from symptom onset. Outcomes are improved if thrombolytics or PTCA can be delivered in this time period. Better outcomes decrease length of stay.[30] Patient education campaigns aimed at

reducing delay consume time, money, and other resources, but have not been highly successful. Health care dollars are scarce and should be used in ways that maximize and optimize clinical and financial outcomes.

A large body of literature has compared costs of alternative treatments for coronary artery disease and MI, primarily angioplasty, intracoronary stents, thrombolysis, coronary artery bypass grafts, and medical therapy. However, there appears to be little, if any, discussion of the financial impact of delay in seeking treatment, despite extensive literature describing the phenomenon. There are two exceptions. In one study, patients who presented to the hospital more than four hours after the onset of symptoms had lengths of stay that were 9% longer than patients who presented sooner.[43] Ostensibly, longer lengths of stay would be related to higher costs although this line of reasoning was not carried through in the study.

Another article developed a simulation model for evaluating cost effectiveness of thrombolytic reperfusion therapies.[44] Among other things, the model predicted a three to seven times increase in cost per additional 1-year survivor for patients arriving four hours after the onset of symptoms compared to those arriving less than four hours. The model was based on early results from the thrombolytic trials and from input from experts in the field and the findings have not been demonstrated in an actual prospective study.

As pressures to contain rising healthcare costs continue to escalate, it is likely that economics will assume an increasingly important role in the evaluation of spending on interventions that would decrease delay. Adequate baseline knowledge, on which to judge the impact of interventions aimed at decreasing delay is not currently available. These data should be generated in order to provide a cost perspective that would augment the literature on outcomes and delay.

Study Purpose

Because of health care's finite resources and the need for their appropriate allocation, the study of the financial impact of delay time to assess the potential for cost savings in MI patients is desirable. Quantification of benefits and costs are important if health care providers and organizations who are focused on cardiovascular diseases are to make informed decisions about allocation of resources. Pre-hospital delay time is a continuing concern. Identifying the impact of delay time on cost of care could help direct policy and funding decisions at several levels. Many studies have examined reasons for delay and the resulting clinical consequences, but few if any, have directly linked the impact of delay to cost of care.

Therefore, the purpose of this study was to examine the relationship between the time from patient recognition of symptoms to hospital arrival and cost of care for the ensuing hospitalization in MI patients. It was further the purpose of this study to analyze predictors of cost controlling for age and gender.

Significance

Myocardial infarction is a major national health problem and is the single largest cause of death for both men and women. Approximately 13.7 million Americans have a history of MI and/or angina. A total of 1,500,000 people suffer a new or recurrent myocardial infarction each year, and one third of these will die. Of those who die each year of an MI, at least half do so within one hour of onset of symptoms and before they reach the hospital.[45]

Because the incidence and prevalence of MI is substantial, it follows that the costs associated with treating the disease are also substantial. The AHA has estimated that the direct and indirect costs of coronary heart disease approach $91 billion per year and cardiovascular diseases in total at $259 billion.[45] They constitute four of the top five hospital diagnostic groups in terms of costs for all payors, excluding childbirth and it's

complications, and four of the top five Medicare hospital costs. This would appear to place a significant, potentially avoidable economic burden on the US. health care system. Appropriate deployment of resources toward shortening delay time could have an impact in a significant disease entity.

CHAPTER TWO: Literature Review And Conceptual Framework

Delay

Delay in seeking care when symptoms of MI arise has been generally defined as the amount of time between first awareness or onset of symptoms until hospital arrival or treatment.[9, 41, 46] Studies vary in terms of how the different components that contribute to total delay are divided. This has lead to inconsistencies and contradictions in research findings. It is imperative that comparisons of studies pay strict attention to the definitions of the components of delay time. Understanding of delay time is further complicated by studies from non-US. countries where a call for help may first result in consultation with a general practitioner.

Components of Delay Time

Patient delay. "Patient delay" or "decision delay" represents the largest single component of the time to treatment.[10, 18, 47] It encompasses the time between symptom onset and a first call for help. However, within this relatively straightforward description, there are subtle distinctions. Some studies describe actual symptom onset[10, 11, 21] while others describe a time when chest pain is intensified or becomes prolonged or intolerable such that the patient decides to seek treatment.[22, 48] Or, it is the time required by the patient to recognize the nature and importance of the problem and determine the need to seek care.[41] If a patient describes more than one episode of chest pain, so-called 'stuttering' symptoms, the determination of the onset of symptoms becomes more complex.

Because approximately one-third of patients cannot identify an abrupt onset time, recommendations by the National Heart Lung and Blood Institute (NHLBI) recently suggested using 'initial' onset and 'acute' onset to differentiate the beginning of symptoms.[49] Initial onset is the prodromal period where symptoms have begun, but have not reached an acute definitive level. Acute onset is the level that prompts one to seek medical treatment. While these distinctions may appear to be subtle, they can lead to statistically significant differences when analyzing time delays.

Transport delay. Transport delay, or response time, includes transportation by self or family, or by EMS or ambulance. Transport delay is the time between the call for, or, decision to transport and the patient's arrival at the hospital.[10, 11, 21, 46] Differences in the means of transport (self vs ambulance) are not always identified in studies and can lead to substantial differences in delay time. In some communities and countries, thrombolytics are administered by the EMS staff at the site where the patient is located, again altering the dynamics of this time component. Additionally, pre-hospital delay time can be prolonged, not because of patient indecision, but rather as a result of appropriate emergency measures taken by EMS.

Hospital delay. Hospital delay spans the time of arrival at the hospital to the time of treatment.[10, 21, 46] An important distinction in this component is the location of treatment. In some studies, patients are diagnosed and treated in the Emergency Department (ED) while in others, they are only diagnosed in the ED and treated after they arrive in the CCU.[2, 20, 21] Yet other studies have reported multiple sites where treatment may have been given to patients such as in the ED and/or the CCU.[30, 48] Differences in treatment locations affect delay time, making comparisons between studies difficult.

NHLBI criteria. Despite the differences in the different components of delay time, agreement on more consistent definitions are beginning to emerge. In a recent report, the NHLBI defined delay time as the interval from the onset of symptoms (first awareness) to the initiation of definitive therapy.[49] They specified the phases of delay as:

- Patient/bystander recognition and action: the interval from symptom onset to accessing the emergency response system or to initiating travel to the hospital when transport occurs by some other method. The phase begins when the patient becomes aware that 'something is wrong'.
- Pre-hospital action: the interval from accessing the emergency response system to arriving at the hospital or, when the emergency response system is bypassed, from initiating travel to the hospital to hospital arrival.

- Hospital action: the interval from the patient's arrival at the hospital to receiving definitive care (e.g. thrombolytic or other pharmacological therapy)

Response times for Emergency Medical Services (transport delay) and hospital delay time have been considered controllable, and therefore amenable to study and intervention. The patient-controlled, or patient delay is largely uncontrolled and remains problematic. As mentioned previously, it represents the largest part of delay, particularly in patients who delay more than two hours.[10, 11, 17, 18]

Delay in the Context of Person/Environment/Health

There are numerous and diverse reasons, factors, and variables that have been studied with respect to their influence on delay. In order to describe them in a structured fashion, they will be organized as suggested in the Model of Symptom Management[50] which states that a person's perception of symptoms is influenced by:

- personal variables -- these are intrinsic and exist before the symptom, influence the perception of the symptom, and in turn, may be influenced by the symptom, (i.e. demographic variables);
- environmental variables -- an aggregate of conditions or circumstances that include the context within which a symptom is perceived, i.e. sociological and behavioral variables; and
- health/illness variables -- unique to the health or illness state of each person.

Person-demographic. Age is a demographic factor frequently associated with delay. There is general agreement that older age, particularly over 65 years, is positively correlated with increased delay times.[1, 9, 10, 18, 19, 25, 26, 30, 48, 51-53] One would expect that age could play a role in causing delay for both physiological and psycho-social reasons. Advanced age tends to attenuate pain perception, and older people tend to have more concomitant diseases that could mask or confuse symptoms of MI. Living situations for

the elderly may not be conducive to sharing the experience with someone else who might prompt them to seek care.

A majority of studies have also found that women tend to delay longer than men.[1, 9, 14, 18, 30, 48, 51] In the GISSI I thrombolytic trials, gender was a significant predictor of delay, however, this finding disappeared in the multivariate analysis.[10] One explanation for this finding could be that gender was jointly associated with one or more variables with the outcome producing a classic example of 'confounding' or interaction. Two additional tests would elicit an answer as to which it was. A separate multivariate analysis for men and for women could have been performed to evaluate effect sizes, or, the multivariate model could have been tested for an interaction.

Contradicting the volume of evidence identifying women as delayers, Dracup and Moser found no difference in mean delay times between genders in a substudy of the GUSTO study.[23, 53] In another study consisting primarily of inner-city Blacks, there were no gender differences in terms of delay. All Black patients, regardless of gender, delayed significantly longer than Caucasians.[11]

Several reasons have been offered as an explanation for delay in women. In a qualitative study, it was found that women's decisions to seek help centered around maintaining and relinquishing psychological control; women attempted to maintain control over the situation by self-treatment or ignoring symptoms.[54] Age may be a factor since it is independently correlated to delay and women are older in virtually all studies reported on delay. Because women are older, they are more likely to be widowed and living alone or not working, limiting support systems that may have an influence on shortening delays. Lastly, women tend to have more atypical chest pain so that even if they are aware of 'classic' symptoms, these symptoms may not fit their ideas of a symptom pattern.

Many other demographic factors have been reported in addition to age and gender. Ethnicity as been positively related in some cases to delay,[11, 55] but not in others.[26]

Similarly, low income has been associated with longer delays,[18, 53] and not associated in others.[26] Education levels do not seem to be related to delay.[26, 53]

The type of insurance has been shown to be related to increased delay,[52] but a co-payment requirement was not related.[56] Confusing the insurance issue further, another large observational study (n=3,711) observed that Medicaid recipients delayed 58 minutes longer ($p<0.01$) and Medicare recipients delayed 29 minutes less ($p=0.01$) when compared to those privately insured.[55]

Environmental-sociological/behavioral. Several studies have evaluated qualitative and behavioral variables causing delay. Patients tend to have expectations about what a heart attack will feel like and, if symptoms match their expectations, they tend to have shorter delay times.[57] If symptoms are not similar to a previous heart attack, delay is longer.[18] Similarly, if they think they are having a heart attack, they delay a shorter period.[11] Some patients think (or hope) their symptoms will subside[12, 21, 53] or that they are not cardiac.[18, 26, 53] It has also been found that patients didn't want to bother the physician or ambulance.[21, 53] Another interesting behavior was that if patients have a belief that heart attacks are preventable, it shortens delay.[11] Only one study has found that perception of symptoms between delayers and non-delayers did not affect time delay.[26]

Since most MIs have been shown to occur in the early morning hours,[58] the association of time of the day or day of the week to delay has also been investigated. One large study noted that there was a longer delay if symptoms occurred at night[10] and another showed that delay was longer if pain occurred during the day[48] while another related increased delay to weekdays versus weekends.[9] Others have noted that delay does not appear to be associated with the time of day or day of the week.[18, 21, 26, 52] While many hypotheses could be developed regarding reasons why day and time might affect delay, it is of greater note that there is not agreement between studies.

Other environmental factors are not as obvious in terms of their effect on delay. The person actually making the call for help has been related to decreased delay,[10] increased

delay,[26] or not related at all.[21] Likewise, the setting where symptoms occurred has been shown to increase delay[10] and not be a factor.[26] Dracup and Moser found that patients who experience symptoms outside the home delay a shorter period of time. Possible reasons for discrepancies, other than those listed previously include differences in sample size and US versus non-US based studies.

In a study that investigated patients' first response to symptoms of MI, researchers found that 31% thought they should just relax, and 22% thought they'd wait and symptoms would subside. Several other 1st responses were listed, however only 4% called a physician or 911.

One last environmental factor that most studies have correlated to increased delay was the involvement a general practitioner (GP), or, calling a physician rather than EMS.[10, 17, 21] In non-US countries, GPs are frequently the first-line decision-makers. For patients not experiencing obvious symptoms of MI, they tended to observe them for extended periods of time until symptoms subsided or worsened. Alternatively in the US, some patients contact their physician if symptoms occur, only to wait minutes or hours for a return call. Although involvement of a physician may result in more appropriate triage, this must be weighed against the substantially increased delay times that have been noted and, the likelihood that the patient will miss the 'window of opportunity' for definitive therapy.

Health/illness-health status. Many of the people experiencing symptoms of MI have a previous history of angina, MI, or other cardiovascular diseases and risk factors. Study results are contradictory in terms of whether prior cardiac history affects delay time. While most studies have found that previous history of cardiac disease is not been related to delay time,[10, 11, 17, 21, 25, 26, 37] others have found a positive relationship.[1, 9, 30, 51] It is unclear why there is a discrepancy in the findings but it may be related to methods of data collection, definitions of past medical history, and differences in populations.

A majority of the literature supports the fact that patients with diabetes delay longer than those without diabetes.[1, 9, 10, 30, 51-53] Diabetic neuropathies could dull pain sensations thus masking symptoms that would prompt this population to seek timely treatment.

Symptoms of MI play an interesting role in delay. It would seem obvious that pain intensity would be related to a shortened delay time. However, pain intensity either was not associated with shorter delays,[12, 21, 53] or only weakly so.[18, 26] Contradicting these findings, another study found that mild to moderate pain intensity (versus severe pain) caused greater delay.[10] The presence of associated symptoms of MI such as Killip class ≥ 3, hypotension, cardiogenic shock and depressed left ventricular function shortened delay times in most,[9, 27, 48] but not all[53] studies. These associated symptoms indicate a more severe MI and could cause greater distress prompting patients to view their symptoms in a more critical fashion. Associated symptoms would seem to play a more significant role than pain itself.

As indicated previously, it would seem appropriate that infarct size and severity would influence delay either from pain or associated cardiac symptoms. Swedish investigators found that larger infarcts had shorter delays, even though delay time was not related to pain intensity.[12] In another study, patients with bradycardia, hypotension, ST-segment elevation and Q-wave MI presented significantly earlier than did patients without these findings.[1] The authors in both studies hypothesized that these manifestations of MI may be associated with more severe symptoms, which may lead to earlier presentation. Other studies contradict these findings in that they found that there was no difference in delay time between those sustaining large infarcts and those sustaining small ones.[17, 21] Those who actually sustain an MI have shorter delay times but the difference was not statistically significant when compared to those with unstable angina or non-ischemic chest pain.[17] Sample size, year of study and method of measuring infarct size does not seem to account for these discrepancies as depicted in Table 3.

Table 3. Studies Describing the Relationship of Delay Time and Infarct Size.

	n	Year of Study	Method of Measuring Infarct Size	Infarct Size Related to Delay?
Hofgren[12]	47	1982	ASAT & CK	yes
Turi[1]	778	1978-83	CK	yes
Bleeker[21]	300	1990-91	CK	no
Leitch[17]	87	1987	CK	no

CK = creatine kinase

ASAT = serum aspartate amino-transferase

Conceptual Framework of Delay

Several conceptual models have been proposed to explain delay in the care-seeking process.[46] A brief description of these models are included here, not as an exhaustive review of the models themselves, but rather to demonstrate how scientists conceptualize some of the issues related to delay.

Health Belief Model. The Health Belief model, based on motivational theory and reasoned action, is frequently used to explain care-seeking behavior. Decisions to seek care depend on the perceived barriers, the perceived amount of threat the symptoms engender in a patient and whether taking action for the symptoms presents an attractive option. Vulnerability and susceptibility play a large role in the perceived threat. The value of an action is weighed in terms of reduction in threat, and 'opportunity cost'.[46, 59, 60]

The Health Belief Model was originally developed to examine behaviors associated with preventative health care and has been popular when trying to explain issues relating to patient compliance.[59, 60] It was applied to, and tested on, non-life-threatening situations such as maternal/child health.[59] Application of the Health Belief Model to a life-threatening situation such as MI, rather than preventative medicine as was originally intended, would appear to be invalid. Lastly from an applied perspective, when cardiac symptoms are vague, or, consequences of the symptoms misunderstood by the patient, the perceived threat can be interpreted erroneously.

Self-Regulation Model. The Self-Regulation model describes a process whereby patients develop their own theories about illness based on past experiences and use this knowledge to deal with and interpret current threats. There are three stages that a patient experiences when faced with a threat about their health: 1) a mental representation of the health threat, 2) coping or action plan, and 3) appraisal.[61] As applied to the patient experiencing symptoms of MI, the characteristics are analyzed based on subjective components (how much does it hurt?), a sense of vulnerability to illness, and past experiences or knowledge of what the symptoms may mean.[46] Coping behaviors can range from an action that the patient might take (e.g. stopping activity until the symptoms abate), or calling for medical help. The patient then evaluates the action in terms of appropriateness, opportunity costs, and barriers and resets the previous knowledge base to incorporate this new experience into future decisions.

This model is predicated on the patient being exposed or open to a basic understanding of illness. The literature describing actions of patients with previous knowledge of heart disease does not entirely support this concept.[1, 9, 30, 51] Other mechanisms, most notably denial, could impact a patient's decision to take (or not to take) action. The model also suffers from the same drawback as the Health Belief Model in that it was developed to explain the problems of patient compliance rather than life-threatening situations.

Symbolic Interactionism Model. Symbolic Interactionism is a sociologic model based on a situational-adaptation perspective. Role theory plays an integral part in this model. Roles are constantly being redefined based on social interactions and are developed based on a constant flow of perceptions and self-reflections. Four essential components to a given role have been defined as: 1) the act of the decision (identifying and acting on a deviant pattern), 2) self-concept (affecting the transition from well to sick roles), 3) counter-roles (spouses, family, friends, health professionals, etc.), and 4) periodic evaluation.[46]

The Symbolic Interaction model has similarities with some of the concepts of the previous two models and is more comprehensive in terms of accounting for some of the variables that have been identified as influencing delay. A possible shortcoming of this model is it's reliance on the patient's ability to correctly identify the level of symptom. Additionally, if a person's actions are based on a flow of perceptions and self reflections, then it should follow that anyone who has a history of heart disease would 'perceive' him/herself as a heart disease patient and be more responsive to symptoms. As mentioned previously, the literature does not support this premise.

Integrated Model of Decision Making. An Integrated Model of Decision Making has been proposed by Dracup et al.[46] incorporating the commonalties and strengths of the previous three models. It positions the principle concepts (individual cognitive processes, vulnerability and susceptibility, self-concept, and interaction) with respect to a larger context of the dynamic world around the patient.[46, 49] As applied to patients with symptoms of MI, a persons options include 1) going directly to a hospital, 2) waiting and periodically reassessing the situation, or 3) involving someone else in the process. The focus then shifts from individual processes to interactive processes. The model is initiated with the onset of symptoms. The patient evaluates the perceived threat, performs a 'cost/benefit' analysis on various actions, and then chooses to consult others. The consultation is influenced by sociodemographic and personality factors. Ultimately, the consultation results in some type of action.

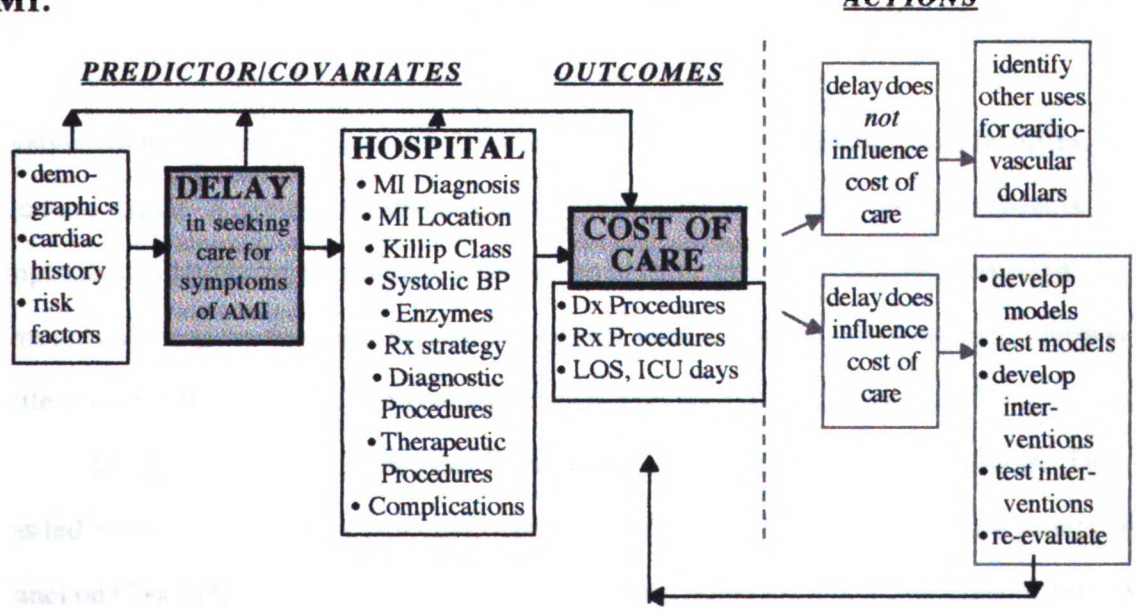
This model is constructed specifically with the symptoms of MI in mind, but is still based on models that were designed and validated for other situations. It incorporates sociodemographic factors lacking in other models, making it more attractive. However, the inherent problems of the previous models are still present. For example, the patient still may not have the understanding to evaluate the perceived threat, and may not have enough information to perform a 'cost/benefit' analysis.

Medical Model. Most discussions of delay in the literature follow a Medical model; i.e. they focus on demographics and clinical characteristics of the patients as predictors of delay. One example divides components of delay into sociodemographic variables (age, sex, education, marital status, household structure), health status (diabetes, previous MI, and intensity of initial symptoms), interactions (who sought help, type of help sought, mode of transportation), and settings (day or night, activity during symptoms, setting of symptoms, and distance from hospital).[10] While this approach clearly defines what has been noted in the literature with respect to variables affecting delay, it only serves to differentiate low and high risk patients. It fails to analyze the delay behavior itself or define potential interventions.

Proposed Conceptual Model for This Study

In addition to the lack of validated theoretical frameworks that examine delay seeking behavior in MI, there are no models that describe the direct impact of delay on cost of care. Therefore, the model displayed below in Figure 1 has been constructed based on findings in the literature regarding delay It is proposed as a starting point to begin to examine this issue and then relate it to cost of care.

Figure 1. A Proposed Model for Examining Costs of Pre-hospital Delay in MI.



The first phase of delay in seeking help for MI (onset or patient recognition of symptoms to hospital arrival) has been well studied. While there are many covariates that have been shown to affect delay, the model focuses on those with the strongest support from the literature. Demographics such as age and gender have been shown to increase delay as described in previous sections; the influence of cardiac history and risk factors has been less consistent. Hospitalization variables can be affected by delay and, in turn, can impact various measures of resource utilization as well as cost of care. If delay is not related to cost of care, a potential policy strategy may be that money that would have been spent on reducing delay could be diverted to other activities for treating MI. If, however, delay does affect cost of care, the rationale for further study could be supported by interested parties including clinicians, professional organizations, insurers, and health care providers. New interventions could be developed and tested and reevaluation of the results in terms of reduction of cost of care could be done.

Economics and Delay

The health care system has undergone enormous changes in the last 15 years in response to rapidly rising costs. It is now recognized that economics is an important aspect in evaluating illnesses, diagnostic alternatives, and therapeutic interventions. Economic analyses in healthcare are necessary because resources (money, people, time, facilities, etc.) are scarce. A systematic analysis of how these scarce resources are to be spent is important in identifying appropriate alternatives of care. However, despite increasing amounts of literature dealing with cost analyses of various clinical interventions,[62] there is little evidence that it is used in a systematic manner to guide decision making.[63]

In the past, many cost analyses have lacked methodological standardization. This has led to the introduction of potential biases and difficulties in comparing study results. A Panel on Cost Effectiveness in Health and Medicine ('the Panel') was convened by the US

Department of Public Health to address this issue and recommendations were developed and published in an attempt to standardize concepts and methods for performing economic analyses.[64-67] Because these recommendations are recently proposed, it is unclear what impact they will have on future research. Many of the discussions and recommendations from the Panel are explained in the following sections.

Measuring Costs and Benefits

Cost analyses describe the costs and outcomes or benefits of one or more groups. More intensive interventions may be compared to less intensive ones. Different types of treatments can be compared for the same disease or problem. The perspective from which the analysis is carried out is an important consideration. Results can be substantially different depending on the specific costs and outcomes that are measured, or, the perspective of the analysis. Costs, outcomes, and analysis perspective must be clearly stated in any study involving cost analysis. This information is critical in evaluating and comparing results.

Costs. The foundation for all types of financial analyses are monetary costs. Costs are consumption of a resource that otherwise could have been used for another purpose[68, 69] and are principally comprised of expenditures (direct costs) and value of output lost due to cessation or reduction of productivity from an illness (indirect costs).[70, 71] Another way to segment costs is to evaluate a) costs arising from direct expenditures in the health care sector, b) those attributable to 'other treatment costs' such as resources used by patients and their families, and c) resource use in non-health care sectors.[72] The researcher must identify the range of costs that are both attainable and appropriate to the study at hand.

Direct medical costs are actual expenditures resulting from the use of medical care including diagnosis, treatment, continuing care, rehabilitation and terminal care.[70] They can include the costs of such items as hospitalization, medications, physician's services, laboratory tests, procedures, clinic visits, and x-rays. Indirect costs of illnesses are those that occur because of loss of life, lost time from other activities such as household

production, or loss of livelihood from disability or morbidity.[68] Indirect costs relate primarily to those incurred by the patient and are usually measured by wages, salaries, supplements, and the imputed value of household work.[70] (Note: Indirect costs of an illness should not be confused with the 'indirect costs' that are associated with facility overhead.)

In performing economic analyses in health care, it is important to distinguish between 'costs' and 'charges' as they represent different concepts. Costs are true expenditures or resources consumed. Charges are typically (though not always) higher than costs and are set by the marketplace or by regulation. Charges do not reflect the true cost of providing medical care due primarily to the practices of cost-shifting, cross-subsidization, and regional variances.[72] Yet, costs are often used interchangeably creating serious methodological problems.[73]

Even though costs are considered the more accurate reflection of consumption they are frequently difficult to obtain. There may be sensitivities about reporting costs in the literature as providers are sometimes reluctant to reveal their costs to the competition. Additionally, some hospitals still have not installed sophisticated cost accounting systems that enable accurate tracking of costs. For these reasons, charges are frequently substituted intentionally. In some cases, charges may even be more appropriate depending on the analysis perspective. Cost to charge ratios can be used to convert charges to costs, but this may not be completely accurate since the differential between charges and costs can vary by product, service, and department.

Costs and benefits that will occur in the future should not be evaluated on an equal basis with today's costs and benefits because of the time value of money. While inflation is frequently thought of as the reason for discounting future dollars, it is really the value of the invested dollar that drives this concept. Interest rates (or other investment rates) are the driving force behind determining the present value of money. The rate at which future dollars should be discounted is controversial and inconsistent. It varies with economic

conditions. For applications in healthcare, the Panel recommended a 3% discount rate with a sensitivity analysis for 0, 5, and 7%.[65, 67]

While the use of discounting dollars is unquestioned by economists, the use of discounting health benefits, such as future life-years saved, is more troublesome. Life years cannot be invested as can money, to yield more life years in the future. And it is somewhat debatable to claim that life years in the future are more or less valuable than life years today. However, it is argued that because costs are discounted, the benefits on the other side of the equation must also be discounted.

Benefits/Outcomes. Measuring clinical outcomes and benefits is a critical part of any economic evaluation. Indeed, the only ethical way of using economics is to first make choices about what is clinically correct and then analyze ways to deliver that care in a cost efficient manner. The literature varies with respect to the outcome measured. The issue surrounding the most valid method still remains controversial.[67] Health outcomes can generally be classified as biochemical, physiological, anatomical, histological, and clinical.[74] The clinical grouping is concerned with morbidity and mortality and health related quality of life (HRQOL). The most popular approach to expressing a total health effect or HRQOL is a measure known as 'quality-adjusted life years' (QALY).

Analysis perspective. When performing an economic analysis, it is important at the outset, to determine from whose perspective the analysis is being done -- society's, the patient's, the payor's, or the provider's. The perspective determines the specific costs (or charges) and outcomes that are included in an analysis. It is recommended that the investigator carry out an analysis from more than one point of view, with at least one of these being from the standpoint of the actual decision-maker.[68]

In their recent consensus statement, the Panel concluded that society's perspective was the most ethically justifiable since it represented the public interest rather than the interest of specific groups.[66] Society's perspective requires an examination of the impact of all direct and indirect costs for this specific situation as well as the broader implications for

the health care of a particular person in the future. However, a societal perspective is particularly difficult, time consuming, and expensive to perform therefore it is recognized that in most cases, only a partial analysis can be done.

Economic Models

The measurement of costs is similar across all economic evaluations and the specific values measured are dependent on the nature and goals of the study. However the nature of the consequences, or outcomes, stemming from the suggested alternatives vary. These models do not exist in isolation and are not necessarily mutually exclusive. In fact, it has been suggested that they are complementary and should be used together where possible to enhance understanding of the issues under study.[66] Table 4 compares and contrasts how outcome measurement can vary between methods.

Table 4. Comparison of Models of Economic Analyses

Model	Outcome Measurement	Advantages	Disadvantages
cost identification/ minimization	outcomes (however defined) are assumed equal; only looks at cost differences	leads to decisions based strictly on cost	ignores quality of life component
cost comparison	any type of outcome can be measured as long as it is well defined.	versatile	• ignores quality of life • may not be comparable to other studies because of differing outcomes
cost effectiveness	Δ cost ÷ Δ outcome = incremental cost effectiveness ratio; outcome is typically expressed in life years gained; may be specified as a physiologic or disease state change	both costs and outcomes are considered; provides the cost per unit of outcome	ignores quality of life component
cost utility	Δ cost ÷ Δ QALY * outcomes = quality adjusted life years	includes quality of life component	• more difficult to do • need final outcome data
cost benefit	outcome is assigned a monetary value	enables comparisons between all sectors of society	difficult to put dollar values on life

* QALY = Quality Adjusted Life Year = Utility (variously measured) x Life Years

Economic Modeling: Application to the Phenomenon of Delay

In an analysis of the clinical and economic impact of delay, several of the above mentioned issues are important to consider. Calculation of direct and indirect medical costs of delay is ideal, however the ability to completely identify both of these components may be difficult and dependent on the methodology. Indirect costs are not typically available in the case of a historical prospective design because access to patients is limited due to the nature of secondary analysis and patient confidentiality. A prospective observational study wherein patients could be interviewed during, and after hospital admission would provide the most accurate descriptions. If an analysis were conducted from the perspective of the payor, charges would be an appropriate representation of the cost of delay. If the analysis is performed from the provider's perspective, costs would be of more interest. The patient's perspective would probably use charges, although these can be mitigated by the specific type of insurance. Discounting becomes an issue in studying delay if 1.) patients are followed for an extended period of time, and/or 2.) data collection proceeds over an extended period of time (typically more than one year).

The economic impact of delay could be of interest to any of the perspectives mentioned previously including the payor, provider, patient, or society. If costs and charges are both available, the analysis can be done from all but society's perspective. Society's position however would require a longer range perspective in order to determine the impact.

In a study such as the one proposed below, delay's effect on several clinical outcomes can be measure along with the effect on cost. With the restrictions imposed by a historic prospective design where long term follow-up is not possible, only outcomes and cost of care in the hospital can be compared between short and long delayers. However this could provide a baseline for determining future research.

Summary and Limitations of Current Knowledge

The examination of economic impacts of various clinical alternatives are beginning to emerge in many areas. They are being used more frequently by payors and providers as a decision making tool for optimizing courses of care. The medical products industry is using cost analyses as a means of proving the value of new products. Professional organizations and Nursing have been slow to adopt this method of evaluation. Analyzing clinical and financial outcomes of nursing interventions has recently begun to establish a presence.[75] Payors, consumers, and accreditation agencies are demanding more data on financial impacts of care in addition to clinical results. In 1994, the Expert Panel on Quality Health Care was convened by the American Academy of Nursing for the purpose of exerting leadership at national and state levels for quality assessment and measurement in health care. In defining outcomes as the 'favorable or unfavorable changes in actual or potential health status of individuals and communities attributed to prior or concurrent care', the Expert Panel stressed the need to include both clinical and economic outcomes.[75] A carefully constructed argument presented by the Expert Panel asserts the need for increasing Nursing's participation in outcomes assessment.

Studying the costs and consequences of delay in seeking care for symptoms of MI is within the Nursing domain as presented in the Expert Panel's opinion statement. It could provide useful information to direct and define efforts directed at interventions or, in the development of new systems that decrease delay.

The economic impact and consequences of delay have not been well studied. As mentioned previously, a simulation model developed for evaluating cost effectiveness in thrombolytic reperfusion therapies described a three to seven times increase in cost per additional one-year survivor for patients arriving four hours after the onset of symptoms compared to those arriving less than four hours.[44] These results were based on expert opinion and extrapolation of data from a variety of sources and have not been demonstrated in an actual prospective study.

Research Questions

This study examined the impact of delay time on cost of care. It was done from the perspective of the health care provider. The specific research questions were:

1. What are the sample characteristics with respect to covariates, the predictor variable (delay time) and the outcome variable (cost)?
    - Are there meaningful differences in the important covariates between those who were excluded due to missing delay times and those who were included?
    - Does the sample differ based on gender in terms of covariates, delay, and cost?
    - Is there a difference in the covariates, the predictor variable (delay time) and the outcome variable (cost) between those with short delay times and those with long delays?
2. Is the time from onset of symptoms to hospital arrival related to cost of care?
3. Does delay time and sets of covariates (demographics, cardiac history, risk factors, hospitalization factors) predict cost when controlling for age and gender?

The null hypothesis was – patient delay is not related to cost of care when controlling for age and gender. The alternative hypothesis is - patient delay is positively related to cost of care when controlling for age and gender.

CHAPTER THREE: Methodology

Research Design

This study used a historic prospective design and employed a secondary analysis of two existing data sets; the National Registry of Myocardial Infarction (NRMI) and the TSI cost accounting system employed at the study sites. The predictor variable was time (in minutes) from patient recognition of symptoms to hospital arrival (delay time). The primary outcome variable was total cost of care (in dollars) for the admission. (Other potential covariates are listed in Table 8.)

Setting

While the NRMI collects data from hospitals on a national level, this study was limited to enrollees at the University of California at San Francisco (UCSF)/Stanford Health Care's San Francisco campus which includes Moffitt and Long Hospitals (ML) and Mount Zion Hospital (MZ). Moffitt and Long is a 560 bed, urban, university-affiliated hospital with full cardiac services including a full-time cardiac catheterization laboratory. Mount Zion hospital is a 365 bed urban, community based, university-affiliated hospital with cardiac services, however, the catheterization laboratory only operates during daytime hours. Both hospital sites utilize, and are tied to, the same accounting system.

The study was limited to the hospitals within the UCSF/Stanford Health Care system. Differences in accounting methods between hospitals make it difficult to accurately combine cost information from different institutions, and hospitals are reluctant to share cost and/or charge data with those outside their respective organizations because of competitive concerns.

Sample

The target population for this study was patients with a discharge diagnosis of acute myocardial infarction. The accessible population was patients discharged from ML and MZ

with a diagnosis of an initial MI. The sample consisted of those patients meeting the inclusion criteria for the National Registry of Myocardial Infarction (described in subsequent sections) between January 1, 1995 and September, 1997. Inclusion criteria for the NRMI are 1.) a discharge diagnosis of an MI, 2) an ICD-9 code between 410.01 and 410.91 at discharge, and 3) the current MI is the first episode of care for a newly diagnosed MI (i.e. it is not a rehospitalization for an MI that occurred within the previous 8 weeks).

NRMI exclusion criteria include: 1.) an ICD-9 code with a fifth digit containing a '2', (indicating the admission is related to an MI within the last 8 weeks), and 2) a fourth or fifth digit in the ICD-9 code that is unspecified.

Due to the nature of the research questions in this Dissertation study, further exclusions were:

- MI symptom onset occurring during hospitalization for another diagnosis,
- transfer in to or out of the study sites, and
- absence of one of the variables defining symptom onset to hospital arrival (MI symptom onset date and time, hospital arrival date and time), or a delay time of '0' minutes.

Sources of Data

To ensure that there was no bias with respect to the primary outcome variable, the predictor variable from the NRMI data source was collected prior to, and independent of, the outcome variable from the TSI data source. The following describes the two data sets used in this study.

National Registry of Myocardial Infarction

The NRMI 1 was a Phase IV (post-marketing), multi-centered, observational, cross-sectional, collaborative endeavor sponsored by Genentech, Inc.. The purpose was to collect prospective data on the treatment of patients with acute myocardial infarction that could be used (1) globally to analyze national practice patterns for infarct treatment, (2)

locally to assess individual hospital practice patterns and outcomes to facilitate the continuous quality improvement process, and (3) by the sponsor to monitor the frequency of specific adverse events with the use of their product.[22] The NRMI 1 was initiated in 1990 and enrolled approximately 300,000 patients from over 1,100 US hospitals until its closure at year end 1994.

Data for this Dissertation study were taken from the NRMI 2, an expanded data set from NRMI 1 that also identified patient risk factors related to outcomes, captured data related to the timely utilization of hospital resources, and reflected recent advances in early management of MI.[76] It was initiated in January of 1995. There are 254 variables in the database.

The specific methods for NRMI data collection are described in detail elsewhere.[22, 76] In brief, a registry coordinator from each participating hospital records data on a simple two page form (the Case Report Form {CRF}) designed by the NRMI investigators and the sponsor. Data are sent to a central data collection center (ClinTrials Research, Inc., Lexington, KY), on a regular basis for processing. Cumulative results are available once per quarter in hard copy and on floppy diskette.

At the two hospital sites, the data for the NRMI are extracted from a medical record review by the same people each quarter; the registry coordinator and/or a data abstractor. The Principal Investigator (PI) for the Dissertation project was also involved with data abstraction for several months before the close of enrollment in order to gain familiarity with the database and data collection procedures. The coordinator and abstractors are advanced practice nurses in cardiology and were familiar with diagnosis and treatment of MI patients as well as research methodology. In many cases, they were also familiar with specific patients because of their hospital roles. They had undergone training specific to collection of information for this database and followed precise guidelines and operational definitions when completing the forms.

The primary predictor variable, delay time, was extracted from 4 raw variables, hospital arrival time and date and symptom onset time and date. Every effort was made to verify times by cross-referencing all available records at the abstractors disposal including, but not limited to, physicians and nurses notes and flow sheets from Emergency Medical Technicians if the patient arrived by ambulance. Time of symptom onset was the most frequently missing variable of the four raw variables comprising delay time. In some cases where a specific time was not mentioned in the chart but references to 'dinner time' or other times such as TV programs were, systematic responses were followed. For example, 'dinner time' was assumed to be 6:00 pm. If a range of times was reported, the earliest was used.

Data are double-key entered at ClinTrials. Audits are performed electronically by the central facility to detect out-of-range variables, inconsistencies, errors, and omissions. Queries are telephoned, or response sheets are sent, to local registry coordinators for resolution.[22] The Registry also holds periodic meetings on a regional basis to review findings and discuss data entry.

Data for the sample were available to the PI for this study in hard copy form from the CRF. A floppy diskette was also available (formatted for Excel spreadsheets) for the specific study sites. A code (dictionary) book defining each variable was provided with the data disk. Operational definitions were included in the Reference Binder. The PI obtained and reviewed both of these items before initiation of the study.

TSI Cost Accounting System

Cost of care was obtained from the TSI system utilized by the two study sites. TSI is a cost accounting database system that tracks all costs and charges accumulated on a per patient basis for each episode of care. Both costs and charges were available through the TSI system.

The TSI system receives information daily from MedPac which is a central processing information system. Among other things, the MedPac system downloads basic

demographic information on each patient as well as codes and details on resource utilization with charges for each episode of care. Costs are derived from the charges based on the resource utilization.

The TSI system is audited on three levels. Total costs and charges on a hospital level are reviewed on a monthly basis for the purpose of detecting a change beyond 10% from the previous month. If a change greater than that is noted, a more detailed analysis is performed to examine outliers and possible errors. This same procedure is also done on a department level. The third level of audit is performed by ICD code. Medians and ranges are observed for outliers and possible errors. Outliers are examined and corrective action is taken if errors are detected (personal communication, TSI administrator, August, 1997).

Preliminary Evaluation of the Sources of Data

A preliminary evaluation of the NRMI data set was undertaken with the following goals:

- establish feasibility of using the data on the floppy disk from ClinTrials,
- establish feasibility of converting data from an Excel spreadsheet to a statistical software package,
- examine the predictor variable (time from symptom onset to hospital arrival) for missing or incomplete data and potential problems,
- examine other variables of interest for missing or incomplete data and potential problems,
- randomly select 10 patients to compare data entry with CRF for accuracy, and
- randomly select 10 patients to verify appropriateness of responses -- i.e., is the 'patient story' appropriate.

For the preliminary evaluation, 226 cases were available representing enrollees from January, 1995 to March, 1997. The results were as follows. The floppy disk from ClinTrials containing NRMI information was easily downloaded into an Excel spreadsheet

and converted to SPSS. A sampling of data were cross-checked between the two software programs to ensure that all data were transferred accurately and completely.

The predictor variable, time from symptom onset to hospital arrival, had 80 missing datapoints. Upon examination of the data, this was found to be due to: 1) missing data from one of the four variables that comprise the derived time (n=59), 2) symptom onset began after hospital arrival (n=17), 3) data recording or entry errors in one of the four variables that comprise the time (n=3), and 4) one patient had 0 minutes because s/he was in the ED for another reason when the chest pain began. Those missing due to data entry errors were reexamined. The errors were obvious and corrected. The final number of eligible patients was 149. The only other major variable with a meaningful number of missing values was ejection fraction.

Of the 149 patients remaining, there were 17 patients who were transferred out of the study site before care was completed, and there were five patients who were transferred in. This left 127 patients remaining (56%) from the original 226.

An audit of 10 patients comparing the data entered by ClinTrials and the data recorded by the abstractors on the CRF revealed no errors. Additionally, each of the 10 patients was reviewed for potential misinterpretations of questions or answers and to validate the patient 'story'. The CRFs accurately represented the major variables of interest.

A preliminary evaluation of information from the TSI cost accounting system and an assessment of the ability to match the NRMI identifiers to the TSI system was undertaken with the following goals.

- to examine the format of the accounting data,
- to become familiar with the accounting data that was available,
- to examine the dependent (outcome) variable -- total cost of care -- for missing or inconsistent data,

- to examine the extent of missing data in the areas of potential subanalyses,
- to review for other unforeseen potential sources of error,
- to determine the degree of difficulty entering or merging the cost data with the NRMI dataset, and
- to test the ability to perform statistical analyses with a combined data set.

Only non-name patient identifiers were used to extract the specific cases from the TSI system to conform to stipulations made by the Committee on Human Research (CHR) approval guidelines. The identifiers included:

- ICD-9 code number (410.x1) (for sorting),
- patient initials,
- gender,
- birthdate,
- admission and discharge date, and
- hospital medical record number.

Total costs and total charges for ten randomly selected patients from the NRMI database, were retrieved and examined. There were no missing cost data for the 10 cases. Preliminary data included direct costs (fixed and variable) as well as indirect costs (overhead) in a straightforward presentation.

In summary, the pilot test demonstrated that it is possible to extract and match the data from the TSI database using non-name identifiers. Availability of data on floppy diskette from both sources eliminated the need to reenter data which added to the accuracy.

Human Subjects and Administrative Approvals

Written permission to use data from the NRMI database as well as publish results was obtained from the corporate sponsor, Genentech. Additionally, the cooperation of the

accounting administrator pertaining to the use of their cost accounting system was enlisted. Lastly, the Registry Coordinator for UCSF agreed to support and assist in the research project as needed.

Approval from the CHR for both site's participation in NRMI 2 was obtained by NRMI. Approval from CHR was not ordinarily required for the use of secondary data sets, as would be the case with this study. However, because the acquisition of cost data was a separate issue from the NRMI and required the use of patient identifiers for matching NRMI patients with cost data, an expedited review by CHR was applied for and granted.

Key Definitions

The Table below lists operational definitions for the predictor variable, delay time, the primary outcome variable, cost of care, and other pertinent variables.

Table 5. Operational Definitions

Variable	Definition [76]
delay time	onset of symptoms to hospital arrival: *onset of symptoms*: - onset of cardiac ischemic symptoms related to this acute event.; the date and time the symptoms appeared, or became constant in quality or intensity; time that the symptoms prompted the patient to seek care *hospital arrival*: - date and time of admission to an acute care facility
chest pain on presentation	chest discomfort or pressure, arm or jaw pain (does not include associated symptoms such as nausea, vomiting, palpitations, syncope, or cardiac arrest)
MI	documented by local hospital criteria including cardiac enzymes, electrocardiogram, or cardiac angiography
length of stay	date and time of discharge or death minus hospital arrival

ICU days	24 hours = 1 day; for partial days, <12 hours is rounded down, >12 hours is rounded up
additional procedures	procedures and interventions performed prior to discharge other than those previously identified as an initial reperfusion strategy. Included are: PTCA (repeat or rescue), coronary artery bypass graft (CABG), intra-aortic balloon pump (IABP), ventilator, pacemaker, stress test, echocardiogram
clinical events /complications	events that occurred after onset of MI symptoms up to the time of discharge or death. Included are: hypotension requiring intervention, recurrent ischemia and angina, recurrent MI, congestive heart failure or pulmonary edema (CHF/PE) requiring therapy, cardiogenic shock, pericarditis, sustained ventricular tachycardia or fibrillation (VT/VF), cardiac rupture, or sudden cardiac arrest.
Other definitions specific to this study but not utilized by NRMI:	
cost of care	direct and indirect (overhead) costs and charges incurred during the hospital stay; specifically excluded are indirect medical costs associated with lost productivity, non-hospital expenses incurred as a result of this admission (e.g. hotel, meals for patient or family)

Other variables of interest were self explanatory and the reader is referred to the NRMI Reference Manual for specific details if more information is desired.

Data Collection and Management Procedures

The NRMI disks were obtained for both sites containing patients with completed records through July, 1997 (MZ) and September, 1997 (ML). The NRMI disk was first screened for outliers, errors, duplicates, and incorrect data. Outliers were individually reviewed to verify the accuracy of information. If the information in the outlier was

deemed accurate, the outlier was discussed with experts in the field and methods of handling them were decided on an individual basis.

A list of cases containing non-name patient identifiers was submitted to the TSI administrator for extraction of cost and charge data from the cost accounting database. The identifiers included ICD-9 code, patient initials, date of admission and discharge, gender, birthdate, and medical record number. Any manually entered data were double-entered and each variable had a range of values such that entries beyond that range were detected. The data containing the NRMI and TSI data were saved on floppy disk in two secure locations.

Data Analysis

All data were analyzed using the statistical software program SPSS (Mac version 6.1) on a Macintosh Power PC computer. A level of significance was established at $p = 0.05$.

Data Analysis Plan

Appendix A describes the plan for data analysis of the three research questions. In brief, all data were initially screened for missing and out of range values and for distributional characteristics. Frequencies and measures of central tendency were performed for all demographic variables, cardiac history and risk factors, hospitalization characteristics, as well as the primary predictor variable, delay, and outcomes (costs, charges, length of stay, and ICU days). Comparisons described in Question #1 were done using x^2 and t-tests as appropriate. Research Question #2 utilized Pearson's product moment correlation to examine the relationship of cost of care to delay time. Because delay time and costs had a skewed distribution, log transformations were made to obtain normal distributions. The transformed numbers were used when appropriate to answer the relevant research questions.

Multivariate logistic regression was performed to select the most parsimonious model for determining whether delay time predicts high cost of care in MI patients while

controlling for age and gender. (Question #3). Several potential covariates for the model were dichotomized to permit inclusion in the logistic regression analysis. Table 6 below lists those covariates and their respective codings. The specific point of dichotomizing the variable was determined primarily by the distribution in the data set and clinical indicators with regard to the outcome variable.

Table 6. Coding of Variables for Use in the Logistic Regression Analysis

Variable	Original Values	Code
Age	continuous	0 = <=73 years
		1 = ≥=74 years (median = 73)
Gender		0 = men
		1 = women
Race	several ethnicities	0 = Caucasian
		1 = non-Caucasian
Payor	7 different groups	0 = government (Medicare, Medicaid, VA Champus)
		1 = private and all other
Cardiac History	angina, CABG, CHF, previous MI, PTCA	0 = none
		1 = any
Cardiac Risk Factors	family history, diabetes, hypercholesterolemia, hypertension, current smoker, stroke	0 = none
		1 = any
Hospital site		0 = ML
		1 = MZ
Admission Diagnosis	MI, r/o MI, unstable angina, or other (mostly CHF)	0 = other
		1 = MI
Ejection Fraction	continuous	0 = ≥ 40%
		1 = ≤ 39%
Killip Class	1, 2, 3, 4	0 = no symptoms (Class 1)
		1 = symptoms (Classes 2, 3, & 4)
Blood Pressure: systolic	continuous	0 = ≥ 90 mmHg
		1 = ≤ 89 mmHg

Variable	Original Values	Code
MI location	anterior, inferior, or other	0 = all other 1 = anterior
Additional Procedures - diagnostic	catheterization, echocardiogram, stress test	0 = none 1 = any
Additional Procedures - treatment	CABG, repeat or rescue PTCA, pacemaker, balloon pump, ventilator	0 = none 1 = any
Complications	recurrent angina or MI, AV block, cardiac arrest, CHF, pericarditis, cardiac rupture, cardiogenic shock, ventricular tachycardia (VT) or fibrillation (VF)	0 = none 1 = any (hypotension requiring therapy was deleted for these analyses as it covaried with hypotension on admission)
Delay	minutes: continuous	0 = ≤ 359 minutes (<6 hours) 1 = ≥ 360 minutes (> 6hours)
Length of Stay	continuous	0 = ≤5.5 days 1 = ≥5.6 days (mean = 6.6, median = 5.3, ± 4.6)
Total Costs	continuous	0 = < median $14,777 1 = ≥ median $14,778

Sets of variables were individually entered as blocks based on their characteristics: 1) demographic, 2) cardiac history, 3) risk factors, and 4) hospitalization, to examine their ability to predict high cost. Variables in each of the models that attained statistical significance were entered as a block into a final model along with age and gender. Beta coefficients, standard errors, risk ratios, and significance levels were obtained from the SPSS Logistic Regression program. Confidence intervals (95%) for the risk ratios were calculated on an Excel Spreadsheet with the following formula: the beta coefficient ± the critical value for 95% confidence intervals (1.96) times the standard error -- $\beta \pm 1.96$(S.E.) -- and then converted to risk ratios using exp(β). (The 95% confidence

intervals were calculated in Excel because the SPSS version used for these analyses did not contain that capability.)

Power Analysis

Informal power estimates with respect to the outcome cost, were derived from tables during the planning of this study.[77] All estimates were based on an anticipated sample size of 200 and an assumed two-sided alpha of 0.05. Using a t-test with an assumed effect size of 0.3, this study had a power of approximately 0.15 to detect a difference in the mean cost between short and long delayers. Using a correlation coefficient with an effect size of 0.20, this study had a power of approximately 0.20 to detect a relationship between delay time and cost.

CHAPTER FOUR: Results

Sample Description

There were 548 patients enrolled in the NRMI database at the 2 sites. Moffitt and Long contributed 295 cases from January, 1995 through September, 1997. Mount Zion contributed 253 from January, 1995 through June, 1997. Mount Zion cases from July - September 1997 were not included because the data disk containing the most recent entries was not available at the time of this analysis. Table 7 below displays reasons for the removal of cases beyond the exclusionary criteria listed for NRMI and this study (see Chapter Three) resulting in the final sample size of 298.

Table 7. Cases Excluded from Sample

	ML	MZ	TOTAL
Cases that met NRMI and			
Dissertation Study criteria	295	253	548
less			
duplicate entries	- 4	- 0	544
missing medical record number	- 0	- 23	
Available for analysis	291	230	521
less			
missing delay time and/or transferred in or out	- 124	- 97	
delay time of '0' minutes	- 2	- 0	
TOTAL	165	133	298

Cost data could not be obtained for those with missing medical record numbers, therefore they were eliminated. Cases with missing delay times were eliminated since this was the main predictor variable. Cases transferred to or from other hospitals were eliminated because of the inability to access cost records at the transfer site. There were

two patients with '0' delay time; one was in the ED at the time of onset, and the reason for the other was not able to be determined from the data available. These were eliminated because a log transformation can not be done for '0'.

Question #1

- What are the sample characteristics with respect to covariates, the predictor variable (delay time) and the outcome variable (cost)?
  - Are there meaningful differences in the important covariates between those who were excluded due to missing delay times and those who were included?
  - Does the sample differ based on gender in terms of covariates, delay, and cost?
  - Is there a difference in the covariates, the predictor variable (delay time) and the outcome variable (cost) between those with short delay times and those with long delays?

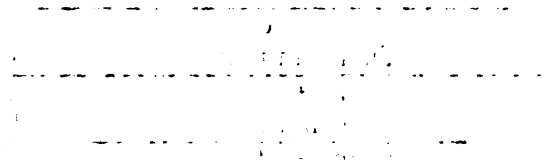
All tables for these questions will follow the same general format and are separated into the following sections: demographics, cardiac history and risk factors, hospitalization characteristics, and primary predictor and outcome variables. Characteristics for the entire sample are listed in table below.

Table 8. Sample Frequencies and Measures of Central Tendency

		Total Sample (n=298)
Demographics		
Age (yrs.)	mean, ±s.d.	71.2, ±14.2
	median, min-max	73, 27 - 99
		% (n)
Gender (men)		62.1 (185)

	Total Sample (n=298)	
Race:		
Caucasian	57.4	(167)
Black	10.3	(30)
Hispanic	5.5	(16)
Asian, Pacific Islander	16.8	(49)
Native American & other	3.4	(10)
unknown	6.5	(19)
Payor:		
private	20.3	(60)
government (Medicare, Medicaid VA/Champus)	73.2	(216)
self-pay, other	5.8	(17)
unknown	0.7	(2)
Cardiac History *		
(any)	55.0	(164)
previous MI	27.2	(81)
angina	17.4	(52)
CHF	17.1	(51)
PTCA	8.4	(25)
CABG	7.4	(22)
Risk Factors *		
(any)	76.8	(229)
stroke	11.1	(33)
diabetes	29.2	(87)
hypertension	50.3	(150)
current smoker	15.1	(45)
family history	11.7	(35)
hypercholesterolemia	22.1	(66)
Covariates - Hospitalization Characteristics		
Transport:		
self	37.6	(109)
ambulance	62.4	(181)
Chest Pain Present on Admission	70.0	(198)
Admission Diagnosis		
MI	49.5	(146)
r/o MI	30.2	(89)
unstable angina	12.2	(36)
other	8.1	(24)
Initial Reperfusion Treatment:		
none	57.4	(171)
thrombolysis	14.1	(42)
PTCA	28.5	(85)
Killip Class: §		
1	69.1	(206)
2	17.4	(52)
3	9.4	(28)
4	4.0	(12)
CK-MB Enzymes 2x Normal	84.1	(243)
Q Wave Present	10.4	(31)
ST Elevation Present	55.0	(164)

		Total Sample (n=298)
MI Location:		
anterior		29.2 (87)
inferior		29.9 (89)
other		40.9 (122)
Ejection Fraction (%)	mean, ±s.d.	44.5, ±12.6
	median, min-max	45, 15 - 70
BP (mmHg): §	mean, ±s.d.	142, ±36.2
systolic	median, min-max	140, 0 - 260
diastolic	mean, ±s.d.	79, ±24.0
	median, min-max	80, 0 - 160
Heart Rate (bpm) §	mean, ±s.d.	88, ±28.8
	median, min-max	87, 0 - 240
Additional Procedures *:		% (n)
(any)		81.9 (244)
CABG		6.7 (20)
catheterization		32.6 (97)
echocardiogram		50.3 (150)
balloon pump		7.0 (21)
repeat thrombolysis		0.0 (0)
laser/athrectomy/stent		3.7 (11)
pacemaker		5.4 (16)
repeat PTCA		15.4 (46)
rescue PTCA		1.3 (4)
stress test		24.5 (73)
ventilator		14.8 (44)
Complications *:		
(any)		42.3 (126)
recurrent angina		15.8 (47)
AV block		2.3 (7)
cardiac arrest		4.0 (12)
CHF		13.4 (40)
Rx/hypotension		21.8 (65)
pericarditis		1.3 (4)
recurrent MI		2.7 (8)
cardiac rupture		0.7 (2)
cardiogenic shock		6.0 (18)
VT/VF		4.0 (12)
Deaths		8.1 (24)
Primary Predictor Variable		
Delay Time (minutes)	mean, ±s.d.	258, ±328.6
	median, min-max	120, 5 - 1505
Primary Outcome Variables		
Length of Stay (days)	mean, ±s.d.	6.6, ±4.6
	median, min-max	5.3, 0 - 34.9
ICU Days	mean, ±s.d.	2.5, ±2.3
	median, min-max	2, 0 - 13
Total Costs ($)	mean, ±s.d.	18,440, ±13,249
	median, min-max	14,777, 2,469 - 76,621



		Total Sample (n=298)
Total Charges ($)	mean, ±s.d.	41,199, ±32,077
	median, min-max	32,121, 5,806 - 190,024

* = items are not mutually exclusive

§ = measured on admission

A majority of the sample were men (62%) and Caucasian (57%). The mean age was 71 years (±14). The government comprised the largest reimbursing agency, probably due to the effect of the older population and coverage by Medicare. Most were transported to the hospital by ambulance. Half of the cases had an admission diagnosis of MI but less than half were treated with reperfusion strategies such as thrombolytics, PTCA, or CABG.

Evaluation by Killip class showed that 69% had no heart failure symptoms on admission and the mean ejection fraction was 44.5% (±13%). Slightly less than one third of the sample had anterior infarcts, as was the case with inferior infarcts. Fifty-five percent of the cases had ST elevation on admission but only 10% had a Q wave present. Vital signs (mean systolic and diastolic blood pressure and mean heart rate) were in the high normal range.

Additional procedures following the initial reperfusion strategy are also listed. Half of the patients had an echocardiogram, 32% had a cardiac catheterization, and 25% had a stress test. Because no one received a repeat dose of thrombolytics, this variable was eliminated from subsequent analyses. The most frequent complication was hypotension requiring therapy followed by recurrent angina. Eight percent of the sample died during the hospital stay. Of the 24 deaths, 17 were listed as cardiac related. The remaining seven did not have a cause of death recorded.

The mean and median for the predictor variable, delay time, were 258 minutes and 120 minutes respectively with a large standard deviation of ±329. The discrepancy between the mean and median is evidence of the skewed distribution of this variable. Length of stay was 6.6 days for the entire hospitalization with the mean number of ICU days at 2.5. The mean of the outcome variable (costs) was $18,440/patient with a median

of $14,777. Median delay time and median costs (versus the mean) probably provide a more accurate representation of central tendency in this population since lengthy delays or high costs in several patients have skewed the distribution to the right. Charges were roughly 2.25 times costs. This ratio remained fairly consistent in the analyses and therefore cost and charges are not reported separately.

Exclusion of Cases Due To Missing Delay Times – Characteristics and Differences

Because 43% of the sample available for analysis was eliminated as demonstrated in Table 7 above, primarily for missing delay time, the total sample available for analysis (after eliminating duplicate entries; n= 544) was examined to determine statistically significant differences between the two groups that could impact the cost. Table 9 below lists the covariates of interest.

While age and payor were not different between the two groups, there was a significantly higher proportion of women who were eliminated due primarily to missing delay times. In terms of race, the percentage of Caucasians was not different between groups, however more Blacks and fewer Hispanics were in the excluded group. There were no differences in cardiac history and risk factors.

The principal differences in hospitalization characteristics between groups centered around the complex of variables dealing with symptoms on presentation at the hospital. The group that was eliminated had less chest pain on admission, was less likely to be diagnosed with an MI and was less likely to undergo thrombolysis or PTCA. Additionally, they were less likely to have ST elevation. There were no differences in terms of outcome variables, namely ICU days and length of stay.

Table 9. Comparison of Included Cases and Excluded Cases

	Total Sample (n=544)		Inclusions (n=298)		Exclusions (n=246)		p
Demographics							
Age (yrs.) mean, ±s.d.	72.0, ±13.6		71.2, ±14.2		72.8, ±12.8		
Age (yrs.) median, min-max	74, 27 - 99		73, 27 - 99		75, 42 - 96		ns
	%	(n)	%	(n)	%	(n)	
Gender (men)	57.9	(315)	62.1	(185)	52.8	(130)	0.03
Race:							0.05
Caucasian	57.4	(303)	57.4	(167)	57.4	(136)	
Black	11.9	(63)	10.3	(30)	13.9	(33)	
Hispanic	4.7	(25)	5.5	(16)	3.8	(9)	
Asian, Pacific Island	16.7	(88)	16.8	(49)	16.5	(39)	
Native American & other	1.9	(10)	3.4	(10)	0.0	(0)	†
unknown	7.4	(39)	6.5	(19)	8.4	(20)	
Payor:							ns
commercial, HMO	19.7	(106)	20.3	(60)	18.9	(46)	
government	74.0	(399)	73.2	(216)	75.0	(183)	
self-pay, other	5.0	(27)	5.8	(17)	4.1	(10)	
unknown	1.3	(7)	0.7	(2)	2.0	(5)	†
Cardiac History and Risk Factors							
previous MI	27.0	(147)	27.2	(81)	26.8	(66)	ns
angina	17.5	(95)	17.4	(52)	17.5	(43)	ns
CHF	19.7	(107)	17.1	(51)	22.8	(56)	ns
PTCA	7.5	(41)	8.4	(25)	6.5	(16)	ns
CABG	7.2	(39)	7.4	(22)	6.9	(17)	ns
stroke	12.3	(67)	11.1	(33)	13.8	(34)	ns
diabetes	30.7	(167)	29.2	(87)	32.5	(80)	ns
hypertension	50.6	(275)	50.3	(150)	50.8	(125)	ns
current smoker	14.3	(78)	15.1	(45)	13.4	(33)	ns
family history	10.8	(59)	11.7	(35)	9.8	(24)	ns
hypercholesterolemia	20.0	(109)	22.1	(66)	17.5	(43)	ns

		Total Sample (n=544)		Inclusions (n=298)		Exclusions (n=246)		p
Hospitalization Characteristics								
Transport:		%	(n)	%	(n)	%	(n)	ns
self		40.2	(214)	37.6	(109)	43.4	(105)	
ambulance		59.8	(318)	62.4	(181)	56.6	(137)	
Chest Pain Present on Admission		51.8	(270)	70.0	(198)	30.3	(72)	0.00
Admission Diagnosis:								0.00
MI		38.1	(206)	49.5	(146)	24.5	(60)	
r/o MI		29.6	(160)	30.2	(89)	29.0	(71)	
unstable angina		10.6	(57)	12.2	(36)	8.6	(21)	
other		21.7	(117)	8.1	(24)	38.0	(93)	
Initial Reperfusion Treatment:								0.00
none		69.9	(380)	57.4	(171)	85.0	(209)	
thrombolysis		10.7	(58)	14.1	(42)	6.5	(16)	
PTCA		19.5	(106)	28.5	(85)	8.5	(21)	
Killip Class:								ns
1		65.4	(356)	69.1	(206)	61.0	(150)	
2		20.0	(109)	17.4	(52)	23.2	(57)	
3		11.0	(60)	9.4	(28)	13.0	(32)	
4		3.5	(19)	4.0	(12)	2.8	(7)	
Enzymes 2x Normal		81.2	(427)	84.1	(243)	77.6	(184)	ns
Q Wave Present		10.5	(57)	10.4	(31)	10.6	(26)	ns
ST Elevation Present		41.9	(228)	55.0	(164)	26.0	(64)	0.00
MI Location:								0.00
anterior		27.4	(149)	29.2	(87)	25.2	(62)	
inferior		24.3	(132)	29.9	(89)	17.5	(43)	
other		48.3	(263)	40.9	(122)	57.3	(141)	
ejection fraction (%)	mean, ±s.d.	43.2, ±13.0		44.5, ±12.6		41.3, ±13.3		
	median, min-max	45, 15 - 70		45, 15 - 70		40, 15 - 70		0.02
BP (mmHg):	mean, ±s.d.	141, ±35.6		142, ±36.2		139, ±34.8		ns
systolic	median, min-max	140, 0-260		140, 0 - 260		139, 0-234		
diastolic		77, ±23.9		79, ±24.0		74, ±23.6		
		78, 0 - 160		80, 0 - 160		74, 0 - 138		0.04

		Total Sample (n=544)	Inclusions (n=298)	Exclusions (n=246)	p
Heart Rate (bpm)	mean, ±s.d.	90, ±27.7	88, ±28.8	92, ±26.1	ns
	median, min-max	88, 0-240	87, 0-240	90, 0 - 180	
Additional Procedures *:		% (n)	% (n)	% (n)	
CABG		6.1 (33)	6.7 (20)	5.3 (13)	ns
catheterization		30.0 (163)	32.6 (97)	26.8 (66)	ns
echocardiogram		52.6 (286)	50.3 (150)	55.3 (136)	ns
balloon pump		5.7 (31)	7.0 (21)	4.1 (10)	ns
laser/athrectomy/stent		3.7 (20)	3.7 (11)	3.7 (9)	ns
pacemaker		4.2 (23)	5.4 (16)	2.8 (7)	ns
repeat PTCA		14.7 (80)	15.4 (46)	13.8 (34)	ns
rescue PTCA		0.9 (5)	1.3 (4)	0.4 (1)	ns †
stress test		21.9 (119)	24.5 (73)	18.7 (46)	ns
ventilator		15.3 (83)	14.8 (44)	15.9 (39)	ns
Complications *:					
recurrent angina		15.8 (86)	15.8 (47)	15.9 (39)	ns
AV block		2.0 (11)	2.3 (7)	1.6 (4)	ns †
cardiac arrest		3.5 (19)	4.0 (12)	2.8 (7)	ns
CHF		15.8 (86)	13.4 (40)	18.7 (46)	ns
Rx/hypotension		21.0 (114)	21.8 (65)	19.9 (49)	ns
pericarditis		0.7 (4)	1.3 (4)	0.0 (0)	ns †
recurrent MI		2.8 (15)	2.7 (8)	2.8 (7)	ns
cardiac rupture		0.4 (2)	0.7 (2)	0.0 (0)	ns †
cardiogenic shock		6.1 (33)	6.0 (18)	6.1 (15)	ns
VT/VF		4.4 (24)	4.0 (12)	4.9 (12)	ns
Deaths		10.3 (56)	8.1 (24)	13.0 (32)	ns
Outcome Variables					
Length of Stay (days)	mean, ±s.d.	6.9, ±5.0	6.6, ±4.6	7.4, ±5.4	ns
	median, min-max	5.6, 0 - 34.9	5.3, 0 - 34.9	6.0, .2 - 28.7	
ICU Days	mean, ±s.d.	2.6, ±2.7	2.5, ±2.3	2.7, ±3.1	ns
	median, min-max	2.0, 0 - 22	2, 0 - 13	2.0, 0 - 22	

* = items are not mutually exclusive

† = cell sizes are small (< 5) therefore analysis of this factor is unstable

Gender Differences

Gender differences with respect to delay have been noted in the literature.[1, 9, 14, 18, 30, 48, 51] Because of these reports, this study compared men and women in terms of the predictor and outcome variables as well as pertinent covariates. Table 10 below displays those results.

Table 10. Comparison of Men and Women in Covariates, Primary Predictor Variable, and Outcome Variables.

		Men (n=185)		Women (n=113)		p
Demographics						
Age (yrs.)	mean, ±s.d.	67, ±13.9		78, ±11.6		0.00
	median, min-max	67, 27 - 93		80, 37 - 99		
Race:		%	(n)	%	(n)	0.05
Caucasian		58.4	(104)	55.8	(63)	
Black		6.7	(12)	15.9	(18)	
Hispanic		4.5	(8)	7.1	(8)	
Asian, Pacific Islander		18.5	(33)	14.2	(16)	
Native American/other		5.1	(9)	.9	(1)	†
unknown		6.7	(12)	6.2	(7)	
Payor:						0.00
commercial, HMO		26.9	(49)	9.7	(11)	
government		65.4	(119)	85.8	(97)	
self-pay, other		6.6	(12)	4.4	(5)	
unknown		1.1	(2)	0	(0)	†
Cardiac History and Risk Factors						
previous MI		30.8	(57)	21.2	(34)	ns
angina		17.3	(32)	17.7	(20)	ns
CHF		15.1	(28)	20.4	(23)	ns
PTCA		11.9	(22)	2.7	(3)	0.01 †
CABG		9.2	(17)	4.4	(5)	ns
stroke		8.1	(15)	15.9	(18)	.04
diabetes		26.5	(49)	33.6	(38)	ns
hypertension		45.4	(84)	58.4	(66)	0.03
current smoker		17.3	(32)	11.5	(13)	ns
family history		11.9	(22)	11.5	(13)	ns
hypercholesterolemia		22.7	(42)	21.2	(24)	ns
Hospitalization Characteristics						
Transport:		%	(n)	%	(n)	0.02
self		42.7	(76)	29.5	(33)	
ambulance		57.3	(102)	70.5	(79)	
Chest Pain Present on Admission		72.5	(129)	65.7	(69)	ns
Admission Diagnosis:						ns
MI		48.9	(90)	50.5	(56)	
r/o MI		29.3	(54)	31.5	(35)	
unstable angina		14.7	(27)	8.1	(9)	
other		7.1	(13)	9.9	(11)	

		Men (n=185)		Women (n=113)		p
Initial Reperfusion Treatment:						0.03
none		53.0	(98)	64.6	(73)	
thrombolysis		13.0	(24)	15.9	(18)	
PTCA		34.1	(63)	19.5	(22)	
Killip Class:						ns
1		71.4	(132)	65.5	(74)	
2		15.1	(28)	21.2	(24)	
3		9.7	(18)	8.8	(10)	
4		3.8	(7)	4.4	(5)	
Enzymes 2x Normal		87.2	(157)	78.9	(86)	ns
Q Wave Present		11.4	(21)	8.8	(10)	ns
ST Elevation Present		57.3	(106)	51.3	(58)	ns
MI Location:						ns
anterior		30.3	(56)	27.4	(31)	
inferior		28.6	(53)	31.9	(36)	
other		41.1	(76)	40.7	(46)	
Ejection Fraction (%)	mean, ±s.d.	44.5, ±12.6		44.6, ±12.5		ns
	median, min-max	45, 15 - 70		45, 20 - 68		
Systolic BP (mmHg)	mean, ±s.d.	143, ±33.1		142, ±41.0		ns
	median, min-max	143, 60 - 230		140, 0 - 260		
Additional Procedures *:		%	(n)	%	(n)	
CABG		8.1	(15)	4.4	(5)	ns
catheterization		37.3	(69)	24.8	(28)	0.03
echocardiogram		49.2	(91)	52.2	(59)	ns
balloon pump		8.1	(15)	5.3	(6)	ns
laser/athrectomy/stent		3.8	(7)	3.5	(4)	ns †
pacemaker		5.9	(11)	4.4	(5)	ns
repeat PTCA		16.8	(31)	13.3	(15)	ns
rescue PTCA		.5	(1)	2.7	(3)	ns †
stress test		27.6	(51)	19.5	(22)	ns
ventilator		15.1	(28)	14.2	(16)	ns
Complications *:						
recurrent angina		16.8	(31)	14.2	(16)	ns
AV block		1.1	(2)	4.4	(5)	ns †
cardiac arrest		4.3	(8)	3.5	(4)	ns †
CHF		10.8	(20)	17.7	(20)	ns
Rx/hypotension		19.5	(36)	25.7	(29)	ns
pericarditis		2.2	(4)	0.0	(0)	ns †
recurrent MI		2.7	(5)	2.7	(3)	ns †
cardiac rupture		.5	(1)	.9	(1)	ns †
cardiogenic shock		5.9	(11)	6.2	(7)	ns
VT/VF		4.3	(8)	3.5	(4)	ns †
Deaths	% (n)	5.9	(11)	11.5	(13)	ns
Primary Predictor Variable						
Delay Time (minutes)	mean, ±s.d.	251, ±322		268, ±340		ns
	median, min-max	120, 5 - 1505		120, 15 - 1497		
Outcome Variables						
LOS (days)	mean, ±s.d.	6.4, ±4.5,		6.8, ±4.8		ns
	median, min-max	5.2, 0.1 - 30		5.5, 0 - 34.9		

		Men (n=185)	Women (n=113)	p
ICU days	mean, ±s.d.	2.5, ±2.2	2.5, ±2.4	ns
	median, min-max	2.0, 0 - 11	2.0, 0 - 13	
Total Costs ($)	mean, ±s.d.	18,799, ±13,755	17,851, ±12,413	ns
	median, min-max	14,927, 2,469 - 72,232	14,600, 3,493 - 76,621	
Total Charges ($)	mean, ±s.d.	42,781, ±33,256,	38,610, ±30,013	ns
	median, min-max	32,828, 5,806 - 186,426	29,871, 6,020 - 190,024	

* = items are not mutually exclusive

† = cell sizes are small (< 5) therefore analysis of this factor is unstable

Demographically, women were significantly older and a higher proportion of women were Blacks and Hispanics than men; there were more Asian men (18.5%) than women (14.2%). The government was more likely to be the primary payor for women; more men were covered by private, commercial or HMO plans. In terms of cardiac history, men were more likely to have had a PTCA in the past, and a higher proportion of women had a history of stroke or hypertension.

Women were more likely to have taken an ambulance to the hospital. Significantly fewer women received initial revascularization procedures. There were no differences between genders in chest pain on admission, admission diagnosis, MI severity (Killip class, ejection fraction), ST elevation, MI location, or delay time. The cost of women's hospitalizations did not differ from the cost of men. There were no differences in other indicators of resource utilization such as length of stay, additional procedures (except a higher percentage of follow-up cardiac catheterizations in men) or in cardiac complications.

Differences Between Short and Long Delayers

For the purposes of this analysis, delay was dichotomized at less than six hours (short delay) or greater than six hours (long delay). Six hours was chosen based on data from thrombolytic trials that show the effect of treatment after six hours is equivalent to no treatment at all.[28] The Table below describes the results of this comparison.

Table 11. Comparison of Those Delaying Less Than 6 hours and Those Delaying Longer than 6 Hours in Covariates, Predictor, and Outcome Variables.

		≤359 min. delay (n=233)		≥360 min. delay (n=65)		p
Demographics						
Age (yrs.)	mean, ±s.d.	71.6, ±14.3		69.8, ±13.6		ns
	median, min-max	74, 27 - 99		71, 36 - 94		
		%	(n)	%	(n)	
Gender	men	63.5	(148)	56.9	(37)	ns
Race:						ns
Caucasian		61.1	(138)	44.6	(29)	
Black		9.3	(21)	13.8	(9)	
Hispanic		4.0	(9)	10.8	(7)	
Asian, Pacific Islander		16.8	(38)	16.9	(11)	
Native American/other		3.5	(8)	3.1	(2)	
unknown		5.3	(12)	10.8	(7)	
Payor:						ns
commercial, HMO		21.6	(50)	15.6	(10)	
government		71.4	(165)	79.7	(51)	
self-pay, other		6.1	(14)	4.7	(3)	†
unknown		0.9	(2)	0.0	(0)	†
Cardiac History and Risk Factors *						
previous MI		29.2	(68)	20.0	(13)	ns
angina		17.6	(41)	16.9	(11)	ns
CHF		18.5	(43)	12.3	(8)	ns
PTCA		9.0	(21)	6.2	(4)	ns
CABG		7.3	(17)	7.7	(5)	ns
stroke		11.2	(26)	10.8	(7)	ns
diabetes		29.2	(68)	29.2	(19)	ns
hypertension		52.4	(122)	43.1	(28)	ns
current smoker		13.3	(31)	21.5	(14)	ns
family history		11.6	(27)	12.3	(8)	ns
hypercholesterolemia		19.3	(45)	32.3	(21)	0.03
Hospitalization Characteristics						
Transport:						0.00
self		32.0	(73)	58.1	(36)	
ambulance		68.0	(155)	41.9	(26)	
Chest Pain Present on Admission		70.1	(155)	69.4	(43)	ns
Admission Diagnosis:						ns
MI		50.9	(117)	44.6	(29)	
r/o MI		29.1	(67)	33.8	(22)	
unstable angina		10.4	(24)	18.5	(12)	
other		9.6	(22)	3.1	(2)	†
Initial Reperfusion Treatment:						ns
none		54.5	(127)	67.7	(44)	
thrombolysis		16.3	(38)	6.2	(4)	†
PTCA		29.2	(68)	26.2	(17)	

		≤359 min. delay (n=233)		≥360 min. delay (n=65)		p
Killip Class:						ns
1		67.8	(158)	73.8	(48)	
2		16.7	(39)	20.0	(13)	
3		10.7	(25)	4.6	(3)	†
4		4.7	(11)	1.5	(1)	†
Enzymes 2x Normal		85.3	(191)	80.0	(52)	ns
Q Wave Present		10.4	(24)	10.8	(7)	ns
ST Elevation Present		55.8	(130)	52.3	(34)	ns
MI Location:						ns
anterior		30.5	(71)	24.6	(16)	
inferior		28.8	(67)	33.8	(22)	
other		40.8	(95)	41.5	(27)	
Systolic BP (mmHg)	mean, ±s.d.	141, ±37.2		149, ±31.7,		ns
	median, min-max	140, 0-260		150, 77-218		
Ejection Fraction (%)	mean, ±s.d.	43.9, ±12.5		46.7, ±12.6		ns
	median, min-max	45, 20-70		50, 15-68		
Additional Procedures *:						
CABG		5.2	(12)	12.3	(8)	0.04
cath		31.3	(73)	36.9	(24)	ns
echocardiogram		48.9	(114)	55.4	(36)	ns
balloon pump		7.7	(18)	4.6	(3)	ns †
laser/athrectomy/stent		3.9	(9)	3.1	(2)	ns †
pacemaker		6.0	(14)	3.1	(2)	ns †
repeat PTCA		15.5	(36)	15.4	(10)	ns
rescue PTCA		1.3	(3)	1.5	(1)	ns †
stress test		21.0	(49)	36.9	(24)	0.01
ventilator		16.7	(39)	7.7	(5)	ns
Complications *:						
recurrent angina		16.3	(38)	13.8	(9)	ns
AV block		2.6	(6)	1.5	(1)	ns †
cardiac arrest		4.3	(10)	3.1	(2)	ns †
CHF		14.2	(33)	10.8	(7)	ns
Rx/hypotension		24.0	(56)	13.8	(9)	ns
pericarditis		1.3	(3)	1.5	(1)	ns †
recurrent MI		3.4	(8)	0.0	(0)	ns †
cardiac rupture		0.9	(2)	0.0	(0)	ns †
cardiogenic shock		6.9	(16)	3.1	(2)	ns †
VT/VF		4.7	(11)	1.5	(1)	ns †
Deaths		10.3	(24)	0.0	(0)	0.01
Outcome Variables						
LOS (days)	mean, ±s.d.	6.6, ±4.9		6.3, ±3.3		ns
	median, min-max	5.3, 0 - 34.9		5.2, 1.7 - 14.2		
ICU days	mean, ±s.d.	2.6, ±2.4		2.0, ±1.8		0.01
	median, min-max	2.0, 1 - 13		2.0, 0 - 10		
Total Costs ($)	mean, ±s.d.	18,541, ±13,373		18,077, ±12,887		ns
	median, min-max	15,081, 2,469 - 76,621		14,145, 3,493 - 72,232		

		≤ 359 min. delay (n=233)	≥ 360 min. delay (n=65)	p
Total Charges ($)	mean, ±s.d. median, min-max	41,455, ±32,910 32,334, 5,806 - 190,024	40,284, ±29,116, 30,838, 7,494 - 179,920	ns

* = items are not mutually exclusive

† = cell sizes are small (< 5) therefore analysis of this factor is unstable

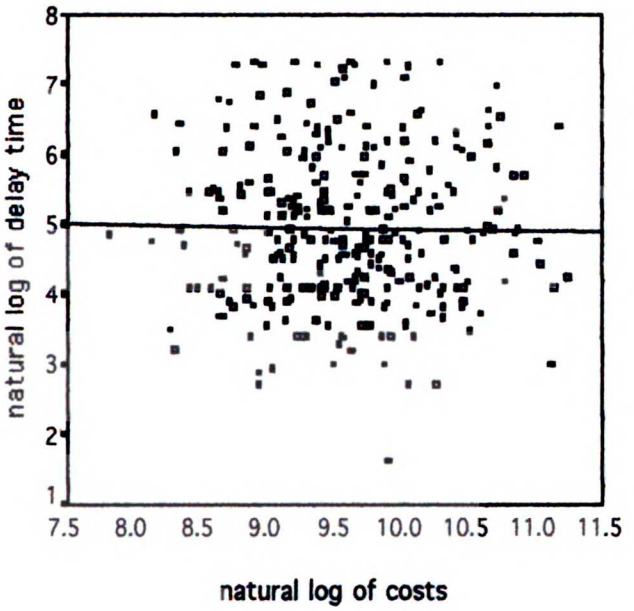
No demographic or cardiac history differences were found between those who delayed less than 6 hours and those who delayed longer (except that those with hypercholesterolemia delayed longer). An ambulance was called more frequently in the short delay group but there were no other differences with respect to presenting signs and symptoms or initial reperfusion strategy. There were significantly more follow-up CABG procedures in the long delay group and more stress tests performed. In terms of outcome variables, those with long delays had a shorter ICU stay however this did not translate into a difference in the cost. All of the deaths occurred in people who arrived at the hospital in less than six hours from symptom onset.

Question #2

- Is the time from onset of symptoms to hospital arrival related to cost of care?

The scatterplot showing the relationship of delay and cost of care is displayed below (Figure 2).

Figure 2. Scatterplot of delay time and total costs (transformed)



The cost of care was clearly not associated with delay time ($r = -0.02$; $p = 0.79$). This would seem to confirm the results described above where there was no difference in costs between short and long delayers.

Question #3

- Does delay time and sets of covariates (demographics, cardiac history, risk factors, hospitalization factors) predict cost when controlling for age and gender?

The sample was dichotomized into low and high cost based on the median value of $14,777. In order to evaluate which independent variables including delay created the most parsimonious model for predicting costs, five sets of variables were regressed on cost:

- demographic predictor variables and delay,
- cardiac history variables and delay,
- risk factor variables and delay,
- hospitalization characteristic variables and delay, and

- a final model containing variables from the previous four sets that appeared to be the strongest predictors of cost (based on significance levels of p = <0.05) controlling for age and gender.

The results for each set and the final model shown in Table 12 through Table 16 follow the same general organization. The estimated beta coefficient (β), standard error for the coefficient (S.E.), risk ratio (RR), 95% confidence intervals (CI), and p value are given.

Demographic Model

The first model containing four demographic variables and delay produced no statistically significant independent predictors of high cost (≥ $14,777). The overall predictive value was 58.0%. The model was better at predicting lower costs than higher costs (67.4% and 48.6% respectively). The Table below provides further detail for the demographic model.

Table 12. Estimates of Coefficients, Risk Ratios and 95% Confidence Intervals for Demographic Variables and Delay on High Cost.

	Variable	β	S. E.	Risk Ratio	95% CI	p
age	≥ 74 years	–0.275	0.283	0.76	0.44, 1.32	0.33
gender	women	0.209	0.270	1.23	0.73, 2.09	0.44
race	non-Caucasian	–0.193	0.247	0.82	0.51, 1.34	0.44
payor	private & other	0.549	0.302	1.73	0.96, 3.13	0.07
delay	≥ 360 minutes	–0.124	0.293	0.88	0.50, 1.57	0.67

Model chi-square = 6.9, df = 5, p = 0.23

Cardiac History Model

The cardiac history model with five variables and delay also produced no statistically significant independent predictors of high cost (≥ median). The model's overall predictive value was 56.0%. The model was better at predicting costs above the median than below the median (62.4% and 49.7% respectively). The Table below provides further detail for the cardiac history model.

Table 13. Estimates of Coefficients, Risk Ratios, and 95% Confidence Intervals for Cardiac History Variables and Delay on High Cost.

Variable (presence = 1)	β	S. E.	Risk Ratio	95% CI	p
angina	–0.192	0.310	0.83	0.45, 1.52	0.54
CABG	–0.553	0.467	0.58	0.23, 1.44	0.24
CHF	0.016	0.327	1.02	0.53, 1.93	0.96
previous MI	–0.459	0.296	0.63	0.35, 1.13	0.12
PTCA	0.381	0.456	1.46	0.60, 3.58	0.40
delay	–0.229	0.285	0.80	0.45, 1.39	0.42

Model chi-square = 5.25, df = 6, p = 0.51

Cardiac Risk Factor Model

The cardiac risk factor model with six variables and delay also produced no statistically significant independent predictors of high cost (≥ median). It's overall predictive value was 57.0%. The model was balanced in terms of predicting costs below and above the median (57.0% and 57.0% respectively). The Table below provides further detail for the risk factor model.

Table 14. Estimates of Coefficients, Risk Ratios, and 95% Confidence Intervals for Cardiac Risk Factor Variables and Delay on High Cost.

Variable (presence = 1)	β	S. E.	Risk Ratio	95% CI	p
family history	–0.031	0.382	0.97	0.46, 2.05	0.94
diabetes	–0.213	0.263	0.81	0.48, 1.35	0.42
hypercholesterolemia	0.454	0.298	1.57	0.88, 2.82	0.13
hypertension	0.196	0.244	1.22	0.75, 1.96	0.42
current smoker	0.451	0.347	1.57	0.79, 3.10	0.19
stroke	0.085	0.378	1.09	0.52, 2.28	0.82
delay	–0.280	0.289	0.76	0.43, 1.33	0.33

Model chi-square = 6.48, df = 7, p = 0.49

Hospital Characteristics Model

The 13 potential covariates for this category listed in the previous comparison tables contained several variables that could be considered redundant in this model. These were

tested for collinearity and eliminated as follows. Killip Class and ejection fraction were highly associated. Because there were more cases containing Killip Class, ejection fraction was eliminated. Hypotension on admission was highly associated with hypotension as a complication requiring therapy, therefore hypotension as a complication was eliminated from the 'complications' grouping. Additional treatment procedures was significantly associated with complications and therefore eliminated. (An analysis was performed containing all 13 variables for completeness. The results were substantially similar to those described here.)

The hospital characteristics model, therefore, contained six variables and delay. There were two statistically significant independent predictors of high cost. These were additional cardiac diagnostic procedures (RR = 3.41 {95% CI 1.87, 6.21}) and complications (RR = 3.23 {95% CI 1.87, 5.58}). Both were significant at p = <0.00. This model produced the best overall predictive value of 67.4%. The model was equal in terms of predicting higher costs and lower costs (each at 67.4%). The Table below provides further detail for the hospital characteristics model.

Table 15. Estimates of Coefficients, Risk Ratios, and 95% Confidence Intervals for Hospitalization Characteristic Variables and Delay on High Cost.

Variable		β	S. E.	Risk Ratio	95% CI	p
delay	• ≥ 6 hours	–0.066	0.312	0.94	0.51, 1.72	0.83
Killip class	• symptomatic (2,3,4)	0.461	0.287	1.59	0.90, 2.78	0.11
systolic BP	• ≤ 89	–0.030	0.590	0.97	0.31, 3.08	0.96
admission diagnosis	• MI	0.462	0.388	1.59	0.74, 3.40	0.23
reperfusion therapy	• PTCA or thrombolysis	0.538	0.399	1.71	0.78, 3.74	0.18
additional diagnostic procedures	• any	1.23	0.306	3.41	1.87, 6.21	<0.00

Variable		β	S. E.	Risk Ratio	95% CI	p
complication	• any (except hypotension)	1.72	0.278	3.23	1.87, 5.58	<0.00

Model chi-square = 53.74, df = 7, p = <0.00

Final, Combined Model

Only additional diagnostic procedures and complications (without hypotension) reached significance in the four preliminary models. They were entered into the final model along with age and gender. Again, the only two statistically significant independent predictors of high cost in the final model were additional diagnostic procedures (RR = 2.92 {95% CI 1.65, 5.15}) and complications excluding hypotension (RR = 3.43 {95% CI 2.03, 5.82}). In the final model the predictive value was 64.4%. Costs below the median were correctly predicted 60.4% of the time and costs above the median were correctly predicted 68.5% of the time. The Table below describes the final model.

Table 16. Estimates of Coefficients, Risk Ratios, and 95% Confidence Intervals for the Final, Combined Model on High Cost.

Variable		β	S. E.	Risk Ratio	95% CI	p
age	• ≥74 years	–0.456	0.274	0.63	0.37, 1.08	0.10
gender	• women	0.156	0.281	1.17	0.67, 2.03	0.58
additional diagnostic procedures	• any	1.071	0.290	2.92	1.65, 5.15	<0.00
complications	• any (except hypotension)	1.234	0.269	3.43	2.03, 5.82	<0.00

Model chi-square = 39.12, df = 4, p = <0.00

Post Hoc Analyses

The following section details post hoc analyses that were performed in an effort to explain the findings to the three primary research questions. The rationale for each post-hoc analysis is given and details of the results can be found in the Appendices as noted.

Subset Analysis of Short (< 1 Hour) Delay

Because data from the GISSI trials[2] showed an even better clinical outcome if delay was only one hour, a parallel analysis using delay at ≤ 1 hour was done and the results are displayed in Appendix B. The findings were substantially similar to those where the cut point was six hours. The exceptions included:

- a higher proportion of people delaying less than one hour had
    - a previous MI,
    - received pacemakers during the hospitalization, and
    - were placed on ventilators;
- and, a lack of difference in:
    - hypercholesterolemia in the cardiac history,
    - CABGs,
    - stress tests, and
    - number of deaths.

Even thought costs were not statistically different, it should be noted that the mean and median costs were $979 and $1,156 respectively less in the < 1 hour delay group.

Subset Analysis of Those Arriving Within Six Hours of Symptom Onset

A basic assumption in this study's hypothesis was that those arriving early would be eligible to receive some form of reperfusion therapy. In this study however, over half (55%) of the patients who arrived within six hours of onset of symptoms did not receive PTCA or thrombolysis. This fact could be a reason for a lack of association. That is, if

patients did not receive a therapy that has been shown to improve clinical outcomes, can one expect that there be an association to outcomes and cost? Therefore, a subset analysis of only those arriving within 6 hours of symptom onset (n=233) was done in an attempt to determine possible reasons for not receiving therapy. This analysis compared characteristics of those receiving a reperfusion therapy to those who did not. Complete results can be found in Appendix C. The findings are described below.

Those not receiving a reperfusion therapy were significantly older (p=<0.00) and were more likely to be women (p = <0.02). There were no differences in race. A significantly higher proportion of patients not receiving reperfusion had a history of cardiac disease and/or risk factors; this was most striking for those with a previous MI, CHF, stroke, diabetes, and hypertension. Interestingly, significantly more smokers received reperfusion.

There were 11 cases with contraindications noted on the CRF in the group arriving in less than six hours. Of these 11, one listed 'primary PTCA' as the contraindication, eight listed advanced age and/or history of stroke. One case noted the patient was in cardiac arrest. The last had a history of gastrointestinal bleeding.

Significantly more patients received reperfusion at ML (p = 0.02). The arrival times were fairly evenly distributed between shifts (32%, 37%, and 31% for day, evening, and night shifts respectively). However, a higher proportion of patients received reperfusion if they arrived on the day shift versus either the evening or night shift (p = 0.01).

In the group that received reperfusion, significantly more patients had chest pain (p = <0.00), a clear MI diagnosis (p = <0.00), higher Killip Class (p = 0.01), positive enzymes (p = <0.00), ST elevation (p = <0.00), and either anterior or inferior MI location (p = <0.00). Ejection fraction was significantly higher in those receiving reperfusion (p = 0.01).

If patients received reperfusion therapies, they were more likely to have an additional procedure performed; specifically a balloon pump, laser/athrectomy, or pacemaker. They were also more likely to have AV block or hypotension requiring therapy. While total length of stay was not different, ICU days and total costs were significantly higher ($p = <0.00$).

A logistic regression analysis of this subset (using methods similar to those previously described in the data analysis section above) was performed to determine the predictors of receiving a reperfusion treatment. The four preliminary groups (demographics, cardiac history, risk factors, and hospitalization characteristics) presented in Appendix D1-D4 produced 10 significant variables. These 10 variables were entered into the final model while controlling for gender with the results listed in the Table below.

Table 17. Estimates of Coefficients, Risk Ratios, and 95% Confidence Intervals for the Final Model in the < 6 Hour Subset Analysis on Reperfusion Treatment

Variable		β	S. E.	Risk Ratio	95% CI	p
age	≥ 74 years	–0.771	0.412	0.46	0.21, 1.04	0.06
gender	women	–0.165	0.382	0.85	0.40, 1.79	0.67
payor	private	0.700	0.416	2.01	0.89, 4.55	0.09
history of CHF	yes	–2.265	0.663	0.10	0.03, 0.38	<0.00
previous MI	yes	–0.755	0.397	0.47	0.22, 1.02	0.06
diabetes	yes	–0.501	0.371	0.61	0.29, 1.25	0.18
current smoker	yes	0.448	0.495	1.56	0.59, 4.13	0.37
history of stroke	yes	–0.423	0.571	0.66	0.21, 2.01	0.46
Killip Class	2, 3, or 4	–0.430	0.391	0.65	0.30, 1.40	0.27
hospital site	MZ	–0.783	0.342	0.46	0.23, 0.89	0.02
arrival time	evening or night shift	–0.765	0.350	0.47	0.23, 0.92	0.03

Model chi-square = 81.8, df = 11, p = <0.00

The final model produced three statistically significant independent predictors for receiving reperfusion therapy in this subset. These predictors were: no history of CHF (RR = 0.10 {95% CI 0.03, 0.38}), admission to the ML hospital setting (RR = 0.46, {95% CI 0.23, 0.89}), and arrival time during the day shift (RR = 0.47, {95% CI 0.23, 0.92}). Additionally, there was a trend toward younger age being predictive of receiving therapy as well as no previous MI.

Subset Analysis Using Cost Per Day As An Outcome

Since there were no relationships between cost of care and delay time, a subanalysis was performed using cost ÷ length of stay (cost per day; CPD) as this would incorporate a component of resource utilization. It was thought that this might provide more information regarding intensity of care rather than costs alone. Differences in CPD between short and long delayers were analyzed as well as predictors of high CPD.

Costs per day did not differ in the short and long delay groups (Appendix E1). In a logistic regression analysis similar to those previously described however, the final model produced slightly different predictors than the final model describing the independent predictors of cost alone (Appendix E2-E6). There were five statistically significant predictors of high cost per day. These were: younger age (RR 0.35, {95% CI 0.19, 0.64}), Caucasian race (RR 0.43, {95% CI 0.25, 0.74}), no previous history of angina (RR 0.50, {95% CI 0.25, 1.00}), receiving a reperfusion therapy (RR 2.67, {95% CI 1.55, 4.61}), and presence of a complication (RR 2.01, {95% CI 1.16, 3.51}).

Subset Analysis Examining Predictors of Delay Time

Another possible explanation that the null hypothesis was not rejected is that this sample may have differed from other populations reported in the literature. In addition to inspecting the sample description in Table 8, the dataset was examined for predictors of delay time using methods similar to those established previously (Appendix F1-F3). However in this case, only indicators of MI severity were used rather than the full hospitalization characteristics model. There were three statistically significant predictors of

long delay in the final model (Appendix F4). These were: minority race (RR 1.88, {95% CI 1.06, 3.35}), government payor (RR 0.43, {95% CI 0.20, 0.91}), and history of hypercholesterolemia (RR 2.09, 95% CI 1.11, 3.95}).

Subset Analysis of Deaths in the Short Delay Group

All of the deaths occurred in patients who arrived with less than six hours of delay. Because this was an unexpected finding, a subset analysis was performed to investigate the differences between those who died and those who survived, as well as causes of death. The complete results can be found in Appendix G. In brief, those who died were older and had a higher proportion who were transported by ambulance. There was a higher proportion of MI as the admission diagnosis ($p = <0.00$) and symptomatic presentation by Killip Class ($p = <0.00$). The non-survivors had a lower ejection fraction ($p = 0.01$) and systolic blood pressure ($p = <0.00$). Non-survivors had a higher proportion of complications ($p = <0.00$), and used more ICU days ($p = 0.04$). There were no differences with respect to gender, race, cardiac history, initial reperfusion strategy, presence of ST elevation, length of hospital stay, or costs between survivors and non-survivors.

Of the 24 deaths, 15 listed cardiac related causes, four were listed as 'do not resuscitate' (the precipitating factor for death was unclear), and five had no cause of death listed. All those who died had a history of cardiac disease and/or risk factors for cardiac disease. Twenty percent of the patients died within five hours; for 50%, death did not occur until four days or longer.

Analysis with an Interaction Term for Age and Gender

Finally, an argument could be made that age and gender may covary and therefore an interaction term should have been used rather than each variable separately. Covariances between these two variables were consistently in the range of 30-36%. Since this could be considered borderline covariance in some disciplines, the key analyses were performed

CHAPTER FIVE: Discussion

Principal Findings

Relationship of Delay Time to Cost of Care

This study examined the impact of patient delay in seeking care for MI on hospitalization cost using three statistical methods: 1) a comparison of cost in patients who delayed less than six hours and those who delayed longer, 2) an examination of the association between delay time (in minutes) and cost (in dollars), and 3) an evaluation of delay is a predictor of high cost (< median).

In this sample, there were no differences in cost between those with short delays and those with long ones, there was no association between delay and cost, and lastly, delay was not a significant predictor of high cost. The null hypothesis could not be rejected. The following discussion attempts to analyze these findings.

If delay time was short, reperfusion therapy was given, and clinical outcomes were improved, the hypothesis of this study reasoned that cost of care for the hospitalization would be reduced in the short delay group. However, there was no difference between patients arriving less than six hours or over six hours in terms of costs or charges. Equally as striking was that there were no differences in clinical outcomes as measured by complications during hospitalization, and all deaths occurred in the short delay group. Several post hoc analyses revealed important findings and possible explanations for these results.

Because there were no differences in outcomes or cost using delay dichotomized at six hours, a one hour cutoff was examined as an alternative based on information from the GISSI trials indicating that results were more pronounced in the shorter time period.[2] The results were substantially similar to the six hour analysis (Appendix B). Despite the fact that costs were not statistically different however, mean and median costs of the < 1 hour group were lower by $979 and $1,156 respectively. The lower amount, while not statistically significant, could be financially significant in the aggregate to health care

providers. This difference would be even more substantial to Medicare or other reimbursing agencies when viewed as charges. The lack of statistical significance may have been a function of sample size. The trend toward lower cost in the <1 hour delay group is worthy of further research in larger samples.

As with the < 6 hour analysis, the < 1 hour analysis also showed a lack of difference in complications and mortality. It may be that the benefits of a reduction in infarct size may only become functionally apparent months or years later. This has been shown to be the case in other studies.[32-34]

Patients must present to the emergency room in less than six hours after the onset of symptoms in order to receive reperfusion therapies and obtain the maximum physiologic benefits. Studies have shown that in-hospital, short, and long term mortality and clinical outcomes are improved when delay time is short.[2, 3, 28, 29, 34-36] Ultimate viability of myocardium after coronary occlusion is limited and dependent on duration and severity of ischemia.[7, 8]

It has also been reasoned that cost could be reduced if delay was reduced. A simulation model designed to examine the relationship between incremental costs and benefits of coronary thrombolysis reperfusion therapy described a three to seven times increase in cost per additional one-year survivor for patients arriving four hours after the onset of symptoms compared to those arriving less than four hours.[44] This finding, however, has not been subsequently verified in actual studies.

A basic assumption in this study was that those arriving early would receive some form of reperfusion therapy. This was not the case. Therefore, it could be hypothesized that since more than half (55%) of the patients who arrived within six hours of onset of symptoms did not receive PTCA or thrombolysis, an association of early treatment with cost could not be made. It was important to understand why reperfusion treatments were not given in this group as it may impact future study in this area. If the maximum treatable population had been achieved in the short delay group, additional cost benefits may not be

achievable given the constraints of patient characteristics and current diagnostic techniques. Few studies have reported the percentage of total patients presenting with symptoms of MI receiving thrombolytics or PTCA. Most include only those receiving a treatment making it difficult to speculate that this is a 'typical population'. A more likely explanation is that this sample represented a more 'real world' population and therefore findings may not be similar to those describing treated populations.

There were several possible explanations for not receiving reperfusion therapy including:

- contraindications and issues with respect to medical judgement
- availability of therapy (e.g., was catheterization laboratory open 24 hours?), or
- an unclear symptom complex making diagnosis more difficult.

Two relative contraindications for receiving a reperfusion therapy (particularly thrombolysis) available in the NRMI database were advanced age and a history of stroke. A post hoc analysis found that there were significantly more patients over the median age of 73 years who did not receive a therapy and a significantly lower proportion of patients receiving reperfusion who claimed a history of stroke. The NRMI database also includes a variable for noting contraindications to thrombolytics (but not PTCA). In general, these verified the previous statement about age and stroke. These findings would indicate that patients with contraindications appropriately did not receive a reperfusion therapy.

Medical judgment could have also played a role in not administering thrombolytics or performing a PTCA. Patients with a lower ejection fraction and some cardiac history and/or risk factors did not receive reperfusion treatments. A smaller proportion of symptomatic cases (as measured by Killip Class) received reperfusion than those without heart failure symptoms. These data would seem to indicate that those who did not receive reperfusion treatments were a sicker population. It could be reasoned that there was a reluctance on the clinician's part to expose the patient to the added risk of acute reperfusion strategies. Indeed, clinical practice guidelines from AHA/ACC for reperfusion therapies

warn of the relative risks for patients with intracranial hemorrhage, advanced age, and increasing numbers of cardiovascular risk factors (thrombolytics), and, for angiography, hemodynamic instability.[78]

The post hoc analysis also suggests that availability of therapy played a role in patients not receiving a reperfusion treatment. This was a particular issue since one of the sites (MZ) did not have a 24 hour catheterization laboratory. Significantly more patients received reperfusion at ML ($p = 0.02$) where there was 24-hour access to a catheterization laboratory. Also, patients arriving during the day shift were more likely to receive reperfusion therapies. This finding, if confirmed in other studies, could raise challenging policy and legal issues for all hospitals if indeed clinical outcomes and costs were different. For the purposes of this study, it may, in part, explain the number of patients not receiving a reperfusion treatment.

Most importantly, the subanalysis of the < 6 hour delay group revealed a pattern of unclear symptoms on admission. Those without a clear diagnosis of an MI on admission were less likely to have reperfusion administered and significantly fewer patients with chest pain and ST elevation had no reperfusion. As mentioned above, a smaller proportion of with Killip Class ≥2 received reperfusion than those in Class 1, and, a smaller proportion of patients without a clearly defined anterior or inferior MI (i.e., classified as 'other' MI) were not given reperfusion. This sample was older than most reported in the literature and it has been shown that older patients are also more likely to have non-diagnostic ECGs on admission.[79]

Therefore, the low percentage of eligible patients who actually received a reperfusion therapy might be explained by contraindications and appropriate medical judgment; but also that there were a large number of patients presenting with symptoms that could not be diagnosed, assumedly until the 'window of opportunity' has passed. It would also seem that site and arrival time influenced delivery of therapy. (It should be

remembered that qualification for enrollment NRMI is based on diagnosis of MI at discharge and not on admission.)

As a comparison to this study's finding that only 45% of the < 6 hour group received a reperfusion therapy, one author reporting on national data from NRMI noted that 50.7% of the patients in the database under the age of 55 received thrombolytics while 31.2% received PTCA.[79] These rates declined significantly with age and could somewhat verify the 45% finding in this study. Other literature describing characteristics of the NRMI dataset do not include percentages of patients receiving therapy,[22, 48, 79-81] therefore it is difficult to compare this study's findings to other NRMI data. In fact, there are few studies that report on the percentage of patients treated versus not treated. Reports on the MITI trial are an exception. In their study comparing prehospital with hospital thrombolytics, they report that 71% of patients received some form of acute intervention, defined as thrombolysis, PTCA, CABG, or angiography.[82] If this were generally true, the current sample may not be representative of other populations.

The findings of this post hoc subset analysis are relevant to this study. The high proportion of patients not receiving reperfusion due to contraindications and medical judgement, availability, and undiagnostic signs and symptoms makes it difficult to link delay ⇨ therapy ⇨ improved clinical outcomes ⇨ cost. An alternative explanation could be that reperfusion therapies are now given to the maximum number of people possible given the circumstances of admission.

Costs per day were evaluated in a post hoc analysis to determine if the incorporation of an 'intensity of care' component would provide different information than the analysis of cost alone. While CPD did not differ between the short and long delay group, the logistic regression analysis revealed interesting differences when compared to the analysis using cost alone. In the previous analysis describing the predictors of high cost, additional diagnostic procedures and complications were found to be significant. The significant independent predictors for high CPD were: younger age, Caucasian race, no history of

angina, receiving a reperfusion therapy, and complications. These results seem to confirm other findings in this study in that younger patients tended to have more reperfusion treatments and that receiving a reperfusion treatment and experiencing complications increased costs. It appears that adding a component of resource utilization such as length of stay, provides new and different information that may be more representative of the clinical and cost picture.

This data set was examined to determine if it was similar to samples of other comparable populations of patients presenting with myocardial infarction. As detailed in Table 8, the sample in the current study is somewhat older when compared with other studies.[16, 20, 23, 39, 53, 82, 83] However, many of these studies investigated the effects of thrombolytics, consequently patients with advanced age were excluded, thereby lowering the mean age of other samples. The proportions of men and women appear to be similar to other reported studies. There are few studies that detail race and payor in a manner that is interpretable for the purposes here. Ethnicity will probably vary widely depending on geographic region or country. It should be expected that this population would be heavily dominated by Medicare insurance because of age. Reported proportions of samples with prior cardiac history range widely. A history of a previous MI ranges from 13%[84] to 57% [85]. This study reported 27%. History of angina is more consistent at ± 35%[9, 20, 30, 82] however this study reported only 17%. Relying on retrospective data abstraction may be partially responsible for this discrepancy and it probably doesn't affect this study's outcome. Reported proportions of CHF, PTCA, and CABG are consistent with the literature.[30, 82, 84] Proportions of those with cardiac risk factors also vary widely. History of stroke is not often reported. The sample in the current study appears to have a higher proportion of diabetics[9, 20, 30, 85] and a higher proportion of hypertension history[9, 20, 30, 47, 82, 83] compared to other studies with similar populations. One could speculate that the sample in this study was more representative of the MI population as a whole and that characteristics differ because all patients were included, not just those receiving a treatment.

This has important implications in terms of interpreting the results since this could be more representative of the 'real world'.

Proportions of history of hypercholesterolemia are within range of other samples.[9, 30, 82, 83] However in this study the proportion of cases with hypercholesterolemia was noted to be higher in the long (> 6 hours) delay group and was found to be a significant predictor of delay. This is a difficult finding to interpret and may have occurred merely by chance.

In the logistic regression of demographic, cardiac history, and risk factors in this study, race, payor, and hypercholesterolemia were found to be independent predictors of delay. It is difficult to relate this to other studies since these are variables that are not often reported. These findings may be an important basis for future investigations. Additionally, they may help guide patient education efforts to specific subsets of patients.

With the information available, the sample in this study would seem to differ primarily as to older age, and a higher prevalence of hypertension and diabetes. There are no studies in regards to how these factors might affect costs, although it has been shown that they do affect clinical outcomes.

Summary

To summarize the principle findings; while delay time and hospitalization cost were not related, nor was delay time predictive of cost, post hoc analyses revealed important information that may prove to be more characteristic of MI populations than those previously reported. The initial alternative hypothesis (there is an association between delay time and cost) was predicated on the concept that short delay times allow administration of more aggressive therapies, which in turn have been shown to produce better outcomes. It was assumed that better outcomes (fewer subsequent procedures, fewer complications, and shortened length of stay) would result in lower costs. Since a large proportion of patients delaying less than six hours did not get reperfused this hypothesis may have not been testable in the present study. An examination of those arriving at the hospital within six hours of the onset of symptoms who were technically

eligible for reperfusion showed that many not receiving a treatment had unclear diagnoses, contraindications and high risk, or reduced availability. This would imply that extenuating circumstances weigh more heavily in the choice of therapies than delay time alone or that the maximum treatable population has been achieved. Further cost reductions from decreased delay time may not possible. However, the fact that costs were lower (though not statistically significant) in the < 1 hour group may indicate that there may still be some opportunity for cost reduction in shorter delay times.

Use of cost/day, rather than cost alone, revealed more information about the population and may be a more useful variable for future research. This sample was somewhat different than others reporting of acute MI populations; it was older and had a higher prevalence of diabetes and hypertension. It was not apparent that these factors should account for lack of difference in clinical outcomes and cost of care.

In the current study, not only were there no differences in hospitalization cost between short and long delayers, clinical outcomes were similar. However complications did predict higher cost as might be expected. Other studies have shown that clinical benefits of receiving an optimal reperfusion therapy are frequently not apparent until the longer term. It would seem natural that cost benefits might therefore not be apparent for some time in the future.

Secondary Findings

Gender Comparisons (see Table 10 in Chapter Four)

Numerous studies have examined gender differences in terms of cardiovascular disease and delay in seeking help for symptoms of MI. Therefore, this study sought to describe gender differences in the current sample and to determine what, if any, impact they had on cost.

Women in this study were significantly older (mean difference, 11 years; p = <0.00) as has been shown in other studies. But, unlike other studies,[1, 9, 14, 18, 30, 48, 51] this

study showed that delay time in women was not different from men. Their presenting signs and symptoms were similar to men yet men were more likely to receive a reperfusion therapy. While gender bias can not be ruled out, a more likely explanation is that the lower proportion of women receiving a treatment was a function of older age and history of stroke. Additionally, significantly more women were covered by Medicare. While reimbursement shouldn't influence treatment decisions, the possibility that it did can not be ruled out.

Despite the difference in initial interventional therapy, there was a distinct similarity between genders in terms of additional diagnostic and therapeutic procedures required as well as complications. This presents a perplexing analysis problem in the face of other studies demonstrating improved clinical outcomes in patients receiving thrombolysis or PTCA. One could argue that the choice of therapy is not relevant to complications, but a more likely appraisal is, as before, that longer term follow-up is needed to measure differences in benefits.

Women had a lower mean and median cost of care (5%) when compared to men although this did not reach statistical significance. The added expense of the reperfusion therapy should have increased the cost slightly in men. Reperfusion treatments increase the cost of treating MI during the hospitalization phase, however the increase can vary widely.[86] While the 5% was not statistically significant, it could potentially be financially significant to payors or providers. This difference is worthy of future research to verify this trend in a larger sample. If the trend is real, it would be valuable to understand the exact resources that contribute to the cost difference.

Comparisons of Short Versus Long Delayers (see Table 11 in Chapter Four)

Although there was no difference in cost of care between those who delayed less that six hours and those who delayed longer, several other interesting differences emerged. The literature on delay has shown that knowledge or history of cardiac disease does not ensure more rapid response to symptoms of heart attack,[10, 11, 17, 21, 25, 26] however other

studies contradict these findings.[1, 9, 30, 51] Fifty-five percent of patients in this sample had some history of previous cardiac disease and 77% had cardiac risk factors however this did not appear to decrease delay time.

When each history or risk factor variable was examined separately, one exception was noted. More patients with hypercholesterolemia delayed longer, and hypercholesterolemia was also found to be an independent predictor of delay. Others have found no difference.[9] It is difficult to determine with the data available from the registry why this might be the case. It could be hypothesized that because this group may have assumed a greater personal awareness of the symptoms, they could have judged those symptoms unimportant delayed longer. Another explanation is that this was merely a chance observance. When delay was dichotomized at one hour, those with a previous MI were more likely to have arrived early ($p = <0.00$). Although unmeasureable in this study, this might indicate that the symptoms were similar to a previous MI and the patient recognized it as such. Patients who delayed one hour or less used ambulances more often, were put on a ventilator and had pacemakers inserted more often suggesting a greater urgency for seeking medical care.

A subset analysis of the deaths in the short delay group revealed that these were sicker patients and, not surprisingly, they delayed a shorter period of time. There was no difference in cost between survivors and non-survivors. One might assume that non-survivors, who were short delayers and who appeared to be sicker, might have consumed more resources in a shorter period of time. However, the deaths occurred over a wide range of time (0 - 16.9 days; median 3.7 days) thus approximating a pattern of a more typical patient.

Significance of Findings and Implications

To date, researchers have found that reperfusion therapies minimize or eliminate myocardial damage from MI. Further, it has been shown that, in order to optimize the

benefits of various reperfusion strategies, patients must arrive at the hospital within a maximum time limit of six hours after symptom onset. Pre-hospital delay has been the focus of research, as well as a number of public awareness and education campaigns. These campaigns consume time and resources, but most have hypothesized that it is worth the effort despite the lack of demonstrated success.

Virtually any interventions in nursing and medicine have been, or will be, subject to evaluation of their cost effectiveness. Heart disease is the number one cause of morbidity and mortality in the Western world. Approximately six million patients per year present to EDs with chest pain or similar symptoms[87] and over 1.5 million people in the United States have a new or recurrent MI each year.[45] Therefore cost effective strategies to diagnose and treat MI rapidly and efficiently are highly important.

In order to determine the cost effectiveness of public campaigns that decrease delay time, one must first establish whether costs are related to delay time, and if so, determine what the baseline costs of delay are. This investigation found that delay time does not impact cost of care and, as revealed in post hoc analysis, there are several issues that have important implications for health care clinicians.

- A majority of patients arriving within a six hour time frame after onset of symptoms did not receive a reperfusion therapy. This warrants further prospective investigation as to the reasons for not receiving available treatments and to determine if the maximum treatable population has been reached.. This finding has significant implications in terms of continued efforts to promote shorter delay times.
- Accurate, rapid, and efficient diagnosis of MI in the ED remains a significant clinical and technological challenge. A report establishing the current methods and their relative clinical utility concluded that there is much work to be done.[87] The current study would seem to substantiate this statement.

- There was a trend toward lower costs in the < 1 hour delay group that was not present in the <6 hour group. Consideration of a shorter delay time may be important in terms of future research into cost implications.
- Measures of cost alone may not yield as much information as a variable that includes a component of resource utilization. Future research in this area should include a measure of 'service intensity', not just cost alone.
- Gender differences though present in some variables, were not as striking as others have reported. While an initial reperfusion treatment was performed less often, there are sound reasons why this may have occurred. This finding could imply that potential gender bias has been recognized and acted on.
- The hospitalization phase has been shown in other studies to represent only a portion of total costs to patients, providers, payors, and society. A longer follow-up period may be needed to realize clinical and financial benefits when studying the impact of delay time on costs.
- Lastly, and most importantly, there was not enough information in this study on which to base a change of attitude or policy with respect to educating the public about delay. Even though shorter delay times did not result in decreased cost thereby justifying expenses related to programs aimed at reducing delay, improved clinical outcomes have been documented and argue for continued efforts to reduce delay until these findings are confirmed.

Limitations

The most common sources of potential bias for a historic prospective study utilizing secondary databases are presented in the following section along with their relevance to this study.

Selection Bias

Patients who did not survive to hospital arrival, and those who may have had symptoms and never recognized those symptoms or sought help are by their nature, not included. This could have a subsequent effect not only on mean and median delay times, but cost as well. However, in this observational study, generalizability can only be extended to other populations who are similar in their presentation to the hospital. In this restricted context, it is unlikely that selection bias is a major problem.

Another potential issue with respect to selection bias was the large number of cases that were eliminated due to missing delay times. Even though NHLBI reports that one third of patients presenting to EDs cannot identify an abrupt onset time,[49] for completeness sake this study sought to identify characteristics within this sample that may have shown evidence of selection bias. The group that was eliminated had less chest pain, was less likely to have ST elevation or be diagnosed on admission with an MI and was less likely to undergo a reperfusion therapy (Table 9). The location of the MI may also have been more obscured since there was a higher proportion listed as 'other'. These findings are similar to the only other study reporting a large excluded population for missing delay times.[9] It could be hypothesized that symptom onset (and therefore delay time) was not reported because the diagnosis of MI may not have been immediately considered. Because administration of a reperfusion therapy was not predictive of cost in the group as a whole, those excluded should not represent a potential for selection bias.

Misclassification Bias

Misclassification bias can occur with respect to the predictor variable, the outcome variable, and covariates or confounders and is unavoidable to some degree. There are two types of misclassification: differential, and the less harmful non-differential bias. There is no reason to believe that the bias in the present study is differential. The predictor and outcome variables came from two different data sources making it unlikely to have misclassification of the outcome variable based on knowledge of the predictor variable. All

data with the predictor variable were entered and cleaned before the outcome data (costs and charges) were acquired and merged into the dataset. It is most likely that any misclassification that occurred would be non-differential and as such would tend to have a dilution effect that produces a more conservative finding, moving the answer toward the null hypothesis.[88]

NRMI Database - An Existing, Observational Dataset

This study used the NRMI database which is an existing, ongoing, observational study. While use of existing databases is advantageous in that they can answer important research questions without the cost and time required for data collection, they can present some potential limitations. The investigator has no control over variable selection and measurement. All data collection methods have been predetermined and these may not coincide with the current investigators goals. Definition of variables may be inconsistent with the needs of secondary analyses, or they may be ill-defined. Data collection procedures are frequently unknown and may be subject to idiosyncrasies that may impact the results.

For the present study, variables were examined in detail before initiation of the research by the investigator. A detailed data dictionary and reference manual were provided with the data disks. These sources carefully outlined data collection parameters and variable definitions. The primary investigator spent six months collecting data with the data abstractors to gain additional understanding of the procedures and definitions. A clear understanding of the variables contained in the dataset allowed the investigator of the present study to accurately and easily recode variables that were necessary for some of the analyses. Because of these references and interactions with the database, it is felt that any possible limitations of using an existing information source are far outweighed by the many advantages presented by this rich database.

As an observational database, NRMI is not a controlled, randomized clinical trial designed to test the effectiveness of various therapeutic interventions. It is strictly a study

that tracks the use of various interventions in clinical practice. Comparisons of outcomes across treatment groups may be inappropriate. Because the present study did not try to prove a cause and effect relationship, the potential limitations from an observational study are not a major problem.

Another issue with respect to the NRMI database is that the information supplied to the central processing facility is abstracted from medical records that, in and of themselves, may have some degree of error. Data from medical records are criticized because they have not been collected using rigorous methodological oversight. These limitations are attenuated somewhat in the present study because a large part of the abstracted data from the records were objective (i.e. not subject to interpretation) and many were presented in the form of a computer printout. The data were abstracted by Clinical Nurse Specialists (CNSs) in Cardiovascular Nursing who were specially trained in collection methods. Additionally, some of the CNSs were employed in the hospital's CCU and were often familiar with the specific patient's case.

Statistical Inference

Statistical issues such as small sample sizes, large differences in sample number between groups, and large variances for delay time and hospitalization cost may have precluded achieving statistically significant findings. Additionally, many of the confidence intervals were wide indicating that risk ratios should be interpreted with caution.

Settings

All patients used in this study were enrolled in two sites within the same city. This was advantageous in that they shared the same cost accounting structure. The ability to generalize findings beyond this community may be a limitation, however, the sites were different in terms of structure (teaching medical center versus community hospital), patient diversity particularly in ethnic minorities, and also in terms of their treatment protocols. Mount Zion did not have a full time catheterization laboratory and relied more heavily on thrombolysis whereas ML was the opposite. These factors probably enhanced

generalizability and were more representative of the MI population as a whole. However, since this was an observational study, by its nature findings must be limited to the characteristics of the study sample.

Summary

The research design in this study was constructed with an awareness of the potential limitations mentioned above. Because of this, it is felt that the objectives of the study were not compromised and that, where appropriate, references have been made to these limitations. The NRMI is a rich database supported by a skilled group of abstractors. The variables were clearly defined and were well understood by the investigator. Potential selection and misclassification biases were recognized and were reflected in the conclusions.

Future Research

This study demonstrated that there was no relationship of delay time to cost of hospitalization. Yet there were a number of findings that deserve future research. The following are some potential questions.

The first recommendation for future research would be the duplication of this study in other settings using a prospective design. There may have been factors peculiar to the specific hospital settings or geographic region that obscured a potential relationship. A prospective study would improve the frequency rate of reporting symptom onset time, and potentially the accuracy since the data would be collected with that specific aim in mind.

It may be that any benefits that accrue to early arrival to the hospital may not be apparent until some follow-up period. This has been shown to be the case in studies that have followed patient outcomes after MI for a number of years. If outcomes and/or complications are not substantially different in the hospital, but are during follow-up, it is reasonable to expect that costs will also be different. A finding of improved outcomes and

decreased costs at follow-up would have interesting health policy implications particularly with respect to reimbursement strategies.

It may also be beneficial to investigate more rapid, accurate diagnostic methods and techniques that would make an impending MI more clearly apparent to the admitting staff. Since there was a large proportion of patients in the present study who did not receive reperfusion therapy for what looks like a diagnosis that could not be accurately determined in time to qualify for reperfusion, attention to diagnostic methods could be of benefit. An NHLBI Working Group recently determined that there is a dearth of research related to the diagnostic performance and efficacy of important technologies in the ED for evaluation of patients presenting with signs and symptoms of acute cardiac ischemia. They conclude that clinical judgment is often required to make diagnostic decisions and that there should be an effort to improve the rapidity and effectiveness of diagnostic methods.[87]

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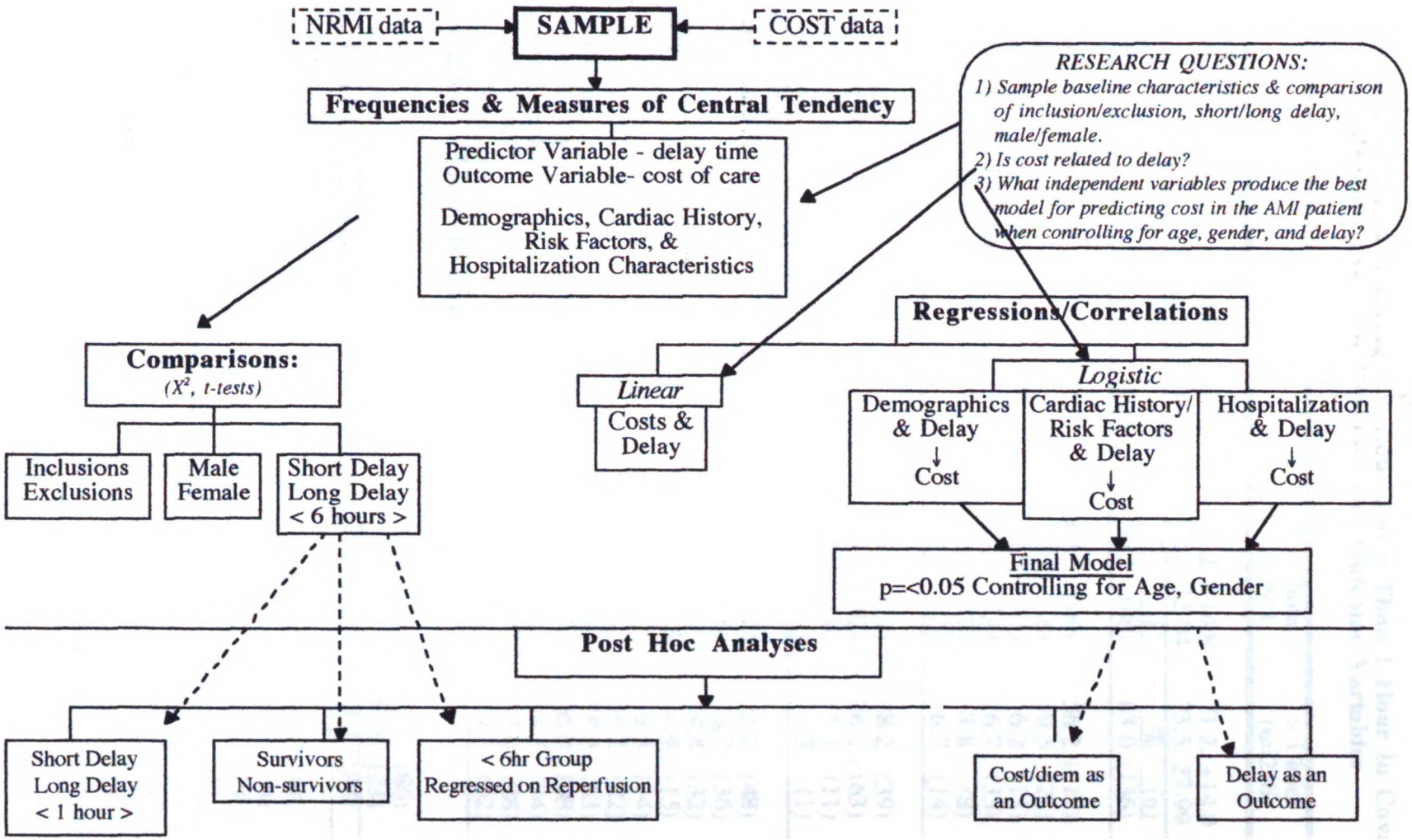
Appendix A
Data Analysis Plan



Appendix B.
Comparison of Those Delaying < 1 Hour and ≥ Than 1 Hour in Covariates, Primary Predictor Variable, and Outcome Variables

		< 1 hour (n=81)		> 1 hour (n=216)		p
Demographics						
Age (yrs.)	mean, ±s.d.	71.2, ±14.8		71.2, ±14.0		ns
	median, min-max	72.0, 32-94		73.5, 27-99		
		%	(n)	%	(n)	
Gender	(men)	59.3	(48)	63.0	(136)	ns
Race:						ns
Caucasian		60.5	(49)	56.2	(118)	
Black		9.9	(8)	10.5	(22)	
Hispanic		3.7	(3)	6.2	(13)	†
Asian, Pacific Islander		17.3	(14)	16.7	(35)	
Native American & other		2.5	(2)	3.8	(8)	†
unknown		6.2	(5)	6.7	(14)	
Payor:						ns
commercial, HMO		26.3	(21)	18.2	(39)	
government		65.0	(52)	76.2	(163)	
self-pay, other		7.5	(6)	5.1	(11)	
unknown		1.3	(1)	.5	(1)	†
Cardiac History & Risk Factors: *						
previous MI		39.5	(32)	22.2	(48)	<0.00
angina		19.8	(16)	16.7	(36)	ns
CHF		23.5	(19)	14.8	(32)	ns
PTCA		12.3	(10)	6.9	(15)	ns
CABG		8.6	(7)	6.5	(14)	ns
stroke		13.6	(11)	10.2	(22)	ns
diabetes		29.6	(24)	29.2	(63)	ns
hypertension		51.9	(42)	50.0	(108)	ns
current smoker		13.6	(11)	15.7	(34)	ns
family history		8.6	(7)	13.0	(28)	ns
hypercholesterolemia		17.3	(14)	24.1	(52)	ns
Covariates - Hospitalization						
Transport:						0.05
self		28.8	(23)	41.1	(86)	
ambulance		71.3	(57)	58.9	(123)	
Chest Pain Present on Admission		67.5	(52)	70.7	(145)	ns
Admission Diagnosis						ns
MI		46.3	(37)	50.5	(108)	
r/o MI		31.3	(25)	29.9	(64)	
unstable angina		8.8	(7)	13.6	(29)	
other		13.8	(11)	6.1	(13)	
Initial Reperfusion:						ns
none		60.5	(49)	56.5	(122)	
thrombolysis		11.1	(9)	14.8	(32)	
PTCA		28.4	(23)	28.7	(62)	

		< 1 hour (n=81)	> 1 hour (n=216)	p
Killip Class:				**ns**
1		70.4 (57)	68.5 (148)	
2		13.6 (11)	19.0 (41)	
3		9.9 (8)	9.3 (20)	
4		6.2 (5)	3.2 (7)	
Enzymes 2x normal		79.7 (63)	85.7 (180)	**ns**
ST Elevation Present		50.6 (41)	56.5 (122)	**ns**
MI Location:				**ns**
anterior		28.4 (23)	29.6 (64)	
inferior		23.5 (19)	31.9 (69)	
other		48.1 (39)	38.4 (83)	
Ejection Fraction (%)	mean, ±s.d.	44.7, ±14.1	44.6, ±12.0	ns
	median, min-max	45, 20-70	45, 15-68	
Systolic BP (mmHg):	mean, ±s.d.	136, ±42.0	145, ±33.6	ns
	median, min-max	136, 0-260	144, 53-260	
Other Procedures: *		% (n)	% (n)	
CABG		7.4 (6)	6.5 (14)	ns
cardiac catheterization		28.4 (23)	33.8 (73)	ns
echocardiogram		48.1 (39)	50.9(110)	ns
balloon pump		6.2 (5)	6.9 (15)	ns
laser/athrectomy/stent		3.7 (3)	3.7 (8)	ns †
pacemaker		9.9 (8)	3.7 (8)	0.04
repeat PTCA		13.6 (11)	15.7 (34)	ns
rescue PTCA		1.2 (1)	1.4 (3)	ns †
stress test		18.5 (15)	26.9 (58)	ns
ventilator		25.9 (21)	10.2 (22)	<0.00
Complications: *				
recurrent angina		16.0 (13)	15.7 (34)	ns
AV block		3.7 (3)	1.9 (4)	ns †
cardiac arrest		4.9 (4)	3.7 (8)	ns †
CHF		12.3 (10)	13.4 (29)	ns
Rx/hypotension		28.4 (23)	19.0 (41)	ns
pericarditis		0.0 (0)	1.9 (4)	ns †
recurrent MI		3.7 (3)	2.3 (5)	ns †
cardiac rupture		1.2 (1)	0.5 (1)	ns †
cardiogenic shock		6.2 (5)	5.6 (12)	ns
VT/VF		6.2 (5)	3.2 (7)	ns
Deaths		11.1 (9)	6.9 (15)	ns

Outcome Variables				
LOS (days)	mean, ±s.d.	6.5, ±5.7	6.6, ±4.1	ns
	median,	4.8,	5.6,	
	min-max	0-30	0.2-34.9	
ICU Days	mean, ±s.d.	2.7, ±2.4	2.4, ±2.2	ns
	median,	2.0,	2.0,	
	min-max	0-11	0-13	
Total Costs	mean, ±s.d.	17,700, ±13,449	18,679, ±13,213	ns
($)	median,	13,811,	14,967,	
	min-max	3,896-69,372	2,469-76,621	

* = items are not mutually exclusive

† = cell sizes are small (< 5) therefore analysis of this factor is unstable

Appendix C.
Comparison of Those Receiving and Not Receiving a Reperfusion Therapy in the Group Delaying < 6 Hours: Covariates, Primary Predictor Variable, and Outcome Variables

		No reperfusion (n=127)		Reperfusion (n=106)		p
Demographics						
Age (yrs.)	mean, ±s.d.	76.5, ±12.7		65.7, ±14.0		<0.00
	median, min-max	79, 27-99		67.5, 32-93		
		%	(n)	%	(n)	
Gender	(men)	56.7	(72)	71.7	(76)	0.02
Race:						ns
Caucasian		61.9	(78)	60.0	(60)	
Black		11.1	(14)	7.0	(7)	
Hispanic		4.0	(5)	4.0	(4)	
Asian, Pacific Islander		13.5	(17)	21.0	(21)	
Native American & other		4.8	(6)	2.0	(2)	
unknown		4.8	(6)	6.0	(6)	
Payor:						<0.00
commercial, HMO		15.1	(19)	29.5	(31)	
government		82.5	(104)	58.1	(61)	
self-pay, other		2.4	(3)	10.5	(11)	
unknown		0.0	(0)	1.9	(2)	
Cardiac History & Risk Factors: *						
previous MI		38.6	(49)	17.9	(19)	<0.00
angina		18.1	(23)	17.0	(18)	ns
CHF		31.5	(40)	2.8	(3)	<0.00
PTCA		10.2	(13)	7.5	(8)	†
CABG		10.2	(13)	3.8	(4)	ns
stroke		15.7	(20)	5.7	(6)	ns †
diabetes		36.2	(46)	20.8	(22)	0.01
hypertension		59.8	(76)	43.4	(46)	0.01
current smoker		7.9	(10)	19.8	(21)	0.01
family history		9.4	(12)	14.2	(15)	0.01
hypercholesterolemia		18.1	(23)	20.8	(22)	ns
						ns
Covariates - Hospitalization						
Transport:						ns
self		28.6	(36)	36.3	(37)	
ambulance		71.4	(90)	63.7	(65)	
Site:						0.02
Moffitt Long		47.2	(58)	52.8	(65)	
Mount Zion		62.7	(69)	37.3	(41)	
Arrival Time:						0.01
7am-3pm		43.2	(32)	56.8	(42)	
3pm-11pm		53.5	(46)	46.5	(40)	
11pm-7am		67.1	(49)	32.9	(24)	
Chest Pain Present on Admission		56.3	(67)	86.3	(88)	<0.00

		No reperfusion (n=127)	Reperfusion (n=106)	p
Admission Diagnosis				<0.00†
MI		15.2 (19)	93.3 (98)	
r/o MI		50.4 (63)	3.8 (4)	
unstable angina		17.6 (22)	1.9 (2)	
other		16.8 (21)	1.0 (1)	
Killip Class:				0.01
1		60.6 (77)	76.4 (81)	
2		23.6 (30)	8.5 (9)	
3		11.8 (15)	9.4 (10)	
4		3.9 (5)	5.7 (6)	
Enzymes 2x normal		78.9 (97)	93.1 (94)	<0.00
ST Elevation Present		22.8 (29)	95.3 (101)	<0.00
MI Location:				<0.00
anterior		16.5 (21)	47.2 (50)	
inferior		14.2 (18)	46.2 (49)	
other		69.3 (88)	6.6 (7)	
Ejection Fraction (%)	mean, ±s.d.	41.4, ±12.0	46.4, ±12.6	0.01
	median, min-max	42, 20-68	50, 20-70	
Systolic BP (mmHg):	mean, ±s.d.	144, ±37.8	137, ±36.4	ns
	median, min-max	140, 0-260	136, 0-260	
Other Procedures: *		% (n)	% (n)	
CABG		4.7 (6)	5.7 (6)	ns
cardiac catheterization		29.1 (37)	34.0 (36)	ns
echocardiogram		47.2 (60)	50.9 (54)	ns
balloon pump		2.4 (3)	14.2 (15)	<0.00†
laser/athrectomy/stent		1.6 (2)	6.6 (7)	0.05†
pacemaker		2.4 (3)	10.4 (11)	0.01†
repeat PTCA		15.7 (20)	15.1 (16)	ns
rescue PTCA		0.0 (0)	2.8 (3)	ns †
stress test		24.4 (31)	17.0 (18)	ns
ventilator		18.9 (24)	14.2 (15)	ns
Complications: *				
recurrent angina		12.6 (16)	20.8 (22)	ns
AV block		0.0 (0)	5.7 (6)	<0.00†
cardiac arrest		4.7 (6)	3.8 (4)	ns †
CHF		17.3 (22)	10.4 (11)	ns
Rx/hypotension		18.1 (23)	31.1 (33)	0.02
pericarditis		0.8 (1)	1.9 (2)	ns †
recurrent MI		3.9 (5)	2.8 (3)	ns †
cardiac rupture		0.8 (1)	0.9 (1)	ns †
cardiogenic shock		5.5 (7)	8.5 (9)	ns
VT/VF		5.5 (7)	3.8 (4)	ns †
Deaths		13.4 (17)	6.6 (7)	ns

Outcome Variables				
LOS (days)	mean, ±s.d.	6.2, ±4.5	7.1,± 5.4	ns
	median, min-max	5.1, 0-26.6	5.6, 0.2-34.9	
ICU Days	mean, ±s.d.	2.2, ±2.4	3.2, ±2.2	0.00
	median, min-max	2.0, 0-13	2.0, 1-11	
Total Costs ($)	mean, ±s.d.	15,399, ±11,415	22,305, ±14,579	0.00
	median, min-max	12,259, 2,469-67,618	17,970, 4,046-76,621	

* = items are not mutually exclusive

† = cell sizes are small (< 5) therefore analysis of this factor is unstable

Appendix D.
Subset Analysis of < 6 Hour Delay Group – Demographic, History, Risk Factor and Hospitalization Predictors of Administration of a Reperfusion Therapy

D1. Estimates of coefficients, risk ratios, and 95% confidence intervals for demographic characteristics on administration of a reperfusion therapy.

Variable		β	S. E.	Risk Ratio	95% CI	p
age	≥74 years	–1.176	0.347	–0.31	0.16, 0.61	<0.00
gender	women	0.081	0.335	1.08	0.56, 2.09	0.81
race	non-Caucasian	–.154	0.299	.857	0.48, 1.54	0.61
payor	private	0.700	0.353	2.01	1.01, 4.02	0.05

Model chi-square = 30.0, df = 4, p = <.00

D2. Estimates of coefficients, risk ratios, and 95% confidence intervals for cardiac history on administration of a reperfusion therapy.

Variable	β	S. E.	Risk Ratio	95% CI	p
angina	–0.171	.375	.84	0.40, 1.76	0.65
CABG	–0.681	.645	.51	0.14, 1.79	0.29
CHF	–2.534	.625	.08	0.02, 0.27	<0.00
previous MI	–0.744	.368	.48	0.23, 0.98	0.04
PTCA	0.121	.554	1.13	0.38, 3.34	0.83

Model chi-square = 43.4, df = 5, p = <.00

D3. Estimates of coefficients, risk ratios, and 95% confidence intervals for risk factors on administration of a reperfusion therapy.

Variable	β	S. E.	Risk Ratio	95% CI	p
CAD	0.109	0.463	1.12	0.45, 2.76	0.81
diabetes	–0.717	0.315	0.49	0.26, 0.91	0.02
hypercholesterolemia	0.023	0.365	1.02	0.50, 2.09	0.95
hypertension	–0.426	0.284	0.65	0.37, 1.14	0.13
current smoker	0.950	0.439	2.58	1.09, 6.11	0.03
stroke	–1.040	0.504	0.35	0.13, 0.95	0.04

Model chi-square = 22.2, df = 6, p = <.00

D4. Estimates of coefficients, risk ratios, and 95% confidence intervals for hospitalization characteristics on administration of a reperfusion therapy.

Variable		β	S. E.	Risk Ratio	95% CI	p
Killip class	• 2, 3, 4	–1.062	0.321	0.35	0.18, 0.65	<0.00
systolic BP	• ≤ 89	0.360	0.580	1.43	0.46, 4.47	0.53
hospital site	• MZ	0.903	0.293	0.41	1.39, 4.38	<0.00
arrival time	• evening or night shift	–0.690	0.298	0.50	0.28, 0.90	0.02

Model chi-square = 23.0, df = 4, p = <.00

Appendix E.
Subset Analysis using Cost + Length of Stay as an Outcome; Comparisons and Predictors

E1. Comparison of cost per day between short and long delayers.

Short vs Long Delay		≤ 359 min. delay (n=233)	≥ 360 min. delay (n=65)	p
Costs/Day ($)	mean, ±s.d.	2,861, ± 1,569	2,674, ± 1,427	ns
	median,	2,393,	2,334,	
	min-max	1,088 – 12,214	1,164 – 8,634	

E2. Estimates of coefficients, risk ratios, and 95% confidence intervals for demographic characteristics on cost per day.

Variable		β	S. E.	Risk Ratio	95% CI	p
age	≥74 years	-1.111	0.297	0.33	0.18, 0.59	<0.00
gender	women	0.091	0.282	1.10	0.63, 1.90	0.75
race	non-Caucasian	-0.811	0.266	0.44	0.26, 0.75	<0.00
payor	private	0.281	0.317	1.79	0.71, 2.47	0.07
delay	≥360 minutes	-0.002	0.306	1.00	0.55, 1.82	0.99

Model chi-square = 35.00, df = 5, p = <0.00

E3. Estimates of coefficients, risk ratios, and 95% confidence intervals for cardiac history on cost per day.

Variable (1 = presence)		β	S. E.	Risk Ratio	95% CI	p
angina		-0.771	0.322	0.46	0.25, 0.87	0.02
CABG		0.607	0.469	1.83	0.73, 4.60	0.20
CHF		-0.569	0.335	0.57	0.29, 1.09	0.09
previous MI		-0.410	0.299	0.66	0.37, 1.19	0.17
PTCA		0.348	0.461	1.42	0.57, 3.49	0.45
delay	≥360 minutes	-0.209	0.287	0.81	0.46, 1.43	0.47

Model chi-square = 12.50, df = 6, p = .05

E4. Estimates of coefficients, risk ratios, and 95% confidence intervals for risk factors on cost per day.

Variable (1 = presence)		β	S. E.	Risk Ratio	95% CI	p
CAD		0.622	0.406	1.86	0.84, 4.13	0.13
diabetes		-0.450	0.268	0.64	0.38, 1.08	0.09
hypercholesterolemia		0.182	0.304	1.20	0.66, 2.18	0.55
hypertension		0.215	0.249	1.24	0.76, 2.02	0.39
current smoker		0.936	0.370	2.55	1.24, 5.27	0.01
stroke		-0.354	0.388	0.70	0.33, 1.50	0.36
delay	≥ 360 minutes	-0.232	0.295	0.79	0.44, 1.41	0.43

Model chi-square = 17.33, df = 7, p = 0.02

E5. Estimates of coefficients, risk ratios, and 95% confidence intervals for hospitalization characteristics on cost per day.

Variable		β	S. E.	Risk Ratio	95% CI	p
delay	≥ 6 hours	0.147	0.306	1.16	0.64, 2.11	0.63
Killip class	symptomatic (2,3,4)	-0.177	0.281	0.84	0.48, 1.45	0.53
systolic BP	≤ 89	1.620	0.689	5.05	1.31, 19.50	0.02
admission diagnosis	MI	0.210	0.367	1.23	0.60, 2.53	0.57
reperfusion therapy	PTCA or thrombolysis	1.106	0.376	3.02	1.45, 6.32	0.00
additional diagnostic procedures	any	0.167	0.287	1.18	0.67, 2.07	0.56
complication	any (except hypotension)	0.549	0.268	1.73	1.02, 2.93	0.04

Model chi-square = 40.88, df = 7, p = <0.00

E6. Estimates of coefficients, risk ratios, and 95% confidence intervals for the final combined model of predictors of cost per day.

Variable		β	S. E.	Risk Ratio	95% CI	p
age	≥ 74 years	-1.043	0.309	0.35	0.19, 0.64	0.00
sex	woman	-0.049	0.296	0.95	0.53, 1.70	0.87
race	non-Caucasian	-0.847	0.279	0.43	0.25, 0.74	0.00
angina	history of	-0.700	0.355	0.50	0.25, 1.00	0.05
smoking	history of	0.509	0.398	1.66	0.76, 3.63	0.20
systolic BP	• ≤ 89	1.384	0.735	3.99	0.94, 16.85	0.06
reperfusion therapy	• PTCA or thrombolysis	0.983	0.278	2.67	1.55, 4.61	0.00
complications	any (except hypotension)	0.700	0.284	2.01	1.16, 3.51	0.01

Model chi-square = 66.11, df = 8, p = <0.00

Appendix F.
Subset Analysis Examining Predictors of Delay Time

F1. Estimates of coefficients, risk ratios, and 95% confidence intervals for demographic characteristics on delay time.

Variable		β	S. E.	Risk Ratio	95% CI	p
age	≥ 74 years	-0.667	0.339	0.51	0.26, 1.00	0.05
gender	women	0.352	0.325	1.42	0.75, 2.69	0.28
race	non-Caucasian	0.625	0.293	1.88	1.05, 3.32	0.03
payor	private	-0.740	0.378	0.48	0.23, 1.00	0.05

Model chi-square = 11.70, df = 4, p = 0.02

F2. Estimates of coefficients, risk ratios, and 95% confidence intervals for cardiac history on delay time.

Variable	β	S. E.	Risk Ratio	95% CI	p
angina	-0.072	0.377	0.93	0.44, 1.95	0.85
CABG	0.201	0.541	1.22	0.42, 3.53	0.71
CHF	-0.385	0.432	0.68	0.29, 1.59	0.37
previous MI	-0.392	0.377	0.68	0.32, 1.41	0.30
PTCA	-0.181	0.607	0.83	0.25, 2.74	0.77

Model chi-square = 3.2, df = 5, p = 0.66

F3. Estimates of coefficients, risk ratios, and 95% confidence intervals for risk factors on delay time.

Variable	β	S. E.	Risk Ratio	95% CI	p
CAD	-0.273	0.459	0.76	0.31, 1.87	0.55
diabetes	0.046	0.321	1.05	0.56, 1.97	0.89
hypercholesterolemia	0.696	0.330	2.01	1.05, 3.83	0.03
hypertension	-0.402	0.298	0.67	0.37, 1.20	0.18
current smoker	0.431	0.379	1.54	0.73, 3.24	0.26
stroke	0.132	0.466	1.14	0.46, 2.84	0.78

Model chi-square = 8.27, df = 6, p = 0.22

F4. Estimates of coefficients, risk ratios, and 95% confidence intervals for the MI severity model on delay time.

Variable		β	S. E.	Risk Ratio	95% CI	p
Killip Class	symptomatic	-0.323	0.379	0.72	0.34, 1.52	0.39
systolic BP	≤ 89	-1.037	1.068	0.35	0.04, 2.87	0.33
ejection fraction	≤ 40	-0.246	0.389	0.78	0.36, 1.68	0.53

Model chi-square = 2.7, df = 3, p = 0.43

F5. Estimates of coefficients, risk ratios, and 95% confidence intervals for the final combined model on delay time.

Variable		β	S. E.	Risk Ratio	95% CI	p
age	≥ 74 years	-0.545	0.317	0.58	0.31, 1.08	0.08
race	non-Caucasian	0.632	0.294	1.88	1.06, 3.35	0.03
payor	private & other	-0.847	0.383	0.43	0.20, 0.91	0.03
hyperchol-esterolemia	presence	0.738	0.324	2.09	1.11, 3.95	0.03

Model chi-square = 15.54, df = 4, p = <0.00

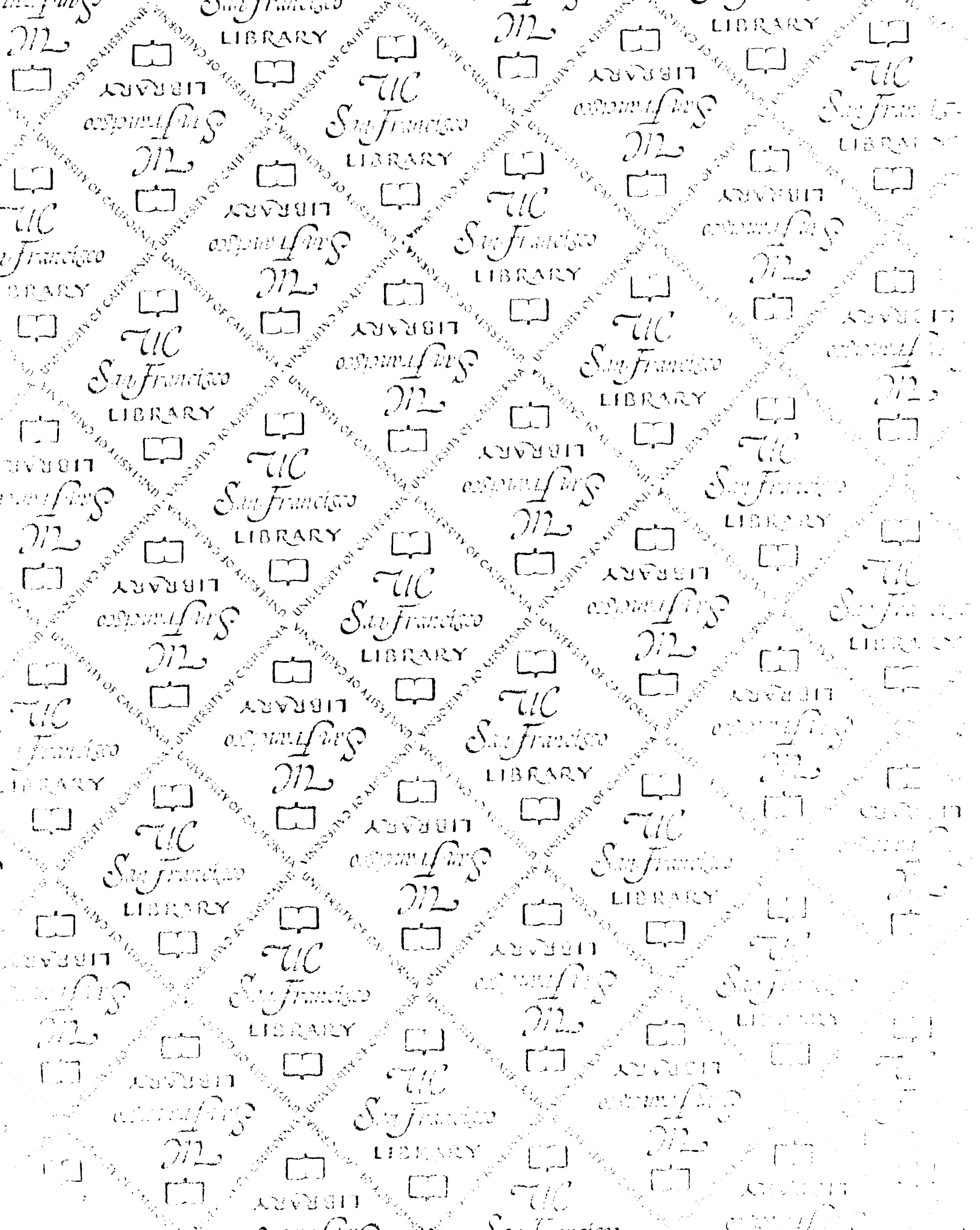
Appendix G.
Subset Analysis of Deaths in the Short Delay Group

		Survivors (n=274)	Non-survivors (n=24)	p
Demographics				
Age (yrs.)	mean, ±s.d.	70.5, ±14.3	79.2, ±10.3	<0.00
	median, min-max	72, 27-99	81, 50-92	
		% (n)	% (n)	
Gender	(men)	63.5 (174)	45.8 (11)	ns
Race:				ns
Caucasian		57.6 (152)	65.2 (15)	
non-Caucasian		43.3 (116)	34.8 (8)	
Cardiac History & Risk Factors:				ns
any		88.7 (243)	100 (24)	
Covariates - Hospitalization				
Transport:				0.04
self		39.3 (105)	17.4 (4)	†
ambulance		60.7 (162)	82.6 (19)	
Site:				ns
Moffitt/Long		55.5 (152)	54.2 (13)	
Mount Zion		44.5 (122)	45.8 (11)	
Arrival Time:				ns
7am-3pm		34.7 (95)	33.3 (8)	
3pm-11pm		36.1 (99)	37.5 (9)	
11pm-7am		29.2 (80)	29.2 (7)	
Admission Diagnosis				<0.00
MI		49.8 (136)	45.5 (10)	
r/o MI		31.1 (85)	18.2 (4)	
unstable angina		12.5 (34)	9.1 (2)	†
other		6.6 (18)	27.3 (6)	
Initial Reperfusion:				ns
none		56.2(154)	70.8 (17)	
thrombolysis or PTCA		43.8(120)	29.2 (7)	
Killip Class:				<0.00
1		72.3 (198)	33.3 (8)	
2		16.8 (46)	25.0 (6)	
3		8.8 (24)	16.7 (4)	†
4		2.2 (6)	25.0 (6)	
ST Elevation Present		55.1 (151)	54.2 (13)	ns
MI Location:				ns
anterior		28.5 (78)	37.5 (9)	
inferior		30.3 (80)	25.0 (6)	
other		41.2 (113)	37.5 (9)	
Ejection Fraction (%)	mean, ±s.d.	45.0, ±12.2	35.0, ±15.3	0.01
	median, min-max	45.0, 15 – 70	30.0, 20 – 65	
Systolic BP (mmHg):	mean, ±s.d.	145, ±35.0	116, ±40.3	<0.00
	median, min-max	143, 0 – 260	120, 0 – 190	
Other Procedures:		% (n)	% (n)	
any		83.6 (229)	62.5 (15)	0.01

		Survivors (n=274)	Non-survivors (n=24)	p
Complications: any		38.7 (106)	83.3 (20)	<0.00
Outcome Variables				
LOS	mean, ±s.d.	6.7, ±4.6	5.0, ±4.8	ns
	median, min-max	5.3, 1.6 – 34.9	4.1, 0 – 16.9	
ICU days	mean, ±s.d.	2.4, ±2.0	4.2, ±3.8	0.04
	median, min-max	2, 0 – 11	2.0, 0 – 13	
Total Costs ($)	mean, ±s.d.	18,400, ±12,976	18,889, ±16,363	ns
	median, min-max	14,777, 2469 – 76,621	13,920, 3,394 – 55,534	

* = items are not mutually exclusive

† = cell sizes are small (<5) therefore analysis of this factor is unstable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